A Multi-Method Investigation of Circadian Rhythms, Sleep, and Affective States: Characterising Modulation, Imaging Reward Mechanisms, and Improving Clinical Measurement

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Abstract

The relationship between biological rhythms (circadian and sleep-wake processes) and reward motivation is proposed to be important, with circadian modulation of reward motivation one pathway in this relationship. To date, the relationship between biological rhythms and reward motivation has largely been investigated in animal studies, with limited exploration of this important interaction in humans. The aim of this project was to incrementally advance understanding of the relationship between biological rhythms and reward motivation in humans. To do this, the relationship between biological rhythms and reward motivation was reviewed (Study 1) and psychometrically examined (Study 2). Study 2 psychometrically quantified the separation of sleep quality, diurnal preference, and mood leading to the generation and initial psychometric testing of a new self-report measure of sleep quality, circadian functioning and depressed mood. The remaining three studies focused on the circadian component of biological rhythms, investigating critical aspects of a putative circadian modulation of reward motivation. Study 3 examined diurnal variation in three psychological components of reward. Findings indicated that unconscious "wanting" and conscious wanting of rewards exhibited diurnal variation peaking at 14:00h with diurnal variation in conscious liking and learning not fitting a waveform peaking at 14:00h. Study 4 systematically reviewed circadian modulation of neural reward functioning in functional magnetic resonance imaging (fMRI) studies. Of the 15 included studies, 13 studies generated some evidence of circadian modulation of reward functioning with altered ventral striatum, medial prefrontal cortex, and default mode network activation most consistently associated with circadian parameters. In Study 5, diurnal variation in reward motivation was examined in a block-design fMRI study in response to a well-validated reward task. The left putamen displayed significantly less activation at 14:00h relative to 10:00h and 19:00h which may reflect a circadian-driven prediction error of the brain. The current findings advance evidence of a relationship between biological rhythms and reward motivation in humans at multiple biobehavioural levels. In particular, this project has found evidence for diurnal variation of reward motivation, a preliminary step in investigating modulation of reward motivation by circadian functioning. Further work is now needed to consider the clinical translation of the relationship between biological rhythms and reward motivation. Additionally, future research

should systematically investigate the relationships between the multifaceted construct of reward motivation and the range of processes involved in biological rhythms.

Acknowledgements

Declaration

In submitting this thesis in partial fulfillment of the requirements for the degree of Doctor of Philosophy (Clinical Psychology) by Associated Papers at Swinburne University of Technology, I declare that the following work:

1.   Contains no material which has been accepted for the award to the candidate of any other degree or diploma, except where due reference is made in the text of the examinable outcome;

2.   To the best of the candidate's knowledge contains no material previously published or written by another person except where due reference is made in the text of the examinable outcome; and

3.   Where the work is based on joint research or publications, discloses the relative contributions of the respective workers or authors.

Signed

Jamie E. M. Byrne

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List of Publications Arising from the Project

Chapter	Co-Authors	Journal/ Book	Status
Positive affect and biological rhythms: Interactions in general population and clinical samples.			
5	**Jamie Byrne** Prof. Greg Murray	*Oxford Handbook of Positive Emotion and Psychopathology*:	In Press
Development of a measure of sleep, circadian rhythms, and mood: The SCRAM Questionnaire.			
6	**Jamie Byrne** Dr. Ben Bullock Prof. Greg Murray	*Frontiers in Psychology*	Published, doi:10.3389/fpsyg.2017.02105
A psychometric investigation of the SCRAM questionnaire.			
7	**Jamie Byrne** Dr. Ben Bullock Prof. Greg Murray	*Chronobiology International*	Accepted, doi: 10.1080/07420528.2018.1533850
Diurnal rhythms in psychological reward functioning in healthy young men: 'wanting', liking and learning.			
8	**Jamie Byrne** Prof. Greg Murray	*Chronobiology International*	Published, doi10.1080/07420528.2016.1272607
The sleep and circadian modulation of neural reward pathways: A systematic review protocol.			
9	**Jamie Byrne** Prof. Greg Murray	*Systematic Reviews*	Published, doi:10.1186/s13643-017-0631-3
Circadian modulation of reward function: Is there an evidentiary signal in existing neuroimaging studies?.			
9	**Jamie Byrne** Hailey Tremain Dr. Nuwan Leitan Dr. Charlotte Keating Prof. Sheri Johnson Prof. Greg Murray	*Neuroscience & Biobehavioral Reviews*	Under Review
Time of day differences in neural reward functioning in healthy young men.			
11	**Jamie Byrne** Dr. Matthew Hughes Prof. Susan Rossell Prof. Sheri Johnson Prof. Greg Murray	*The Journal of Neuroscience*	Published, doi:10.1523/jneurosci.0918-17.2017

Chapter 1: Overview of the Project

The overarching aim of the present project was to incrementally advance understanding of the relationship between biological rhythm function (which for the present purposes refers to both circadian and sleep-wake processes) and reward motivation in humans. A growing body of evidence suggests that biological rhythm function and important outputs of the reward system have a complex relationship (e.g., Harvey, Murray, Chandler, & Soehner, 2011; Logan, Hasler, et al., 2018; Malhi & Kuiper, 2013). The present project advances understanding of the literature by characterising relationships between biological rhythms and reward motivation, and by examining circadian modulation of reward motivation (see Section 1.1. for overview). The thesis document itself is presented as a PhD with associated papers. The included papers are bookended by linking sections and a general discussion chapter (see Section 1.2. for details). Multiple streams of basic science and clinical research (reviewed briefly below) suggest that the interplay between biological rhythms and reward motivation is poorly understood, warranting urgent scientific attention that the present project aims to provide.

Interactions between biological rhythms and reward motivation has been investigated in a number of ways. For example, in animals, the modulation of reward motivation by circadian (see McClung, 2007, 2011, 2013), and sleep (see Tsujino & Sakurai, 2009) processes has been demonstrated. Additionally, relationships between circadian and sleep modulation of reward motivation have been observed in human studies. Examples of circadian modulation of reward motivation include: diurnal and circadian rhythms in positive affect (e.g., Clark, Watson, & Leeka, 1989; Murray, Allen, & Trinder, 2002; Murray et al., 2009; Stone et al., 2006; Watson, Wiese, Vaidya, & Tellegen, 1999), circadian genes altering neural response to a monetary reward task (Forbes et al., 2012), and evening chronotypes being associated with lower mean levels of positive affect relative to morning chronotypes (e.g., Biss & Hasher, 2012; Randler & Weber, 2015). Evidence for sleep modulation of reward motivation has emerged from studies finding altered neural reward functioning following sleep deprivation and in individuals with insomnia symptoms (e.g., Benedict et al., 2012; Casement, Keenan, Hipwell, Guyer, & Forbes, 2016; Venkatraman, Chuah, Huettel, & Chee, 2007), and an observed association between poorer sleep quality and lowered positive affect (e.g., Bower, Bylsma, Morris, & Rottenberg, 2010; E. K. Gray & Watson, 2002; McCrae et al., 2008).

The present project is made up of a number of studies investigating basic science questions (see Table 1) but is motivated by the clinical importance of understanding the relationship between biological rhythms and reward motivation. A proposed dysregulation between biological rhythms and reward processes is implicated in bipolar disorder (cf. Alloy, Nusslock, & Boland, 2015) and substance use disorders (cf. Hasler, Soehner, & Clark, 2014; Hasler, Soehner, & Clark, 2015; Logan, Hasler, et al., 2018). Despite the potential clinical utility (see Wulff, Gatti, Wettstein, & Foster, 2010) and evidence from animal literature of shared relationships between biological rhythms and reward motivation (see Boutrel, Cannella, & de Lecea, 2010; McClung, 2013; Parekh & McClung, 2016; Tsujino & Sakurai, 2009; Vadnie & McClung, 2017), detailed investigation of the complex interplay between biological rhythms and reward motivation in humans is scarce. Investigating the important interaction between various facets of biological rhythm function and variables related to reward motivation in healthy populations provides an important step towards ultimate clinical translation of this work.

1.1   Variables Under Investigation in the Present Project

It is important to recognise that, while the project has a single overarching aim, this broad framework subsumes numerous specific possible questions and relationships that potentially cross levels of the biopsychosocial human system (see Figure 1).

First, biological rhythm function refers to a range of processes, including but not limited to parameters related to circadian function such as objective parameters of diurnal and circadian rhythms (amplitude, phase, etc.), self-reported features such as diurnal preference, and neurobiological features (genotype, melatonergic processes etc.); sleep similarly refers to a range of separable constructs (duration, subjective quality, stage, etc.) and measured variables (total sleep time, sleep quality etc.; e.g., Benca et al., 2009; Carney et al., 2012; Salvatore, Indic, Murray, & Baldessarini, 2012).

Second, reward motivation is a multifaceted construct, and refers not only to neural reward circuitry, but subjective experience and behaviour in the context of rewards; a range of objective (e.g., fMRI, performance on gambling tasks) and self-report measures (e.g., positive emotions) speak to aspects of reward motivation (see Chapter 3; e.g., Colibazzi et al., 2010; Gerber et al., 2008; Knutson, Katovich, &

Suri, 2014). Consequently, as noted by McClung (2013), the domain of research in fact refers to numerous testable relationships between measures of the two broad concepts.
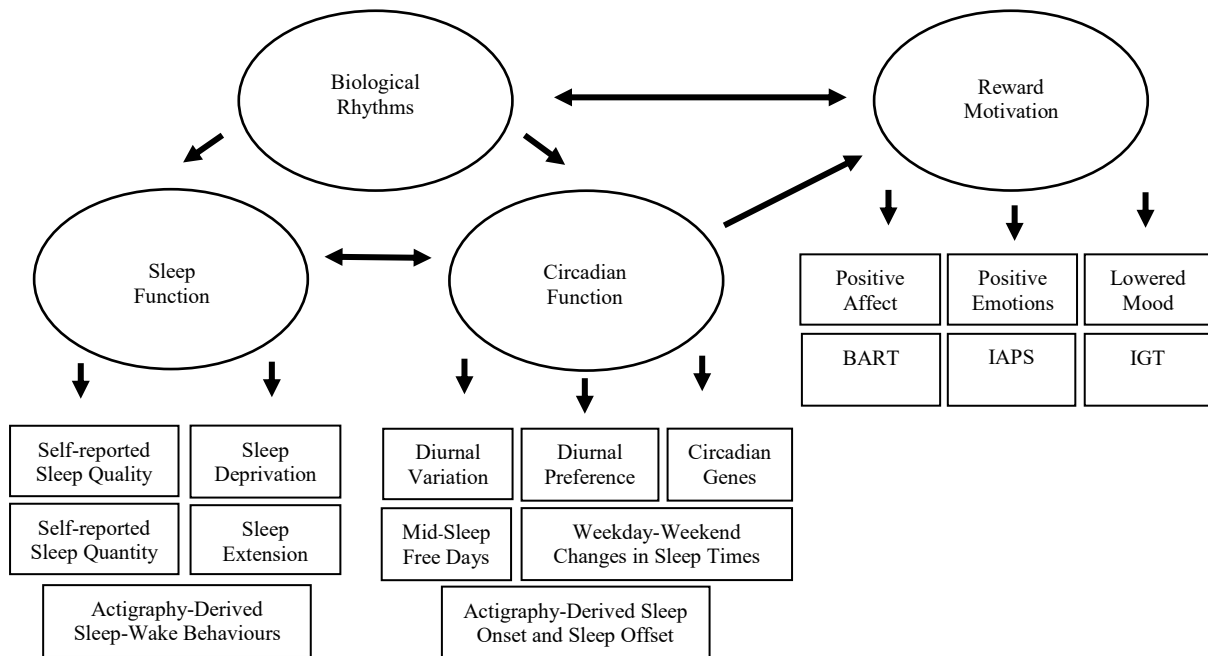
Figure 1. Concepts and measures investigated in the present project. BART = Balloon Analogue Risk Task; IAPS = International Affective Picture System; IGT = Iowa Gambling Task. *Note:* the measured variables in this figure are not hierarchically related, e.g., the IGT is not proposed to be a manifestation of Lowered Mood

As displayed in Figure 1, the multiple studies of the present project measure biological rhythms and reward motivation in a variety of ways. The diagram presented in Figure 1 is not directly tested in the present project; however, it highlights three pathways of interest for this project: The relationship between biological rhythms and reward motivation, the relationship between sleep function and circadian function, and circadian modulation of reward motivation. For feasibility, one pathway not investigated here is the possible reward modulation of circadian functioning (considered further below).

The present project sought to advance the literature by, firstly, investigating five tightly-operationalised specific questions/hypotheses through literature reviews and empirical investigations. To orient the reader to the thesis document, a brief overview of the aims, methods and findings of five studies is presented in Table 1.

These investigations led to a range of peer-reviewed publications (see last column, Table 1). The findings from these five studies are then critically reviewed in a General Discussion, with the aim of identifying directions for future research emerging from each individual study. In this General Discussion an integration of findings and limitations across the individual studies is included where possible.

Table 1

Brief Overview of the Five Studies of the Project and the Associated Publications from the Studies

Study	Scientific Aim(s)	Research questions/hypotheses	Method	Main Results	Key Limitations	Primary Conclusions	Associated Publications
1	To review naturalistic prospective studies of the relationships between biological rhythms and positive affect	Is there evidence of a relationship between circadian function and positive affect? Is there evidence of a relationship between sleep function and positive affect? Is there evidence of biological rhythm dysregulation in mood disorders?	A review of naturalistic prospective studies examining the relationship between biological rhythms and positive affect	Diurnal and circadian variation in positive affect may reflect a broader circadian modulation of reward motivation Sleep parameters influenced next day positive affect with a small number of longitudinal studies suggesting a causal relationship Some evidence exists of a bidirectional effect with positive affect modulating sleep parameters	Not a systematic review Positive affect may influence circadian function	There is evidence of the circadian system modulating levels of positive affect There is strong evidence that sleep parameters are associated with next day positive affect To a lesser extent, positive affect modulates sleep parameters, and the arousal level of positive affect may help explain the direction of this relationship	Byrne, J. E. M., & Murray, G. (In Press). Positive affect and biological rhythms: Interactions in general population and clinical samples. In J. Gruber (Ed.), *Oxford Handbook of Positive Emotion and Psychopathology*: Oxford University Press.
2	To psychometrically quantify the separation of sleep quality, diurnal preference, and mood To design a brief measure of sleep quality, diurnal preference, and mood to help	What is the factor structure of items relating to sleep quality, diurnal preference, and mood? What is the test-retest reliability of the questionnaire? Does the questionnaire have construct validity in	Online questionnaire with multiple samples Seven-day collection of actiwatch data	A three-factor solution of sleep quality, diurnal preference, and mood was the only stable factor structure and was supported by CFA A brief 15-item questionnaire was formed with three scales: Good Sleep, Morningness, and Depressed Mood	Predominantly female and student sample in online data, largely limited to self-report correlates to validate the questionnaire against Actiwatch data limited to young men	The design and preliminary construct validity and reliability suggests the SCRAM questionnaire concurrently measures sleep quality, diurnal preference, and mood while discriminating between the three interacting processes	2a. Byrne, J. E. M., Bullock, B., & Murray, G. (2017). Development of a measure of sleep, circadian rhythms, and mood: The SCRAM Questionnaire. *Frontiers in Psychology, 8*(2105). doi:10.3389/fpsyg.2017.02105 2b. Byrne, J. E. M., Bullock, B., & Murray, G. (Under Review). A psychometric investigation of the

Study	Scientific Aim(s)	Research questions/hypotheses	Method	Main Results	Key Limitations	Primary Conclusions	Associated Publications
	remind clinicians of these interacting processes in treatment planning To investigate preliminary reliability and validity of the new questionnaire	relation to well-validated constructs of sleep quality, diurnal preference, and mood? How does the new questionnaire relate to actigraphy measures of sleep-wake behaviour?		Test-retest reliability was strong for all three scales The scales are strong predictors of well-validated measures of the constructs The Morningness scale was related to actiwatch earlier sleep times and Good Sleep scale was related to actiwatch sleep efficiency	collected 18 months before questionnaire was completed		SCRAM questionnaire. *Chronobiology International*
3	To test for diurnal variation in psychological components of reward	It was hypothesised that wanting and "wanting" would display diurnal variation with a peak in the mid-afternoon Diurnal variation with a peak in the mid-afternoon for liking and learning was explored	18-30 year old (N = 50) men completed tasks measuring "wanting", wanting, liking, and learning at three time-points: 10:00h, 14:00h, and 19:00h counterbalanced	Tasks measuring "wanting" and wanting fitted a diurnal waveform with a peak at 14:00h, and nadirs at 10:00h and 19:00h Tasks measuring liking and learning did not fit this waveform	Only young men were tested Endogeneity of diurnal variation not tested	A diurnal component of increased wanting in the afternoon was observed, while no diurnal variation was seen for liking or learning. Paying careful attention to psychological components of reward is important in understanding the relationship between circadian function and reward motivation	Byrne, J. E. M. & Murray, G. (2017). Diurnal rhythms in psychological reward functioning in healthy young men: 'wanting', liking and learning. *Chronobiology International, 34*(2), 287-295. doi: 10.1080/07420528.2016.1272607
4	To systematically review fMRI studies that generate data concerning circadian	Is there circadian modulation of the reward system in fMRI studies? If so, what brain regions subserve	Systematic review using Preferred Reporting Items for Systematic Reviews and	A signal of circadian modulation of the reward system was observed in 13 of the 15 studies Circadian predictor variables were associated with altered	Heterogeneity of circadian predictor variables and reward	Within the context of significant heterogeneity of studies, there is evidence of circadian modulation of the reward system observed most consistently in the VS,	Byrne, J. E. M. & Murray, G. (2017). The sleep and circadian modulation of neural reward pathways: A systematic review protocol. *Systematic Reviews,*

Study	Scientific Aim(s)	Research questions/hypotheses	Method	Main Results	Key Limitations	Primary Conclusions	Associated Publications
	modulation of the reward system	circadian modulation of the reward system? Is circadian modulation present in both reward anticipation and reward receipt in event-related fMRI designs?	Meta-Analyses guidelines Included resting state, and task-based designs Reward anticipation and reward receipt was examined using event-related designs	VS, mPFC (and to a lesser extent putamen) activation in task-based studies Circadian predictor variables were associated with altered DMN (and to a lesser extent ACC) activation in resting-state studies A signal of circadian modulation was observed in both reward anticipation and reward receipt	outcome variables Small sample sizes, and restricted age range and gender in many samples limits generalisability	mPFC, and DMN. There is stronger evidence of this modulation for reward receipt than reward anticipation	6(237). doi:10.1186/s13643-017-0631-3 Byrne, J. E. M., Tremain, H., Leitan, N. D., Keating, C., Johnson, S. L. & Murray, G. (Under Review). Circadian modulation of reward function: Is there an evidentiary signal in existing neuroimaging studies?. *Neuroscience and Biobehavioral Reviews*
5	To examine diurnal variation in neural reward functioning	It was hypothesised that a diurnal waveform would be observed in neural reward functioning It was hypothesised that the diurnal waveform would be quadratic	HCP gambling task was completed by 16 male participants at 10:00h, 14:00h, and 19:00h with counterbalanced start times Block design using BOLD fMRI protocol with bilateral mPFC, VTA, ACC, caudate, NAc, putamen ROIs	A diurnal waveform was observed in the left putamen with a nadir at 14:00h and peaks at 10:00h and 19:00h	Endogeneity of diurnal rhythm was not tested Sample was restricted to young men	Preliminary evidence of diurnal variation in one brain region involved in reward functioning. The direction of this diurnal waveform may indicate a circadian prediction-type error in neural reward functioning	Byrne, J. E. M., Hughes, M. E., Rossell, S. L., Johnson, S. L., & Murray, G. (2017). Time of day differences in neural reward functioning in healthy young men. *The Journal of Neuroscience, 37*(37), 8895-8900. doi:10.1523/jneurosci.0918-17.2017

As shown in Table 1, the project did not have a single overarching hypothesis or research question. Rather, a number of specific questions and novel hypotheses were explicitly set and tested within specific studies. Four features of the project are outlined here to frame the readers' understanding of the construction of this project:

1. Five distinct investigations of the biological rhythm modulation of reward motivation were undertaken. The first two investigations aimed to characterise the relationship between biological rhythms and reward motivation (measured as positive affect). Study 1 (see Chapter 5) reviewed naturalistic prospective studies of these relationships. Study 2 was methodologically innovative, using psychometrics to quantitatively separate the parameters of circadian function (diurnal preference), sleep (quality), and mood (depressed mood, understood here as lowered positive affect) as independent dimensions. Study 2 describes the generation (Study 2a, see Chapter 6) and initial validation (Study 2b, se Chapter 7) of the Sleep, Circadian Rhythms, and Mood (SCRAM) questionnaire which (a) separates the three dimensions in a brief self-report questionnaire, (b) reminds clinicians to account for these three interacting dimensions in treatment planning. The remaining three studies focussed solely on the circadian predictor variable, investigating critical aspects of a putative circadian modulation of reward motivation, largely using diurnal variation as a measure of circadian function. Study 3 (see Chapter 8) sought to advance understanding of circadian modulation of reward motivation by examining which psychological components of reward may exhibit diurnal variation using Berridge's influential work. Study 4 (see Chapter 9) and Study 5 (see Chapter 10) aimed to examine the neural mechanisms that may underpin circadian modulation of reward motivation. Study 4 includes a protocol paper and presents a systematic review of fMRI studies that have the potential to examine circadian modulation of reward processes. Study 5 aimed to examine diurnal variation in reward motivation through a repeated measures study of neural response to a well-validated monetary reward task at three times of day.

2.   The project is primarily interested in the relationship between circadian function and reward motivation; however, it recognises the importance of considering sleep processes in this relationship. Study 1 and Study 2 include sleep processes (largely sleep quality) as a key variable; and Study 4 includes a protocol which outlines the method for a pair of systematic reviews to examine fMRI studies measuring a sleep and circadian modulation in neural reward processes. Only the systematic literature review examining circadian modulation in neural reward functioning is presented in this thesis.

    a.   A note on the role of sleep function in this project: Sleep and circadian functioning interact continuously (see Section 2.5 for more detail). Given the many ways that sleep functioning may impact both circadian functioning and reward motivation, sleep functioning is a key variable of Study 1 and Study 2 in this project (as above). As circadian functioning and reward motivation is the primary relationship of interest in the present project, the introductory literature reviews presented in Chapter 2 (Circadian System), Chapter 3 (Reward Motivation), and Chapter 4 (Circadian Modulation of Reward Motivation) do not focus on sleep functioning. Relevant information on sleep functioning is included in the introductions of Study 1 (see Section 5.2) and Study 2 (see Section 6.2).

3.   While this project has important implications for clinical research, and is in part based on important research done in clinical populations (see Section 4.5), the project reported here was basic science research. By better characterising the biological rhythm and reward system interaction in non-clinical samples, it was expected that a deeper understanding would emerge on how this relationship may be dysregulated in clinical populations. In Study 3 (and subsequently Study 5) participants with a history of severe mental illnesses (e.g., bipolar disorder or schizophrenia) were excluded.

4.   To contain the project's scope, Study 3, Study 4, and Study 5 examined circadian modulation of reward motivation: In reality, the interaction

between circadian rhythms and reward motivation is likely bi-directional (see Section 11.7.3).

1.2   Overview of the Thesis Document

This thesis is organised into 11 chapters. The thesis is presented for examination with "associated papers", and as such there is some unavoidable repetition in content. As each of the five studies used distinct methodologies, no separate methodology chapter is included in this thesis. Prior to presenting the studies, Chapter 2 provides an extended discussion on the circadian system, and Chapter 3 discusses the conceptualisation of reward motivation and measurement of this system in humans (including positive affect, mood, and emotions). Chapter 4 briefly summarises three lines of evidence consistent with circadian modulation of reward motivation drawn from animal research, examining diurnal and circadian rhythms in positive affect, and a clinical hypothesis of joint dysregulation of circadian and reward systems in bipolar disorder.

The following seven chapters are a series of publications preceded by linking sections. The linking sections briefly summarise the chapter aims and how the study fits within the overall project. For each publication, text, tables, and figures have been replicated verbatim from the published or submitted publication. Formatting has been changed to American Psychological Association 6 referencing (American Psychological Association, 2010). For consistency, the publications have been edited to British English, and there is continued numbering of headings, figures and tables throughout the thesis document. References for each publication have been amalgamated into one reference list at the end of the thesis document (see Section 12). A glossary of commonly used abbreviations and terms is included in Appendix A.

Chapter 5 (Study 1) presents a book chapter reviewing the role of circadian rhythms and sleep in positive emotions, considering the bi-directional relationships between these constructs. Chapter 6 (Study 2a) approaches the interaction between sleep, circadian rhythms and mood (SCRAM) from a psychometric standpoint. This work resulted in the construction of a questionnaire that could distinguish between sleep quality, diurnal preference, and depressed mood in a brief face-valid measure (the SCRAM questionnaire). Chapter 7 (Study 2b) provides preliminary validation of the new SCRAM questionnaire, examining test-retest reliability, prediction of

well-validated measures of sleep quality, diurnal preference, and mood by using the three SCRAM scales, and examines how these scales were related to actigraphy measures. Chapter 8 (Study 3) extends the literature by using Berridge's parsing of psychological reward components to examine diurnal rhythms in three reward processes. Chapter 9 (Study 4) presents a protocol paper for a pair of systematic literature reviews, prior to presenting a systematic review of circadian modulation of the reward system in fMRI studies. Chapter 10 (Study 5) furthers this examination of diurnal variation of reward processes by investigating the putative diurnal rhythm in the neural reward response using a repeated measures fMRI protocol.

Chapter 11 summarises findings of the reviews and empirical studies, considering in more depth the limitations, implications and future research of the present work. It is provisionally concluded that in humans there is a relationship between biological rhythms and reward motivation and that circadian modulation of reward motivation can be observed in behavioural tasks and neural outcome measures.

Chapter 2: The Circadian System

To a layperson the primary driver of sleep is the elapsed time since a previous sleep period. The longer it has been since sleep, the greater the physiological need for sleep. While this process, sleep homeostasis, is one important determinant of sleep propensity, there is a second, more ubiquitous, factor from an evolutionary lens, the circadian system, which drives the timing of sleep-wake behaviour, and many other physiological, behavioural, and psychological processes (Saper, 2013). Chapter 2 introduces the reader to the core features of the circadian system in humans (2.1), followed by a discussion of what a diurnal rhythm is (2.2), and the methodological considerations of measuring circadian rhythms in temporal isolation (2.3) and diurnal rhythms in naturalistic conditions (2.4). Borbély's (Borbély, 1982; Borbély, Daan, Wirz-Justice, & Deboer, 2016) two-process model of sleep regulation is introduced with a discussion of the ways that sleep and circadian rhythms may interact in naturalistic conditions (2.5). This introductory chapter finishes by discussing the importance of accounting for circadian masking factors of sleep processes when measuring diurnal rhythms that are presumed circadian outputs in naturalistic conditions (2.6), before a summary (2.7).

2.1 The Circadian System

In all terrestrial species, including humans, the circadian (*circa*: about, *diem*: a day) system coordinates biological rhythms that allow organisms to adapt to the 24-hour light-dark cycle of the Earth's rotation (Pittendrigh, 1960). As the 'clock' of the body, this system is responsible for being a reliable timekeeper, and the clock's time can be modified through interactions with the outside world (Roenneberg, Kantermann, Juda, Vetter, & Allebrandt, 2013). Indeed, two features of the circadian system are core to its adaptive function: (1) the circadian system generates endogenous cell-autonomous rhythms that are internally synchronised, and (2) the circadian system optimally entrains to the external environment (Pittendrigh, 1960; Pittendrigh & Daan, 1976).

2.1.1 The molecular genetics of the circadian system.
The intrinsic 24-hour biological clock is coordinated at the cellular level through 'clock genes' (Lamont, Legault-Coutu, Cermakian, & Boivin, 2007; Vitaterna et al., 1994; Vitaterna, Takahashi, & Turek, 2001) that are responsible for the generation of downstream circadian rhythms (Ko & Takahashi, 2006; Mohawk, Green, & Takahashi, 2012). The suprachiasmatic nuclei (SCN) serve as the primary

coordinator for the circadian system; synchronising the circadian clocks present in most cells of the body (Mohawk et al., 2012). The SCN coordinates these peripheral oscillators to a uniform endogenous time (Buhr & Takahashi, 2013; Ko & Takahashi, 2006; Mohawk et al., 2012; Mohawk & Takahashi, 2011; Welsh, Takahashi, & Kay, 2010). A closed transcriptional (DNA-mRNA) - translational (mRNA-proteins) autoregulatory feedback loop constitutes the molecular circadian clock. The core transcriptional loop cycles every ~24 hours beginning with the translational protein activators of CLOCK and BMAL promoting the transcription of Period (Per1, Per2 and Per3) and Cryptochrome (Cry1 and Cry2) genes. As these genes accumulate, dimerise, and diffuse back into the nucleus, the PER and CRY products form a negative feedback, inhibiting their own transcription. This negative feedback loop leads to a decreased level of PER and CRY, beginning anew the cycle of their transcription (Mohawk et al., 2012; Rosenwasser & Turek, 2017; Shearman et al., 2000; Welsh et al., 2010).

     2.1.2   Zeitgebers. Organisms entrain to the external environment through *zeitgebers* (GE: time givers; Pittendrigh, 1960; Pittendrigh & Daan, 1976). While zeitgebers may be many things (including: social interactions, food intake, exercise, and, melatonin), light is the zeitgeber the circadian system is most sensitive to, particularly for mammalian species. This is due to direct neurobiological pathways from retina to SCN (Rosenwasser & Turek, 2017). There is a biological and behavioural reason for this adaptive sensitivity to light: The evolutionary fitness of an organism is enhanced by its ability to entrain to the 24-hour cycle of the Earth's rotation, where periods of this cycle face towards the sun (daytime) and away from the sun (night; Daan & Aschoff, 1982; Roenneberg & Merrow, 2003).

     Light information affects the circadian system through non-image forming, photoreceptive pathways, distinct from the rods and cones core to image forming pathways. This third type of visual photoreceptor are the melanopsin-containing intrinsically photoreceptive ganglion cells (ipRGCs; Lucas & Foster, 1999; Sekaran, Lucas, & Hankins, 2003; Sekaran et al., 2005). Light reaches these ipRGCs and travels via the retinohypothalamic tract to the master circadian oscillator of the SCN (Moore & Lenn, 1972; L. P. Morin & Allen, 2006; Ralph, Foster, Davis, & Menaker, 1990). Multiple studies in rodents (David-Gray et al., 2002; David-Gray, Cooper, Janssen, Nevo, & Foster, 1999; David-Gray, Janssen, DeGrip, Nevo, & Foster, 1998;

Lucas & Foster, 1999; Lucas, Freedman, Munoz, Garcia-Fernandez, & Foster, 1999) have demonstrated that blind animals (through neurodegeneration, naturally 'blind' animals [e.g., the blind mole rat, *Spalax ehrenbergi*], and experimental cone and rod mutations) are still able to entrain to the light-dark cycle despite no discernible image vision.

Non-photic zeitgebers (social interaction, exercise, and food) may also be important for circadian entrainment (Mistlberger & Skene, 2004; Webb, Antle, & Mistlberger, 2014). Wehrens et al. (2017), for example, showed that when light exposure was controlled, manipulation of meal time with a 5-hour delay altered temporal expression of *PER2* and glucose concentration. Similarly, physical exercise may accelerate circadian entrainment in dim light (Yamanaka et al., 2010) and bright light (Yamanaka et al., 2014) conditions. The strength of the entrainment signal of non-photic zeitgebers appear to be less dominant than the entrainment strength of light signals. In one study, in temporal isolation with dim light (< 10 lux), exercise was able to advance the circadian rhythm in sleep onset, while the melatonin rhythm was phase delayed (Yamanaka et al., 2010). Yamanaka et al. (2014) suggested that non-photic zeitgebers may strengthen the effects of photic inputs. Under bright light conditions (> 5000 lux) during wake, sleep and melatonin rhythms were phase advanced; however, the melatonin rhythm was advanced three-fold in an exercise group relative to a non-exercise group. Non-photic zeitgebers can entrain circadian rhythms, with entrainment strength dependent on other factors such as the degree of phase shift required for entrainment, length of the internal circadian period, and species dependent sensitivities (humans, for example, seem particularly sensitive to light relative to other animals; hamsters are more responsive to exercise as a zeitgeber relative to rats, cf. Mistlberger & Skene, 2005 for a comprehensive review of non-photic entrainment).

2.1.3   Parameters of the circadian system. Three core clock properties differ individually in humans and across species. Period, phase, and amplitude (see Figure 2) are the measurable parameters of the endogenous circadian clock and manifest in the behavioural entrainment of the circadian system to the external world.
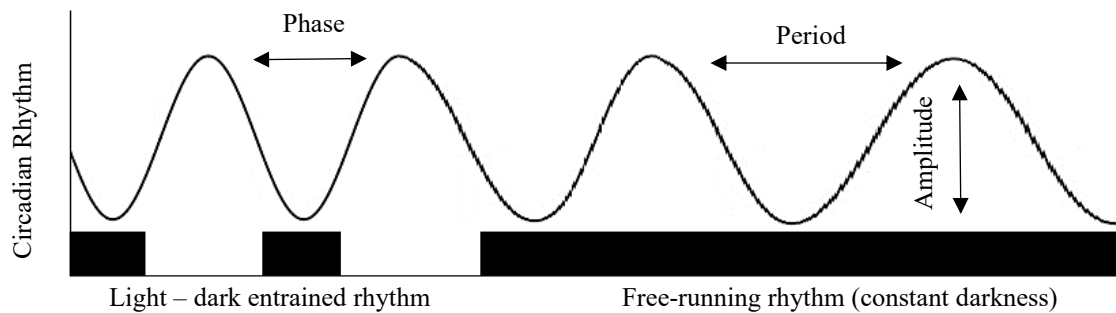
Figure 2. Circadian parameters in both entrained (light-dark) and free-running (constant darkness) conditions

2.1.3.1   Period. Period, or tau (τ), refers to the internal length of the circadian period. In protocols where the circadian system is unmasked from zeitgebers (see Section 2.3.), species will 'free run' at this internal τ which on average in humans is 24.18 hours ($\pm$ .04; Czeisler et al., 1999). Slight gender differences have been observed with women (24.09 hours $\pm$ .2) having a shorter internal period relative to men (24.19 $\pm$ .2; Duffy et al., 2011). Given that the circadian system adaptively entrains to the external environment, the length of the circadian period can only be measured in protocols that remove the individual from the environment (see Section 2.3), minimising any masking influence on the circadian system (Minors & Waterhouse, 1984; Redfern, Waterhouse, & Minors, 1991).

2.1.3.2   Phase. Phase refers to the timing of the peaks and nadirs of an endogenous circadian process (such as core body temperature [CBT]) relative to the external 24-hour time (Daan & Aschoff, 1982; Pittendrigh, 1960). The *phase angle* between a circadian rhythm (e.g., melatonin onset, CBT minimum) and timing of behavioural outputs, such as the timing of sleep or wake onset, can also be assessed (Duffy, Dijk, Hall, & Czeisler, 1999; Pittendrigh & Daan, 1976). Thus, individuals may have 'internal desynchrony' with a delayed phase relative to the external environment, but have an advanced phase internally, with a smaller phase angle between sleep onset and CBT minimum. Cain et al. (2010), for example, found a larger phase angle between rise of melatonin and sleep onset for women, indicating that even though sleep and wake times were equivalent between men and women,

women slept at a later *biological* time relative to men. Further, in a longitudinal study of adolescents, Crowley et al. (2014) found that younger adolescents have a smaller phase angle between the rise of melatonin and sleep onset (~one hour), compared to older adolescents who typically remain awake for ~two hours following melatonin rising. In a recent study, Flynn-Evans et al. (2017) found that a sample of control subjects and those with insomnia tried to initiate sleep at the same external clock time; however, the insomnia group had a later biological circadian phase relative to controls, suggesting a greater misalignment between circadian biology and sleep behaviour. Thus, the insomnia group were trying to initiate sleep at an inappropriate biological time which may contribute to the prolonged sleep latency commonly observed in insomnia.

 2.1.3.2.1 Measuring phase. The timing of circadian phase is most often measured through the onset of melatonin under dim light conditions (DLMO; Klerman, Gershengorn, Duffy, & Kronauer, 2002; Lewy & Sack, 1989). DLMO is the point at which melatonin begins to rise, as measured through levels present in saliva or plasma. Typically this is 2-3 hours before habitual sleep onset (Burgess & Fogg, 2008). The absolute threshold approach to measuring DLMO refers to a salivary concentration between 3pg/ml (Benloucif et al., 2008; Pullman, Roepke, & Duffy, 2012) and 4pg/ml (Pandi-Perumal et al., 2007), with a generally lower (2pg/ml) threshold suggested for plasma concentration (Lewy, Cutler, & Sack, 1999). Relative thresholds can also be used to determine DLMO, taking the time at which the melatonin levels reaches >2 standard deviations above the average of three baseline values (Benloucif et al., 2008). DLMO is suggested to be the gold-standard of collecting circadian phase data (Pandi-Peruman et al., 2007). Compared to rectal temperature measures of CBT and blood collections for cortisol assays, DLMO is a relatively non-obtrusive and data has found it a more reliable measure of circadian phase (Klerman et al., 2002).

 2.1.3.2.2 Relationship between circadian phase and chronotypes. Biological markers of circadian phase have strong associations with sleep phase, sleep variation across the week, light exposure, and time of day preferences, or *chronotypes*, in humans. Individuals with a preference for activity in the evening, or *evening types*, often have a circadian phase in melatonin or CBT that is later relative to *morning types* (Baehr, Revelle, & Eastman, 2000; Paine & Gander, 2016). Duffy et al. (1999)

found that, on average, morning types had an earlier endogenous circadian phase of CBT and melatonin relative to evening types, an earlier phase that could not be accounted for by differences in preferred bedtimes. This finding may also be age dependent. There is broad consensus that, more commonly, older adults report being morning types while younger adults report being evening type (Biss & Hasher, 2012; Duffy et al., 1999; Roenneberg, Wirz-Justice, et al., 2003). This may reflect an advanced phase in older adults relative to younger adults. The phase angle may also be altered across the lifespan. Duffy et al. showed that older adult morning types were observed to have a smaller phase angle between their CBT minimum and wake time, relative to young adult morning types, while young adult evening types had on average a smaller phase angle between CBT minimum and wake times relative to young adult morning types. The authors account for this apparent discrepancy by suggesting that older adults wake up earlier in their phase (just after the CBT minimum) which may lead to more light exposure at times optimally sensitive to an advance of circadian phase. Emens, Yuhas, et al. (2009) found similar results to Duffy et al. with relatively later circadian phase (compared to sleep times) in evening types. Both groups suggest that the phase differences in young adults between morning and evening chronotypes could be driven by differences in circadian period (shorter in the former), rather than differences in light exposure. While chronotype is largely considered a circadian-driven output, Mongrain, Carrier, and Dumont (2006) found that homeostatic sleep processes (see Section 2.5) such as slow-wave activity may have effects on morningness-eveningness preference, independent of circadian processes.

The research literature recognises two commonly used measures of chronotype: the Morningness-Eveningness Questionnaire (MEQ; J. A. Horne & Östberg, 1976) and the Munich Chronotype Questionnaire (MCTQ; Roenneberg, Wirz-Justice, et al., 2003). A third popular measure, the Composite Scale of Morningness (C. S. Smith, Reilly, & Midkiff, 1989) developed from items from the MEQ (J. A. Horne & Östberg, 1976) and a diurnal type scale (Torsvall & Åkerstedt, 1980) is not examined in this project. The most commonly used self-report measure of chronotype is the MEQ. The 19-item questionnaire is related to circadian phase measured as temperature, melatonin, and cortisol (Bailey & Heitkemper, 2001; Duffy et al., 1999; J. A. Horne & Östberg, 1976). Using the MEQ, morning types

show an earlier average peak time in circadian rhythms (e.g., CBT, nutrient intake, sleep, alertness) compared to evening types (Bailey & Heitkemper, 2001). Baehr et al. (2000) compared scores on the MEQ to the CBT minimum and found a ~2 hour delay in the phase of the temperature rhythm of evening types relative to morning types. As the MEQ is quick and easy to administer and demonstrates adequate association with objective measures of circadian phase, it is often used as a screening tool in sleep-laboratory studies, in finding both control (intermediate chronotypes), and morning and evening types.

There is some concern over the scale construction and heterogeneity of the 'morningness-eveningness' construct of the MEQ (Cavallera & Giudici, 2008; C. S. Smith, et al., 1989). In the J. A. Horne and Östberg (1976, 1977) original validating sample no significant difference was found in sleep length between morning and evening chronotypes. More recent work has attended to changes between workday sleep (traditionally weekday) and free day sleep (traditionally weekend; Roenneberg, Wirz-Justice, et al., 2003). There is consensus that evening types are more likely to experience chronic sleep restriction accumulating greater sleep-debt on weekdays, and spending more time asleep on free days, without morning commitments to adhere to, compared to morning types (Giannotti, Cortesi, Sebastiani, & Ottaviano, 2002; Roenneberg, Wirz-Justice, et al., 2003; Taillard, Philip, & Bioulac, 1999).

In contrast to the MEQ, which focuses on an individual's *ideal* timing of sleep, the MCTQ (Roenneberg, Wirz-Justice, et al., 2003) focusses on the actual behavioural, *clock* time of sleep-wake behaviours (Roenneberg et al., 2004; Roenneberg, Wirz-Justice, et al., 2003; Zavada, Gordijn, Beersma, Daan, & Roenneberg, 2005). The MCTQ also measures sleep quantity for both free and work days. Studies suggest that day of the week may modulate sleep length dependent on diurnal preference (Roenneberg, Allebrandt, Merrow, & Vetter, 2012; Wittmann, Dinich, Merrow, & Roenneberg, 2006). Evening types tend to sleep longer on free days, most likely due to increased likelihood of curtailing sleep times during the week to meet occupational commitments. In contrast, on average, morning types typically sleep less on weekends, relative to weekdays, with delayed bedtimes in response to social needs while being unable to have compensatory weekend sleep in. Distinguishing between these two variables may be important in capturing actual sleep behaviours on the MCTQ. The most commonly used variable derived from the

MCTQ is mid-sleep on free days (MSF), often adjusted for individual differences in sleep length (Roenneberg et al., 2004).

The MCTQ may be a more reliable indicator of circadian phase position than the MEQ, through providing a detailed examination of the variable nature of sleep-wake behaviours across the week (Roenneberg, Wirz-Justice, et al., 2003). Zavada et al. (2005) compared 2481 participants' scores on the MCTQ to the MEQ. Aside from scores on the mid-sleep point on free-days, correlation between the MEQ and MCTQ scores was very low across all age brackets for both work and free-days. The lowest correlation was in sleep duration (r <.2, for both free and work days and across all age groups), with the rise-time and sleep-onset times for free and work days showing modest correlations (r <.66, for all age groups; Zavada et al., 2005). Indeed, Kantermann, Sung, and Burgess (2015) found that while both the MCTQ and MEQ were reliable proxies for DLMO, the MCTQ was the stronger predictor of DLMO relative to MEQ. Irrespective of these concerns all of these measures (DLMO, MCTQ, and MEQ) are quite stable, with a recent study (Kantermann & Eastman, 2018) finding that correlations between baseline and > 9 months later (and in some cases up to three years later), were high for all three measures, ranging from r = .78 for the MCTQ, r = .85 for the MEQ, and r = .80 for DLMO (once an extreme outlier was removed).

2.1.3.3 Amplitude. Amplitude refers to the peak-to-trough range of the observed circadian rhythm which may be measured in physiological processes such as CBT, melatonin, heart rate, or locomotor activity. One common way to derive a measure of amplitude is through the 24-hour activity rhythm using actigraphy. Actiwatches, the most common device used in actigraphy, are non-obtrusive wrist-worn devices that measure and record movement continuously across the day and night (Ancoli-Israel et al., 2003). The cosinor curve fitting technique commonly models circadian data (Cornelissen, 2014), but this is problematic given the cosine function is a relatively poor fit for activity data (Bullock, 2011). Non-parametric actigraphy analyses do not rely on the assumptions of cosinor curve fitting and can also derive a measure of the amplitude of the activity rhythm. Van Someren, Kessler, Mirmiran, and Swaab (1997) propose taking the aggregate activity count of the most active 10 hours (M10) and least active five hours (L5) in an individual's day to determine amplitude. The ratio of M10/L5, standardised as a ratio of total activity, is

referred to as relative amplitude, calculated by measuring activity levels across multiple days. One possibility is that amplitude may be an important measure of the strength of the circadian rhythm with some suggestion that reduced amplitude may reflect a less robust circadian system (Aschoff & Pohl, 1978; Dosseville, Laborde, & Lericollais, 2013; Mairesse et al., 2014). Reduced amplitude of the 24-hour activity rhythm has been shown to correlate with vulnerability to mood disorders (Bullock & Murray, 2014; Merikanto et al., 2017). A more recent alternative approach by Smagula and colleagues (2015) is to use Latent Class Analysis to model parameters of amplitude, timing, and robustness, rather than measure each component of the activity rhythm separately.

2.2   Diurnal Rhythms

To fully appreciate the challenges of measuring circadian rhythms in humans, it is important to distinguish between diurnal rhythms and circadian rhythms. A diurnal rhythm is a 24-hour pattern in a physiological, behavioural or psychological variable (Vitaterna et al., 2001). It is important to reserve the term circadian rhythm for that subset of diurnal rhythms that have had their endogeneity confirmed, and relatedly, to recognise that any measured 24-hour variation in a variable will have exogenous and (possibly) endogenous circadian components (Moore-Ede, 1986a). In circadian science, exogenous components are called *masking factors*, as they obscure the true endogenous circadian component of a 24-hour rhythm (Herman, 2017; Minors & Waterhouse, 1984; Rietveld, Minors, & Waterhouse, 1993). The aim of the next section is to introduce the two major protocols used in circadian science to unmask the endogenous circadian component of two physiological 24-hour rhythms (core body temperature and melatonin secretion) that are known to be strongly influenced by the circadian system (Herman, 2017).

2.3   Measuring Circadian Rhythms

When removed from any exogenous rhythmic factors that can influence the internal clock (e.g., zeitgebers such as daylight and social interaction), individuals in temporal isolation show temperature, melatonin and cortisol rhythms that oscillate over a near-24 hour cycle (Blatter & Cajochen, 2007; Daurat et al., 1993; Dijk, Duffy, & Czeisler, 1992; Dijk, Duffy, Riel, Shanahan, & Czeisler, 1999). Two protocols have been designed that disentangle the influence of zeitgebers to unmask the underlying circadian rhythm: *Constant routine* and *forced desynchrony*.

2.3.1   Constant routine protocol. The constant routine protocol is designed to measure circadian parameters (amplitude, phase and period) in (typically) CBT, by 'unmasking' the CBT rhythm from exogenous influences. To this end, constant routine protocols keep participants awake for at least 24 (up to 60) hours, in constant light (or dark) conditions, with a controlled ambient room temperature, a semi-recumbent position and fed equally distributed, isocaloric meals; eliminating zeitgeber influence on the circadian system (Czeisler & Buxton, 2017; Minors & Waterhouse, 1984; Redfern et al., 1991). While this technique controls for external stimuli (which masks endogenous circadian rhythms), it remains confounded by sleep deprivation effects (Murray et al., 2009).

2.3.2   Forced desynchrony protocol. The forced desynchrony protocol is designed to uncouple the sleep homeostat process from circadian rhythms by imposing a (typically) 28-hour activity rest cycle to which the circadian oscillator cannot adapt (Dijk & Czeisler, 1994). The capacity for the endogenous circadian pacemaker to adapt is limited. A maximal daily reset of approximately 2-3 hours (Dijk & Czeisler, 1994; Wright, Hughes, Kronauer, Dijk, & Czeisler, 2001) means that forcing an individual to a 28-hour rest-activity cycle (still maintaining a 2/3 activity, 1/3 rest cycle ratio) decouples sleep and circadian rhythms (Dijk et al., 1999). Under these 28-hour conditions physiological processes that have an endogenous circadian component are unmasked and cycle at the intrinsic circadian τ.

In chronobiological science, many new areas of investigation take the preliminary step of exploring the diurnal rhythms in variables before translation to one of these two gold-standard protocols to investigate their circadian components. Studies exploring diurnal rhythms (rather than circadian rhythms) are easier to conduct because they are less time-intensive, more cost-effective, more flexible in location, and far less arduous on participants. One other caveat is that due to the physiological toll (including sleep deprivation in constant routine) that the protocols have on participants, exclusion criteria are very stringent, often relying on samples that are in extremely good health with no psychological risk factors that may be triggered through destabilising circadian rhythms.

2.4   Features of the Circadian System Interact

Thus far circadian period, phase, and amplitude have been discussed as distinct elements of the circadian rhythm; however, this is a false trichotomy as they

are all interrelated in the broader circadian system. Circadian phase and circadian period are related parameters. Individuals with lower scores on the MEQ (more evening type) tend to have longer internal circadian periods (Duffy, Rimmer, & Czeisler, 2001). The implication being that the longer the circadian period (i.e., the further away from external 24-hour environment) the greater the daily reset to 24 hours would be; this may result in greater error in the ability to achieve specific 24-hour time, through accumulation of minor daily delays (Campbell & Murphy, 2007; Pittendrigh & Daan, 1976). Thus, individuals with longer, and extremely short, periods need larger daily phase shifts in their entrainment to the 24-hour day (Duffy et al., 2011; Duffy et al., 2001). The majority of humans (~79%) need a phase advance, while ~21% of individuals have a circadian period shorter than 24 hours requiring a daily phase delay (Duffy et al., 2011).

Similarly, the amplitude of the circadian rhythm is affected by both the circadian phase and circadian period of rhythms. Individuals who have earlier circadian phases in measured variables and a shorter circadian period, tend to have more regular sleep and wake times (Wittmann et al., 2006). As a result, constant and regular exposure to morning light increases the stability of the rhythm, an important determinant of amplitude (Goulet, Mongrain, Desrosiers, Paquet, & Dumont, 2007; Roenneberg, Daan, & Merrow, 2003; Roenneberg et al., 2004). Indeed, using the MCTQ, data suggests that individuals with an earlier MSF report more outdoor light exposure (Kantermann, Juda, Merrow, & Roenneberg, 2007).

2.4.1   **The phase response curve in humans.** The timing of zeitgebers relative to endogenous circadian timing is crucial to the direction and magnitude of the phase shift that can be induced. Three to four hours before or after the CBT nadir, the magnitude of the phase shifting capacity of light is at its maximum (Reid & Zee, 2009, 2011). Light given after the CBT nadir advances the circadian rhythm, while light prior to the CBT nadir delays this rhythm (Crowley & Eastman, 2017). Given that the circadian system is optimally sensitive to the shorter blue wavelength of the light spectrum, sleep hygiene procedures encourage minimising light sources (most notably technology) at night when light has a delaying property to the circadian system, which in turn delays sleep times (Harvey, 2002, 2015; Harvey, Sharpley, Ree, Stinson, & Clark, 2007).

2.5   Borbély's Two-Process Model of Sleep Regulation.

In pioneering research on the relationship between sleep and circadian rhythms, Borbély (1982) described the regulation of sleep and wake as a function of two interacting processes. Process S is the process of homeostatic sleep pressure which accumulates with length of time awake and subsides throughout sleep. Process C refers to the effects of the circadian system that determines the peaks, troughs and timing of many physiological processes (Borbély, 1982; Daan, Beersma, & Borbély, 1984). The SCN drives Process C by sending alerting signals during the day (peaking at ~10:00h and 18:00h) and reduced signals at night (trough at ~03:00h - 04:00h). Optimally, these two processes are coordinated to work together to promote wakefulness during the day, and sleep at night (Fuller, Gooley, & Saper, 2006).

In a recent research update of the two-process model of sleep regulation, Borbély et al. (2016) indicate that the past three decades of research continues to support this model: Sleep and circadian rhythms interact continuously. With increasing time awake the sleep drive builds, and the circadian signal dips so the processes are synchronised for the major consolidated sleep period each day. Indeed, for most individuals the only time these two systems are recognised as distinct is following rapid travel across multiple time-zones. The phenomenon of jet lag is characterised by desynchrony between the internal system and external environment (Cho, Ennaceur, Cole, & Suh, 2000; Sack et al., 2007; Zelinski, Deibel, & McDonald, 2014). Under these conditions the homeostatic sleep signal readies the body for bed, while the circadian signal maintains the body in an alert state.

Sleep and circadian signals promote alertness and sleepiness at different times. One phenomenon that results from this synchronisation and transition between sleep and circadian signals is the reported mid-afternoon dip in cognition and alertness that some individuals experience (Wertz, Ronda, Czeisler, & Wright, 2006; Wright, Lowry, & LeBourgeois, 2012). In the mid-afternoon the transition to a heightened alerting signal from the circadian system can fail to fully compensate the building sleep pressure. Two potential mechanisms underlying this phenomenon are increased dopamine-related activation (Barbato et al., 2000) and increased neural activity in the hypothalamus (Reichert et al., 2017) in the mid-afternoon. Following this time, the circadian alerting signal continue to rise and the *wake maintenance zone* occurs at the peak of the circadian signal (approximately 2-3 hours before

melatonin production begins) and is associated with a reduced sleep propensity (Dijk & Czeisler, 1994) and increased cognitive performance (Shekleton et al., 2013).

Variability in circadian patterns may lead to altered sleep length dependent on day of the week. Wittmann et al. (2006) proposes that the shifts that occur between weekday and weekend sleep times can be considered a state of *social jetlag*; with weekdays being governed by social timing patterns (e.g., work times), and weekends being driven by biological patterns and compensating for weekday sleep loss. Individuals with a delayed DLMO (in this instance a proxy measure of later sleep times) are at risk of experiencing greater circadian misalignment between weekdays and weekends. Circadian misalignment is greatest on weekdays because of morning commitments, while alignment is better on weekends due to being able to sleep at biologically preferred times (and compensating for the sleep debt accrued throughout the week, Roenneberg, Wirz-Justice, et al., 2003). Consequently, social jetlag is most pronounced in evening types relative to morning types, and least pronounced in those with regular sleep times across the week (Wittmann et al., 2006). Increased social jetlag is associated with an array of negative outcomes, including poorer school grades (Haraszti, Ella, Gyöngyösi, Roenneberg, & Káldi, 2014; Urrila et al., 2017), lower mood (Levandovski et al., 2011), alcohol use (Haynie et al., 2017), and obesity (Roenneberg et al., 2012), although alcohol and drug use has not consistently been shown to relate to social jetlag (Hasler, Franzen, et al., 2017). Phillips et al. (2017) found in students (20.23 ± 1.27 years) that irregular sleep times were associated with altered circadian markers of delayed circadian phase (as measured by DLMO) and a decreased circadian amplitude. Another recent study found that sleep habits in early adolescents (aged 14 years) were associated with marked differences in neurological functioning (Urrila et al., 2017). Urrila et al. (2017) showed that later sleep times on weekends and shorter time in bed on weekdays were associated with smaller brain grey matter volumes in the frontal cortex, anterior cingulate cortex and precuneus brain regions, regions of the brain associated with executive functioning and reward processing (Haber, 2017). Additionally, bedtimes on weekend mediated the relationship between grey matter volume in the frontal superior medial (Brodmann Area 10) and anterior cingulate cortex (Brodmann Area 32) cluster and school performance (Urrila et al., 2017).

2.6 Implications of Circadian Masking Factors for Research into Biological Rhythms in Humans

Due to the multiple pathways through which sleep can affect circadian rhythms, and circadian rhythms can affect sleep, neither of these systems can be studied individually without isolating the unique contribution from each (L. P. Morin, 2013). One example of this is data from C. Schmidt et al. (2009) who showed that extreme morning types (a circadian parameter) are more vulnerable to building sleep homeostatic pressure in the evening, exhibiting slower reaction times on a psychomotor vigilance task. Neural correlates of this response were observed in evening types with greater activation of the locus coeruleus and the suprachiasmatic area; anatomically-connected structures core to sleep and circadian signals. This work highlights chronotype differences in the capacity of the circadian wake-promoting signal to counteract the sleep homeostat in the evening. A well-regarded proxy of the sleep homeostat is the density of slow-wave activity at sleep onset (e.g., Finelli, Baumann, Borbély, & Achermann, 2000). In the study by C. Schmidt et al., morning types had higher levels of slow-wave activity compared to evening counterparts.

It is important to consider that any study attempting to measure diurnal rhythms is masked by sleep-related factors. Most notably investigating reward seeking at different times of day is limited by the length of time since the last sleep period. Participants tested earlier in the morning may have less sleep pressure relative to later times of day in normal sleepers. It is not just sleep that masks circadian rhythms. Discrete times of day may be associated with activities that have different rewarding properties. For example, evening is typically a time associated with more rewarding events such as socialising, relaxation and meal times; whereas morning is typically associated with the beginning of work, an activity that is potentially less rewarding (Kahneman, Krueger, Schkade, Schwarz, & Stone, 2004). These externally conditioned events may mask (partially or fully) the endogenously driven oscillation in processes such as the reward system (reviewed in Chapter 3).

2.7 Summary

In sum, this chapter has described the circadian system and explained how the sleep-wake process interacts with it continuously throughout the 24-hour day. Despite protocols designed to separate circadian rhythms from the sleep processes

(forced desynchrony and constant routine) an important preliminary step is to test for daily patterns in variables of interest: for this project, the reward rhythm. Given that circadian and sleep processes are inextricably linked in nature, interest in one process necessitates accounting for the other. In this multi-study project the focus will be primarily on the circadian processes and their relationship with the reward system. This project focuses predominantly on the circadian system under naturalistic conditions. The term 'circadian rhythm' is used to refer to processes that have a demonstrated endogenously generated rhythm; 'diurnal rhythms' is used to refer to daily rhythms the endogeneity of which has not been proven.

Chapter 3: Reward Motivation

Different levels of analysis offer a variety of approaches to understanding the function and nature of human reward motivation. This chapter introduces the reader to the function of reward motivation from an evolutionary perspective (3.1), followed by a summary of the neurobiological substrates that accompany reward-related processing (3.2). As this project approaches reward motivation from different levels of analysis, three theorists who have operationalised reward motivation from perspectives of neuroscience, motivated behaviour, and affective experience will be introduced. Berridge and colleagues use neuroscience to separate three psychological components of reward motivation (3.3). Reward motivation has been conceptualised by Gray as *approach motivation* in reinforcement sensitivity theory (3.4), and Watson's two-dimensional structure of affect conceptualises positive affect as an important correlate of approach and subjective feelings of progress towards rewards (3.5). A brief review of behavioural reward tasks and positive emotion scales that are used in this project are described throughout this chapter, finishing with concluding remarks (3.6).

3.1   An Evolutionary Explanation of the Reward System

The reward system is conserved across species to facilitate fitness. In mammals (including humans) three evolutionary goals are thought to underpin this preservation: food acquisition, procreation and socialisation. For the species to survive, goal-directed and exploratory actions are needed to hunt and forage for food, seek out potential mates, and to work cooperatively with others (primary rewards; Berridge & Robinson, 1998). Subsequently, adaptive brain mechanisms have been preserved (and continue to evolve) to develop these functions (Berridge & Kringelbach, 2015). This ongoing evolution includes recent adaptations to new (more abstracted) rewards, such as money, in humans (secondary rewards; Sescousse, Caldú, Segura, & Dreher, 2013; Sescousse, Redouté, & Dreher, 2010).

3.2   Reward Neurocircuitry

The reward system has been preserved across species with several neurobiological mechanisms thought to drive behaviour in reward-relevant contexts. The majority of research into the reward system has focused on the neurotransmitter dopamine and the mesolimbic pathways that are particularly rich in these dopaminergic receptors; however, mesocortical and nigrostriatal dopamine pathways are also involved in dopaminergic-driven reward processes (Ikemoto, 2007; Ikemoto,

Yang, & Tan, 2015). Dopamine neurons project out of localised sites in the ventral tegmental area (VTA) and substantia nigra to striatal (including the nucleus accumbens [NAc], caudate and putamen) and frontal regions (see Ikemoto et al., 2015; Volkow, Wise, & Baler, 2017; Yager, Garcia, Wunsch, & Ferguson, 2015 for reviews). The mesolimbic and mesocortical pathways project from the VTA to the ventral striatum (VS, particularly the NAc) and the prefrontal cortex, respectively. The nigrostriatal pathway projects from the substantia nigra to the dorsal striatum (particularly the caudate and putamen; Ikemoto et al., 2015). While this project focuses on the role of dopamine in reward processing, other neurotransmitters such as orexins may play an important role in reward processes. For example, orexins in the lateral hypothalamus have been found to project to the NAc and VTA (Fadel & Deutch, 2002) and an intra-VTA infusion of orexin increased dopamine transmission in the PFC but not the NAc (Vittoz & Berridge, 2006). Speaking to the impact of orexin on reward behaviours, Harris, Wimmer, and Aston-Jones (2005) found orexin neurons become activated by consumption of food and drug reward cues in rats, which an orexin antagonist blocks.

The neural response to reward varies dependent on the 'value' of a reward. Reward value is not static and varies as a function of prior experience and current internal states, and evolving predictions that are formed about the reward potential of an event (Schultz et al., 1997). Dopaminergic neurons signal the reward response in the brain relative to the reward prediction (Pessiglione, Seymour, Flandin, Dolan, & Frith, 2006). Schultz (1998, 2016) defines prediction errors as differences between the received reward relative to the predicted value of the reward. When rewards are novel the dopamine response is positive, when rewards are expected dopamine response is nought, and when expected rewards are omitted the dopamine response in negative (Schultz, 1998). Schultz (1998) formalised this in a simple equation "Dopamine Response (Reward) = Reward Occurred – Reward Predicted" (p.7). A number of associated brain regions have activations that may support this dopamine response. In response to reward stimuli, neurons in the prefrontal cortex (e.g., Ramnani, Elliott, Athwal, & Passingham, 2004) and VS (e.g., Abler et al., 2006; Hare et al., 2008) may also signal reward expectancies and prediction errors. The left putamen has a larger haemodynamic response to unexpected rewards relative to expected rewards (e.g., McClure et al., 2003; O'Doherty et al., 2003). There is

evidence that, at times when expectation of rewards is high, then the accrual of rewards elicits less excitation of reward regions of the brain (e.g., Schultz et al., 1992; see Schultz, 2016 for a review).

Numerous limbic structures are central to the reward system (Schultz, 2002). The cortico-basal ganglia network that the dopamine cells innervate is believed to be the core of the reward circuit, with limbic structures working in parallel with the frontal cortex to integrate information between circuits (Haber, 2010, 2017; Haber & Knutson, 2010). There is preliminary evidence for some functional independence of reward processes. The striatum has been implicated in reward behaviour since Olds and Milner's (1954) seminal work in which rats would frequently work to press a lever that self-stimulated the septal area of the brain. The NAc is proposed to be specifically activated by rewarding stimuli with the predicted value of reward modulating the level of NAc activation (Abler, Walter, Erk, Kammerer, & Spitzer, 2006; Sabatinelli, Bradley, Lang, Costa, & Versace, 2007). Tricomi, Delgado, and Fiez (2004) highlight a role for the dorsal caudate in associating a reward with action, with more broadly the dorsal striatum (including the putamen), strongly associated with motor action-outcomes links in reward contexts (Muranishi et al., 2011; Szczypka et al., 2001). There is also evidence for the amygdala being involved in reward processing. M. J. F. Robinson, Warlow, and Berridge (2014) and Warlow, Robinson, and Berridge (2017) showed that when cocaine or sucrose were presented to rats, they had a strong preference for pairing the reward with stimulation of the central amygdala relative to cocaine or sucrose presented alone, and were willing to work harder to obtain these rewards. This stimulation was unique to the central amygdala; stimulation of the basolateral amygdala did not increase reward motivation.

The anatomical location of the striatum relative to frontal brain regions may facilitate reward behaviour. The striatum sits at the afferent junction for projections from the orbitofrontal cortex (OFC, with caudal regions referred to as part of the insula), dorsal anterior cingulate cortex (ACC), amygdala and midbrain. Frontal regions important to reward include the highly interconnected regions of the OFC, ACC, the medial prefrontal cortex (mPFC), and dorsolateral prefrontal cortex (dlPFC, Haber, 2017). The ventral medial prefrontal cortex has a broader anatomy including the medial OFC and subgenual ACC (Haber & Knutson, 2010).

Specific roles of brain regions in processing reward anticipation and reward receipts have also been suggested. The striatum may be particularly important for processing the value of a reward (Delgado, 2007; Haber & Knutson, 2010; Sescousse et al., 2013), but frontal regions, and the connectivity to the limbic structures, are implicated in appropriate decision-making in the context of rewards (Haber, 2017). The mPFC is thought to play a regulatory role, integrating information from the insula and VS to weigh benefits and costs of reward, and responding to the probability of rewards and value of reward receipt (Costa, Lang, Sabatinelli, Versace, & Bradley, 2010; Knutson, Fong, Bennett, Adams, & Hommer, 2003). The OFC monitors reward receipt, with the medial portion of the OFC, in particular, responding to the value of reward receipt, and the lateral portion responding to losses (Kringelbach, 2005; O'Doherty, Kringelbach, Rolls, Hornak, & Andrews, 2001). In addition, OFC activation has been shown to be positively related to subjective ratings of pleasantness (Kringelbach, O'Doherty, Rolls, & Andrews, 2003). The insula specifically, is suggested to index reward uncertainty (i.e., it tends to activate to risky decisions relative to safe bets; see Singer, Critchley & Preuschoff, 2009 for a review) and conscious urges and interoceptive pleasures involved in addiction pathways (see Naqvi & Bechara, 2009 for a review). The dorsal ACC is implicated in conflict monitoring and the evaluation and encoding of reward probabilities (Bush et al., 2002; Walton, Bannerman, Alterescu, & Rushworth, 2003; Yu, Zhou, & Zhou, 2011). Walton et al. (2003) showed that rats with lesions to the ACC opted for low-cost, low-reward choices, in contrast to rats with lesions to pre/infra-limbic regions and control animals that continued to work hard for rewards, thus suggesting a specified role for the ACC in effort-based reward decision-making. Subsequent work found that dopamine projection to the ACC was not the basis of this reward process (Walton, Croxson, Rushworth, & Bannerman, 2005). In monkeys, Wallis and Miller (2003) found the dlPFC receives inputs from the OFC. This neuronal activity is thought to encode reward value (dlPFC and OFC) and control behaviour (the dlPFC only) in the context of juice rewards.

While there are strong connections within frontal regions and to other limbic structures, the projections from reward-related structures are specific. For example, Brodmann area 25 in the ventral mPFC projects to specific parts of Brodmann area 14, also in the ventral mPFC (Haber, 2017). The projections from these regions to

limbic areas also have some specificity. The dlPFC projects primarily to the dorsal striatum (Haber, Kim, Mailly, & Calzavara, 2006), while the mPFC, OFC, and ACC all connect to the amygdala.

A broad range of neural structures are involved in processing different types of reward stimuli. In fMRI studies the most commonly presented stimuli is money presented visually. Food, erotica, and social stimuli have been shown to generate only slightly varying patterns of neural activation (Pool, Sennwald, Delplanque, Brosch, & Sander, 2016). In a meta-analysis of different reward stimuli, Sescousse et al. (2013) identified common neural structures that respond across money, food, and erotic rewards. Implicated areas included the anterior insula, striatum, amygdala, mediodorsal thalamus, and the pregenual ACC, crossing into the ventral mPFC. There is partial separation in how the OFC responds to rewards (Sescousse et al., 2013; Sescousse et al., 2010). Sescousse et al. (2010) found the posterior portion of the OFC to respond exclusively to erotic stimuli, while the phylogenetically more recent anterior portion of the OFC responded exclusively to monetary stimuli.

In sum, a number of limbic and cortical structures underlie reward functioning in the human brain. The reward neurocircuitry has evolved to subserve reward processes critical to survival. Neural structures have specific functional roles in reward processing and while there is vast overlap, some regional difference in different reward stimuli activation is apparent. Dopamine is implicated as the key neurotransmitter in these processes, with midbrain dopamine neurons projecting widely throughout the brain, but the largest projection is to the striatum.

3.3   The Three Psychological Components of Reward

Berridge and Robinson have proposed three interacting, but dissociable, psychological components to be involved in reward processing (Berridge & Robinson, 1998; Berridge & Robinson, 2003). This is in contrast to the traditional view of reward functioning as a unitary process. These components are: (1) a *wanting*, motivation or drive towards rewards; (2) a *liking*, hedonic association of the reward; and, (3) a predictive cognitive or associative *learned* understanding of rewards reinforced by previous experience (Berridge & Kringelbach, 2008; Berridge & Robinson, 2003; Yeates & Main, 2008).

The three psychological components of reward involve both conscious and unconscious processing, which Berridge and colleagues distinguish by use of

quotation marks (Berridge & Kringelbach, 2008). "Wanting" refers to the unconscious, implicit process of motivation while wanting (no quotations) refers to the conscious, explicit awareness of desire. Similarly, "liking" refers to the unconscious hedonic impact, while liking refers to the conscious enjoyment for the stimulus (Berridge & Robinson, 2003). K. C. Berridge (personal communication, October 17, 2017) believes that learning can also be both conscious and unconscious with a large overlap in the literature's preferred terminology of cognitive (conscious) and associative (unconscious) learning. However, quotation marks are not used for learning because the distinction between conscious and unconscious learning is not perfect. Individuals "can be aware during associative (instrumental or Pavlovian) learning, and some forms of cognitive learning can also be implicit (e.g., word priming)" (K. C. Berridge, personal communication, October 17, 2017).

The "wanting", "liking", and learning processes often work together in the reward-behaviour cycle. The motivational process initiates the anticipatory phase, hedonic processes drive the consumption phase, and learning occurs throughout the cycle to reinforce reward-seeking behaviour (Berridge & Kringelbach, 2015). These reward components frequently work in unison, but their dissociation is an area of interest. Consistent with this hypothesis, partly dissociable neurobiological mechanisms have been identified for each component (Berridge & Kringelbach, 2008).

3.3.1   **Evidence for dissociating reward components in animals.** In animals, the neural substrates of these three components of reward are reasonably well characterised. The motivational "wanting" component of reward functioning can be distinguished from the hedonic "liking" aspects on neural grounds. Dopaminergic projections from the VTA to the NAc are the underpinnings of the "wanting" pathway of reward (Berridge, 2007; Wyvell & Berridge, 2000). Mice genetically modified to have a hyperdopaminergic response have an amplified "wanting" for sucrose while demonstrating no increased "liking" response as measured by facial expression (Peciña, Cagniard, Berridge, Aldridge, & Zhuang, 2003). Berridge and Robinson (1998) added an important caveat to the relationship between dopamine and "wanting". The release of dopamine is brief while the psychological state of "wanting" is relatively long. As such, dopamine may initially trigger neurons in the VS, with ongoing activation of VS neurons sustaining

motivated behaviour. Dopamine may increase "liking" in the rostrodorsal hotspot of the NAc with direct injection of a dopamine agonist in this region doubling hedonic pleasure in rodents (D. C. Castro & Berridge, 2014b). More recent work by D. C. Castro and Berridge (2017) showed that stimulation of the opioid receptors in the anterior OFC, and posterior insula amplified hedonic responses. OFC stimulation also enhanced food-seeking "wanting" behaviours; however, insula stimulation showed a localised increase in "liking" but not "wanting" to food.

The learning component of reward can be distinguished from "wanting" and "liking". The reward component of learning combines Pavlovian principles of cognitively predicting the value of the reward, degree of wanting the conditioned stimulus, and the liking of the unconditioned stimulus (K. S. Smith, Berridge, & Aldridge, 2011). Cognitive predictions refer to the learned representation of the action-outcome relationship; that is, a learned expectation between an action and an outcome (Berridge & Kringelbach, 2008). This can be distinguished from "wanting" and "liking" processes. S. Robinson, Sandstrom, Denenberg, and Palmiter (2005) showed that in mice unable to synthesise dopamine, learning new reward-based associations appear to be relatively unaffected. Similarly, hyperdopaminergic mice did not show increased speed of learning or increased perseveration to learned reward-based associations (Cagniard, Balsam, Brunner, & Zhuang, 2005). Taken together, these data suggest that dopamine is not necessary for reward learning, drawing a clear distinction with "wanting" processes (Berridge, Robinson, & Aldridge, 2009). A pair of studies in mice (Golani, Tadmor, Buonanno, Kremer, & Shamir, 2014; Tadmor, Golani, Dvir, Kremer, & Shamir, 2017) provided further evidence for the distinction of "liking" and "wanting" from learning. ErbB receptors are involved in dopamine level modulation through (for example) inhibiting the ErbB signalling pathway which leads to altered striatal dopamine levels (Golani et al., 2014). In one study, Golani et al. (2014) found this alteration did not result in a change to exploratory behaviours ("wanting"), but lowered sucrose consumption ("liking") and hampered learning in a maze paradigm. Tadmor et al. (2017) further separated these constructs by showing that blockade of the ErbB pathway in adolescent mice led to reduced hedonia in adulthood without any deficits to reward learning.

3.3.2   Evidence for dissociating reward components in humans.

Empirical separation of the three psychological components of reward is less straightforward in humans. Not only is neural manipulation (as described in animal studies above) unethical in humans (Panksepp, Lane, Solms, & Smith, 2017), but the human case brings with it the full complexity of Berridge's distinction between conscious and unconscious levels of reward function (Berridge et al., 2009). In animals, reward functioning has focused on the unconscious "wanting" and "liking" of rewards inferred by behaviour. Reward measurement in humans has the potential to consider conscious ratings of desire and unconscious incentive salience, ratings of conscious pleasure and unconscious hedonic impact, and cognitive and associative learning processes. Separate measurement of these multiple components of human reward function is an ongoing research challenge, and there has been limited work in examining the conscious and unconscious features of wanting, liking and learning (Kringelbach & Berridge, 2009; Pool et al., 2016).

Functional magnetic resonance imaging (fMRI) has been important to developing understanding of the neurobiology of "wanting" and "liking" in humans. Pool et al. (2016) systematically reviewed the literature that aimed to dissociate wanting and/or liking in humans. Using a strict inclusion criterion of explicitly referencing Berridge and Robinson's incentive salience framework (Berridge & Robinson, 1998; Berridge & Robinson, 2003), Pool et al. found 18 of 84 articles that met review criteria had used an fMRI design to test the neural correlates of human wanting and/or liking. From the reviewed studies, fMRI study designs generally examined the relationship between wanting and/or liking, and fMRI in two ways. The first was to seek participants' quantitative ratings of, e.g., *wanting*, *urge*, and *craving* of a (typically) visually presented food stimuli. Then, following ingestion of substances, participants were asked to rate the level of *pleasantness* (e.g., McCabe, Cowen, & Harmer, 2009; McCabe, Huber, Harmer, & Cowen, 2011) or how much they *liked* the food item (e.g., Born, Martens, Lemmens, Goebel, & Westerterp-Plantenga, 2012; Lawrence, Hinton, Parkinson, & Lawrence, 2012). The pattern of activation of different brain areas in response to self-reported ratings of wanting and liking was then examined. Although not discussed by Pool et al., a second way that "wanting" and "liking" has been dissociated in some of the included studies in the review is through event-related designs. In event-related designs, analyses

temporally distinguish between anticipation and receipt (or outcome) of individual reward stimuli, as proxies for "wanting" and "liking" respectively (e.g., Kumar et al., 2014; J. J. Simon et al., 2010). Pool et al. suggested timing between the reward cue and outcome measure is critical to accurately capturing wanting and liking. In order to mobilise an individual to seek out rewards, incentive must occur *before* the reward. If incentive is presented *following* the reward reinforcement learning is the measured process rather than wanting. To measure liking, measurements must be taken during or immediately following reward receipt/ consumption. Measuring liking at a later time relative to reward receipt may be measuring the encoded predictions or expectations of the reward stimuli rather than liking (Pool et al., 2016). Pool et al. conclude that in the reviewed human studies, some studies that have purported to measure wanting and liking have done so in an inconsistent way to the animal literature. They conclude that the literature would benefit from improved measurement of wanting and liking, particularly in the context of a major confound of expected pleasantness.

Knutson is a prominent figure in examining the association between reward anticipation, reward receipt, and associated activation in human brain regions using fMRI paradigms. Knutson, Adams, Fong, and Hommer (2001) found that the NAc selectively increased activation to reward anticipation but not punishment anticipation during a well-validated reward task (Monetary Incentive Delay Task; Knutson, Westdorp, Kaiser, & Hommer, 2000). Knutson, Fong, Adams, Varner, and Hommer (2001) partitioned reward anticipation from receipt in event-related fMRI paradigms. Multiple brain regions increased in contrasts for Reward > Non-Reward Anticipation, including the NAc, right anterior insula, bilateral caudate, left putamen, right medial amygdala, and the mPFC. The contrasts for Reward > Non-Reward Receipts revealed increased activation in prefrontal cortical gray matter including coverage in the mPFC, ACC, and OFC. Many of these subcortical regions (NAc, caudate, thalamus) and the insula and mPFC were also activated in later work by Knutson and colleagues (2003) for reward anticipation. Reward receipt (relative to no reward) activated prefrontal regions including the mPFC, frontal pole, and posterior cingulate cortex. A meta-analysis by X. Liu, Hairston, Schrier, and Fan (2011) found that the anterior insula, ACC, supplementary motor area, left parietal lobule, and middle frontal gyrus had increased activation to reward anticipation

relative to reward receipt; while the bilateral NAc, caudate, thalamus, and medial/lateral OFC preferentially responded to reward receipt over reward anticipation.

The problem of substance misuse provides a vivid clinical example of the distinction between "wanting" and liking aspects of reward processing in humans. Individuals experiencing a drug addiction often report no longer experiencing conscious liking of a drug while still having high levels of unconscious "wanting" towards it (Berridge, 2004; T. E. Robinson & Berridge, 2000). T. E. Robinson and Berridge (2000) highlight an incentive-sensitisation view on addiction. The pathways that normally subserve motivation are thought to undergo an increased sensitisation of the mesolimbic dopaminergic system towards reward cues of "wanting", following chronic administration of drugs of abuse (Alcaro & Panksepp, 2011; Berridge & Robinson, 2016; Olney, Warlow, Naffziger, & Berridge, 2018). T. E. Robinson and Berridge suggest that this abnormal sensititisation is unique to the "wanting" pathways of reward with liking in addiction remaining relatively unaffected.

Balodis and Potenza (2015) reviewed the evidence for neural findings of reward anticipation in populations with addictions. Relative to healthy populations, individuals with addictions or substance dependencies (variously defined: alcohol, cocaine, nicotine) reliably show altered reward anticipation in the VS relative to healthy controls. The direction of the effect was ambiguous, with some reviewed studies finding an attenuated VS signal while others found increased activation of the VS during reward anticipation, relative to controls. Balodis and Potenza suggest some of this variance may be explained by residual drug effects and the stage of addiction, which could impact the observed neural signal. For example, Grüsser et al. (2004) found that activation in the putamen, ACC, and mPFC during visual presentation of alcohol, predicted length of time to relapse in individuals with alcohol dependence.

In sum, three psychological components of reward have been proposed by Berridge and colleagues: wanting, liking, and learning. In the case of humans, these can be theoretically examined at both unconscious and conscious levels. There is neurobiological evidence for the dissociating of the psychological components of reward, with the strongest evidence found to be the mesolimbic dopaminergic

underpinnings of the "wanting" pathways. While there have been recent attempts to separate "wanting" and "liking" in the human context, so far there is no strong evidence for the separation of "wanting" and "liking" using fMRI paradigms in humans. Numerous limbic (NAc, amygdala, caudate, and putamen) and cortical regions (mPFC, OFC, ACC, and insula) are involved in both reward anticipation and reward receipt.

3.4   Reinforcement Sensitivity Theory

To begin this section, it is important to review how reward-related traits have traditionally been measured. This project, with its focus on diurnal rhythmicity, is interested in within-person variability across the day, most readily measured by changes in state reward motivation. The behavioural approach system (see Section 3.4.2) is thought to be a trait measure of reward motivation, but the measures used in this project focus on behavioural state measures of reward motivation (the automatic Balloon Analogue Risk Task and Iowa Gambling Task, see Section 3.4.4). Similarly, one level of reward motivation, affective state, was measured in this project through affective responses to images and a measure of positive emotions (see Section 3.5.1). The modified Differential Emotion Scale was used in this project (see Section 3.5.1, over the more commonly-used Positive and Negative Affect Schedule, given the broader inclusion of positive emotion terms at high and low activation levels in the former. In later sections the interactions between reward measures and circadian variables are discussed (e.g., Section 4.3 and 4.4).

Important work by Gray examined the brain reward systems in humans and led to the development of reinforcement sensitivity theory (RST). The antecedent to Gray's RST was Eysenck's structural theory of personality and a brief review provides helpful context of how reward motivation is understood in the human case. While these theories use a trait view of reward sensitivity, this project examined reward motivation at a state level. Understanding the complexities of reward motivation at the trait level is needed to contextualise the changes in reward motivation at the state level. Finishing this section, two tasks that were used in the current project to measure risky decision-making are introduced as examples of the behavioural manifestation of behavioural approach system activation, a core feature of RST.

3.4.1 Eysenck's theory of personality. In pioneering work, H. J. Eysenck suggested that two dimensional traits, Extraversion and Neuroticism, provided a reliable and valid taxonomy of personality. These features were thought to explain much of the dynamic interplay between the individual and environment (H. J. Eysenck & Eysenck, 1969). Underpinning this system one causal factor, arousability, was theorised to be the driver of conditioned learning signals in reward and punishment contexts (Corr, Pickering, & Gray, 1995; H. J. Eysenck, 1963; Hull, 1952). Eysenck and colleagues later revised this theory to incorporate a third higher order dimensional trait, Psychoticism (S. B. G. Eysenck & Eysenck, 1978), but this trait was not thought of as core to the psychobiological basis of reward and punishment conditioning (J. A. Gray, 1990). In H. J. Eysenck's theory, higher levels of introversion were associated with greater levels of cortical arousal, with lower levels of environmental stimulation leading to higher arousal relative to lower levels of introversion. It was thought that individuals higher in introversion would tend to withdraw from the environment more than individuals higher in extraversion due to the intensified physiological response (H. J. Eysenck, 1963, 1970; H. J. Eysenck & Eysenck, 1985). The second dimensional trait, neuroticism, was later added to this theory, and individuals higher on neuroticism were considered to experience more physiological arousal on average and lower emotional stability relative to those with lower levels of neuroticism (H. J. Eysenck & Eysenck, 1985). Levels of neuroticism were proposed to moderate the strength and ease with which the reward or punishment conditioning was learned (H. J. Eysenck, 1963; J. A. Gray, 1970). In the progression of this theory, H. J. Eysenck (1963, 1970) proposed that individuals higher in extraversion were more easily conditioned by rewards, whereas individuals higher in introversion had a heightened sensitivity to punishment (avoidance conditioning). Varying levels of extraversion and neuroticism were thought to relate to the propensity of an individual to experience activation and arousal from the environment and different speeds of conditioning to environmental stimuli.

3.4.2 Gray's RST. Eysenck's work was core to Gray establishing RST (Corr, 2008). While RST emerged from Eysenck's work examining how differences in extraversion and neuroticism manifest in varying levels of cortical arousal, Gray investigated the broader neurobehavioural systems that underlie the sensitivity to behavioural learning in reward and punishment contexts that Eysenck observed

(Corr, 2008). J. A. Gray (1981) proposed a 30° rotation of the orthogonal Extraversion-Neuroticism dimensions in the conceptual space to represent two new orthogonal dimensions: Anxiety and Impulsivity. These dimensions were thought to better explain sensitivity to punishment and reward, respectively. Gray (and historically Mowrer, 1960) were proponents of a two-dimensional system of reward and punishment with distinguishable biobehavioural processes, with emotions thought to be the primary drivers of behaviour in the respective systems (Corr & McNaughton, 2012).

In the original formulation, Gray proposed that behaviour in the context of rewards and punishments is managed by three brain systems (J. A. Gray, 1967, 1970, 1990). Gray coined the terms Behavioral Inhibition System (BIS) and Behavioral Approach System (BAS) as the conditioned neurobehavioural systems that are respectively involved in aversive and appetitive motivated behaviour. The third system Gray identified was the Fight-Flight System (FFS), which was thought to be related to unconditioned aversive stimuli associated with psychoticism in the Eysenck model. A similar system to BAS, the Behavioural Facilitation System, was proposed independently by Depue and Iacono (1989). Depue and Iacono suggested that the Behavioural Facilitation System initiated motor activity and incentive motivation in the context of reward signals. Given the strong overlap between the constructs noted by both authors (Depue & Iacono, 1989; J. A. Gray, 1982), this project uses the term *BAS*, the predominant term in the literature, to describe this system. Each system was seen as a fundamental adaptation of the organism to the environment to maximise fitness (Corr, 2008; J. A. Gray, 1990).

In the context of this project, BAS is the most relevant of Gray's three systems. Gray (1990) proposed that BAS is exclusively responsive to signals of reward and non-punishment. The activation of BAS leads to *approach motivation* which in turn, can cyclically feedback to signals of reward and non-punishment. There is support for the neurotransmitter dopamine playing an important role in the neural input and output of BAS activity (J. A. Gray, 1990; Wacker, Mueller, Pizzagalli, Hennig, & Stemmler, 2013). Gray suggests that neural structures relevant to BAS may include the caudate-putamen, thought to underpin sensory-motor motivation, and the NAc, most closely related to incentive motivation.

The revised RST (rRST; J. A. Gray & McNaughton, 2003) proposed minimal changes to BAS, retaining its function as the appetitive positive feedback system associated with optimism and hope emotions (Corr, 2008). Gray added *freeze* to the FFS system (Fight-Flight-Freeze System; FFFS) and suggested that this system organised behaviour in the context of all negative stimuli (conditioned and unconditioned). Resultantly, BIS was changed to reflect a mediation system: balancing BAS approach-FFFS avoid conflicts, but also competing BAS-BAS and FFFS-FFFS situations. To resolve these conflicts BIS is thought to engage in processes akin to behavioural economics: BIS creates anxiety, inhibits conflicting behaviours, and carries out risk-assessment using information from the current situation and previous experiences of the conflict. Until resolution, BIS is subjectively experienced as anxiety and worry, and, importantly, distinct from the predominant experience of fear in the FFFS system (Corr, 2008; Corr & McNaughton, 2012; Fowles, 2006; J. A. Gray & McNaughton, 2003).

3.4.3 Self-report measures of BAS. Self-report measures of BIS and BAS may serve to map the general motivational tendencies underpinning approach and avoidance (Corr, 2008). BIS, BAS, and FFFS are thought to be related to underlying affect: BAS is responsible for the subjective experience of positive affect (although not only related to positive affect, see below, Carver, 2004), and the BIS to negative affect (Carver & White, 1994; Corr, 2008). With the redefinition of the rRST, negative affect may also be related to the FFFS or a combination of FFFS-BIS (Torrubia, Avila, & Caseras, 2008). When reward cues are present, individuals high in BAS sensitivity should experience more positive affect relative to those lower in BAS sensitivity (Carver & White, 1994).

The most commonly used self-report measures of approach motivation, the BIS/BAS scales (Carver & White, 1994), extend Gray's conceptualisation of neurobiological approach and avoidance systems through an empirically derived questionnaire with items designed to capture the emotionally generated responses of BIS and BAS. The BIS/BAS scale is a 20-item measure. There is one BIS scale with seven items (e.g., "I feel worried when I think I have done poorly at something important"), while BAS is divided into three subscales: BAS Drive, BAS Reward Responsiveness, and BAS Fun Seeking. BAS Drive has four items (e.g., "I go out of my way to get things I want"), BAS Fun Seeking four items (e.g., "I crave

excitement and new sensations"), and BAS Reward Responsiveness five items (e.g., "When I get something I want, I feel excited and energized"). The three BAS components were defined by their item content: with effortful goal pursuit reflecting a *drive* factor; desire for new rewards and willingness to approach novel potentially rewarding scenarios a *fun seeking* factor; and, the positive response to the anticipation or acquisition of a reward a *reward responsiveness* factor (Carver & White, 1994).

The attainability of appetitive stimuli may impact BAS and the subjective experience of positive affect. Two processes are fundamentally important: A signal for approach/avoidance, and a second "error signal" that monitors rate of progress towards goals (Carver, 2004). When the approach signal is activated, appetitive stimuli are considered attainable, and progress towards goals is considered satisfactory. When goals are achievable there is a subjective state of hope and anticipatory pleasure, and the activation of BAS when goals are obtained leads to positive affect (Carver & Harmon-Jones, 2009; Corr, 2008).

Carver (2004) highlights that BAS may also be related to negative affect. Anger and frustration can occur when goal pursuit is challenged, and when goal disengagement is required, may relate to feeling states of despondency and sadness. In the instance of goal frustration, negative affect which involves environmental engagement, such as anger, relate strongly to each of the BAS dimensions (Carver, 2004). An approach element in emotions is still involved but it shifts to a negative valence (Carver & Harmon-Jones, 2009).

BAS sensitivity at a trait level may measure a general affective tone, reflecting an underlying neurophysiological system (Carver & White, 1994). For example, three studies (Coan & Allen, 2003; Harmon-Jones & Allen, 1997; Sutton & Davidson, 1997) found greater left frontal asymmetry using resting alpha power in those with higher self-reported BAS scores. Left frontal activity has been linked to higher activation to reward cues more generally (Nelson, Kessel, Klein, & Shankman, 2018; Pizzagalli, Sherwood, Henriques, & Davidson, 2005). Carver (2005) highlighted that a greater approach tendency is related to higher sensitivity to incentives and an increase in impulsivity and reactiveness with subcortical drivers; indeed, J. A. Gray (1981) labelled the personality dimension of approach, "impulsivity". BIS may help to moderate this level of impulsivity (Corr, 2008). Corr

(2008) suggested that these two systems create a motivational balance. In the presence of potential rewards, a cognitive *risk analysis* is conducted whereby the environment and memory are scanned to evaluate the balance between risk and reward resulting in changes to cognition and behaviour. When the balance is in favour of reward (BAS), a corresponding increase in attentional bias towards rewards and behavioural engagement in risky decision-making should theoretically be observed.

There is some evidence for the behavioural relevance of the motivational balance of BAS-BIS. Kim and Lee (2011) found that after a winning experience in a gambling task, individuals with high BAS and low BIS made more risky decisions relative to individuals with high BAS and high BIS. Individuals with high BAS had higher confidence levels than low BAS in both winning and losing conditions. The relationship between BAS and risky decision-making was also seen in naturalistic examples of risk-taking behaviour. R. M. O'Connor, Stewart, and Watt (2009) found that alcohol frequency and quantity, and gambling frequency were positively related to BAS Fun Seeking and BAS Drive respectively. BAS Drive was also positively related to money spent gambling, but a negative relationship was found between BAS Fun Seeking and money spent gambling. While this reflects a trait view of reward motivation it contextualises the individual tendency of reward motivation in a state context. In sum, self-report measures of BAS and BIS may map the underlying motivational tendencies of an individual.

3.4.4   State measures of reward motivation. In Study 3 of this project the Balloon Analogue Risk Task and Iowa Gambling Task were used as measures of state "wanting" and learning of rewards. These behavioural tasks have previously been shown to correlate with naturalistic risk-taking (e.g., drug use, alcohol, unprotected sex; Schonberg, Fox, & Poldrack, 2011).

The automatic Balloon Analogue Risk Task (BART; [as opposed to the original manual BART, Lejuez et al., 2002], Pleskac, Wallsten, Wang, & Lejuez, 2008) used in Study 3 as a behavioural measure of "wanting". Across 30 trials, participants enter a number to pump the balloon that many times, with each pump earning 5 cents; if the balloon pops, all winnings are forfeited and the trial ends. Akin to real-world scenarios, there is an inverted U distribution of risk-reward balance: Higher risk leads to greater rewards, but too much risk results in poorer

outcomes (Lejuez et al., 2002). Participants are told the explosion point of each balloon ranges from the 1st to the 128th pump with the average pumps a balloon can take being 64. The best long-term strategy is 64 pumps but this is not necessarily the best strategy for each trial. If the balloon does not pop, participants are told how many pumps they could have achieved for that trial. Increased risk-taking on the BART is associated with increased alcohol, cigarette, and illicit drug use (Lejuez et al., 2002; Pleskac et al., 2008). Risk-taking during the BART is associated with activity in the ventral and dorsal striatum, anterior insula, dlPFC, ACC, and mPFC (Rao, Korczykowski, Pluta, Hoang, & Detre, 2008). There is mixed evidence for the relationship between self-reported BAS and performance on the BART. One study found an interaction between BAS and level of risk-taking as measured by the BART, with high BAS levels showing elevated left-frontal EEG activity regardless of BART risk-taking level, while individuals with moderate BAS scores had a positive linear relationship between risk-taking and left-frontal EEG asymmetry (Black et al., 2014). Conversely, other studies (Braams, van Duijvenvoorde, Peper, & Crone, 2015; Meda et al., 2009) found low interrelationships between BAS and BART scores.

The Iowa Gambling Task (IGT; Bechara, Damasio, Damasio, & Anderson, 1994) is used in Study 3 to simulate reward learning through real-life decision making using uncertainty, rewards and penalties. Participants select a card from one of four decks. Two decks contain greater gains but also greater losses (net loss) and two decks contain smaller gains and also smaller losses (net gain). Risky decision-making can be assessed through perseverance in selecting higher yielding decks despite net losses over many trials. Participants are explicitly told that rewards and losses associated with each deck are pre-programmed and not randomised. Balconi, Finocchiaro, and Canavesio (2015) found that individuals higher in BAS chose from risky decks more often during the IGT. The authors linked this to dysfunctional metacognitive strategies, where individuals are unable to see that their reward decision-making strategy is not working, and increased left-sided hemispheric activation when outcomes were worse than expected.

The relationships between the IGT and the individual BAS subscales are mixed. In one study, high BAS Reward Responsiveness and BAS Fun Seeking were related to selecting more from the risky decks, but BAS drive was not related to IGT

deck selection (Suhr & Tsanadis, 2007). M. Brand and Altstötter-Gleich (2008) found that selection of risky decks on the IGT was not related to BAS Reward Responsiveness or BAS Drive; BAS Fun Seeking was not reported. Surprisingly, I. H. A. Franken and Muris (2006) found that participants higher in BAS Reward Responsiveness earned more money on the IGT. One possibility for this finding was that Franken and Muris used total points earned as the outcome variable rather than the more commonly used variable of deck selections from advantageous/disadvantageous decks. A potential explanation is that sometimes high-risk gambles pay off.

In neuroimaging studies, increased activity in the ventral mPFC was related to decision-making and task performance on the IGT (Northoff et al., 2006). X. Li, Lu, D'Argembeau, Ng, and Bechara (2010) extended the finding that OFC-vmPFC connectivity helped integrate the neural circuitry in the dlPFC and insula/posterior cingulate cortex during IGT performance with the VS and ACC supporting action during reward uncertainty. Relative to healthy controls, individuals who pathologically gambled made more risky choices. During these high risk choices, greater activation was observed in the OFC, caudate, and amygdala relative to healthy controls (Power, Goodyear, & Crockford, 2012).

3.5   Positive Affect

It is important to distinguish between trait affect, a stable individual disposition towards affective experience, and affective state, a transient experience of a mood state (Cohen et al., 1995; Watson, 1988a). Trait differences in affect are thought to modulate levels of state experience, such that individuals with a positive disposition are more likely to experience positive mood states in different situations (Diener & Larsen, 1984).

Positive and negative affect are regarded as two relatively independent underlying dimensions of mood (Watson, 2000b; Watson & Tellegen, 1985). High positive affect can be defined as positive emotional activation and strong goal-motivated engagement with the environment, manifest in a "zest for life" (Watson & Tellegen, 1985, p. 221), whereas the low end of the positive affect dimension is characterised by withdrawal from the environment (Watson et al., 1999). Conversely, high negative affect can be defined as a feeling of distress or unpleasant arousal, with low negative affect reflecting a state of calmness and relaxation

(Tellegen, Watson, & Clark, 1999; Watson, Clark, & Tellegen, 1988; Watson et al., 1995).

Watson and colleagues (Watson, 1988b, 2000b; Watson & Clark, 1994, 1997; Watson et al., 1988; Watson & Stanton, 2017; Watson & Tellegen, 1985) argued that aside from extremely high levels of either negative affect or positive affect, the two dimensions are relatively independent of each other. The absence of negative affect (i.e., relaxed) does not necessarily require a high level of positive affect (i.e., happy, energised; Watson & Clark, 1994). The high ends of positive and negative affect poles may be incompatible though; for example, feeling euphoric and enraged simultaneously is discordant (Watson, 2000b; Watson & Stanton, 2017).

The distribution of the two affect dimensions is fundamentally different. Momentary negative affect is a largely reactive state which helps individuals resolve crises. As such, negative affect has an approximately bimodal (on-off) distribution, while positive affect has a more moderate rhythmic distribution with relationships to a broad range of rewarding situations (Clark & Watson, 1988; Watson, 2000a, 2000b). A number of factors can influence state levels of positive affect, including physical activity, social engagement, and, most importantly for this project, diurnal variation (Clark & Watson, 1988; Clark et al., 1989; Watson et al., 1999). These state factors independently influence positive affect but not negative affect (Watson, 2000b). This independence means that, at any one time, an individual's overall affective state can be characterised by the level of positive and negative affect (Watson, 2000b; Watson & Clark, 1994).

Positive affect is traditionally measured by self-report instruments. The most commonly used measure to capture changes in affect is the Positive and Negative Affect Schedule (PANAS, Watson et al., 1988). The PANAS has two scales: one for positive affect (PA; 10 items, e.g., "interested", "active", "enthusiastic") and one for negative affect (NA; 10 items, e.g., "ashamed", "irritable", "scared"). The PANAS offers multiple measurement time-frames (from "at this moment" to "in general") allowing for measurement of affect at both state and trait levels. Watson and Walker (1996) found that short-term stability was high for both scales (.70 for NA, .74 for PA at a two-month follow-up), while long-term test-retest stability data were more moderate (.42 for NA, .43 for PA at a 62-month follow-up).

An alternative model of the PA-NA dimensional space has been suggested by Russell, Barrett, and Carroll (Barrett & Russell, 1999; Russell, 1980; Russell & Barrett, 1999; Russell & Carroll, 1999a, 1999b; Yik, Russell, & Barrett, 1999). One criticism of the PA-NA schema is the coupling of arousal-laden, positive valence terms to measure positive affect, (e.g., "excited", "alert", and "active") yet, not all positive affects are necessarily high in arousal (Chiew & Braver, 2011; Kuppens, Tuerlinckx, Russell, & Feldman Barrett, 2013; Russell & Carroll, 1999a). Watson et al. (1999) revised their model, suggesting that positive and negative *activation* may be more accurate reflections of the biobehavioural phenomena being described; nevertheless, the majority of relevant literature continues to use the term, *affect* to refer to positive affect in Watson and colleagues' work. Yik et al. (1999) compared four models of two-dimensional circumplex structures of affect (Larsen & Diener, 1992; Russell, 1980; Thayer, 1989; Watson & Tellegen, 1985). Schematically, Yik et al. showed that the structure of affect shared the same circumplex across all four models, with only the rotation and labelling of the axes the main points of contention. Russell (1980) preferred the dimensional poles of valence (from pleasure to misery) and activation (from arousal to sleepiness). This 45° rotation of the Watson and Tellegen (1985) model aligns with the proposed Larsen and Diener (1992) activation and pleasantness dimensions. As the literature evolved, this led Watson et al. to note that they saw the PA and NA dimensions to be characterised by the high ends of the pole in that high levels of PA and NA reflected the underlying "two basic biobehavioural systems of activation" (p. 827) with low levels of PA and NA reflecting an absence of this valenced activation.

Positive affect is thought to represent two components of reward motivation: the subjective manifestation of reward motivation as a positive state is important for initiating action in reward contexts, *and* the outcome of an organism's assessment of progress towards goals (Watson et al., 1999). Watson et al. (1999) argued that positive affect creates a motivational balance in favour of goal-seeking behaviour. Increased vigour and enthusiasm observed in high positive affect states leads to increased efficacy that effort will lead to a reward, and these positive affects result from reward engagement (Watson et al., 1999). Behaviourally, level of positive affect is predictive of environmental engagement, with those higher in trait positive affect engaging more than those lower. As one example, associations have been

found between higher levels of positive affect and increased time spent socialising and positive ratings of social interactions (Berry & Hansen, 1996; Watson, 1988a; Watson, Clark, McIntyre, & Hamaker, 1992). Conversely, lowered positive affect can manifest as low self-reported enthusiasm and energy: in clinical settings, lowered positive affect may be seen as the symptom anhedonia in major depressive disorder (Davidson, Pizzagalli, Nitschke, & Putnam, 2002). At a neural level, higher levels of positive affect are related to increased left frontal activity during goal-striving activities and at-rest (see Nusslock, Walden, & Harmon-Jones, 2015 for a review). Cumulatively, this data suggests that self-reported positive affect may support readiness to engage in reward behaviours and, more broadly, may be associated with neural reward system activation. Suggesting a relationship between self-reported positive affect and broader reward motivation, there is evidence to support that self-reported BAS (Carver & White, 1994) and left anterior electroencephalogram activity (Tomarken, Davidson, Wheeler, & Doss, 1992) are positively correlated with self-reported trait positive affect. Schonberg et al. (2011) suggested that the tendency for risky decision-making is in part driven by positive, anticipatory emotions such as exhilaration at the prospect of potential rewards.

   3.5.1 Moods and emotions. Within the domain of affect, moods and emotions have important functional differences but both are subjective feeling states related to adaptive approach and withdrawal processes (Watson, 2000b). Moods and emotions are not directly observable and are inferred through verbal reports, physiology, behaviour, and neural correlates (Friedman, Stephens, & Thayer, 2014; Knutson et al., 2014). One distinction is that emotions are brief and intense by nature, lasting seconds or minutes; while moods are typically measured in hours, days, or longer in the instances of mood disorders (Davidson, 1994; Ekman, 1992; Ekman & Davidson, 1994; Izard, 2013; Watson, 2000b). The antecedent events to moods and emotions differ. Emotions are quick psychophysiological responses to often unanticipated events, while moods are largely triggered by cumulative events over longer time courses (Davidson, 1994). Watson (2000b) extends this by suggesting that both emotions and moods are responses to events, but moods alone can be driven by internal dispositions. Moods and emotions may also differ functionally: It has been proposed that emotions modulate action, moods modulate cognition (Davidson, 1994). Moods may bias cognition through information

processing (Davidson, 1994). For example, negative attentional biases are commonly observed during a depressed mood, with depressed individuals perseverating on negative information and stimuli relative to positive stimuli (De Raedt & Koster, 2010; Gotlib, Krasnoperova, Yue, & Joormann, 2004; Leyman, De Raedt, Schacht, & Koster, 2006). Alternatively, emotion-specific experiential aspects combine with a distinct autonomic signal to facilitate adaptive action (Ekman, Levenson, & Friesen, 1983; Friedman et al., 2014), for example fleeing a situation when fear is experienced. Positive emotions may have less specific action tendencies relative to negative emotions. Fredrickson (1998, 2001) proposes a *broaden and build* theory of positive emotions. Positive emotions create broad, diffuse, urges to explore and take in new environmental experiences, and thus has the evolutionary advantage of seeking and accruing enduring personal resources.

The differential emotions scale (DES; Izard, 2013) was designed to redress a need for psychometric tools that measure positive emotions. In the original DES (Izard, 1977) only two positive emotions *joy* and *interest* were included, along with eight negative emotions (*anger*, *contempt*, *disgust*, *embarrassment*, *fear*, *guilt*, *sadness*, and *shame*) and *surprise*. Fredrickson, Tugade, Waugh, and Larkin (2003) expanded the selection of positive emotions in the modified DES (mDES) to include *amusement*, *awe*, *compassion*, *contentment*, *gratitude*, *hope*, *love*, *pride*, and *sexual desire*. Two aggregated subscales were created for positive (the nine positive emotions excluding awe, $\alpha = .79$) and negative emotions (the seven negative emotions excluding embarrassment, $\alpha = .69$, Fredrickson et al., 2003). One of the strengths of this extended list of positive emotions is that it encompasses emotions that are high and low in arousal levels, a criticism of the high-arousal positive valence items on the PANAS (Russell & Carroll, 1999a).

The International Affective Picture System (IAPS) is a set of standardised affective stimuli to precisely measure affective states (P. J. Lang, Bradley, & Cuthbert, 2008). The IAPS is a set of emotionally-evocative colour pictures to capture affect and emotion across three major dimensions: affective valence (from pleasant to unpleasant), arousal (from calm to excited), with a third, less strongly related dimension, of power and control (P. J. Lang et al., 2008). In studies using the IAPS, images are selected from the large IAPS database (>1000 images) that has been normed for valence and arousal (the dimension of power and control is rarely

used and sits outside the scope of the current project). M. M. Bradley and Lang (2007) stated the hedonic valence of the image is indicative of whether the appetitive or aversive system is engaged, while the level of arousal is an index of the degree of system activation. Negative, high arousal images include images depicting mutilation, and animal threat; neutral images (low arousal) include neutral objects and neutral faces; positive, low arousal images includes cuddly animals, babies, and nature; and, positive, high arousal images includes erotica and adventure. Typically, when participants view the images, they are asked to rate the level of pleasantness and level of arousal of each image. The subjective ratings of these images are associated with affective response in other systems (including skin conductance, heart rate, and changes in regional blood flow in the brain). For example, increases in pleasantness ratings are related to more zygomatic (smiling) activity and less corrugator (frowning) activity (M. M. Bradley, Codispoti, Cuthbert, & Lang, 2001), and NAc and mPFC activation (Sabatinelli et al., 2007). Regardless of valence, increases in arousal ratings are positively related to level of skin conductance (M. M. Bradley et al., 2001), and amygdala activity (Sabatinelli, Bradley, Fitzsimmons, & Lang, 2005).

3.6   Summary and Implications for the Present Project

This chapter has reviewed the neurocircuitry of the reward system and three different levels of analyses from which reward motivation is conceptualised. The evolutionary function of reward motivation is presumed to initiate behaviours important for hunting, socialising, and procreation. Several neurobiological mechanisms are thought to subserve reward motivation, with a range of data supporting the importance of the mesolimbic dopaminergic pathways that project to the striatum. One influential approach emerging from animal research proposes that reward processing is not a unitary process. In work largely conducted on non-human mammals, Berridge and Robinson presented three psychological components of reward: "wanting", "liking" and learning (Berridge & Robinson, 2003). These processes have dissociable functions and neurobiological correlates, however, in naturalistic, healthy populations they interact continuously (Berridge & Kringelbach, 2008; Kringelbach & Berridge, 2016). Gray's BAS system provides a biobehavioural lens for explaining reward motivation in humans (Corr, 2008; J. A. Gray, 1972). The two-dimensional model of affect presented by Watson and

Tellegen (1985) helps to explain the subjective experience of an activated positive or negative affective state. Positive affect is considered to be the subjective manifestation of reward motivation activation and indexes the subjective assessment of progress towards rewards (Watson et al., 1999). Reward-related activity may be measured in neural reward motivation, behavioural tasks measuring reward motivation, and in self-report measures of positive emotions. This project (specifically Study 3, Study 4, and Study 5) examines circadian modulation of reward motivation. A further consideration in Study 3 is whether the circadian system modulates all three psychological components of rewards.

In this project, reward motivation is measured at different levels of analysis. Partly informed by current understanding of reward motivation in animals, this project measured reward motivation at different levels in the human context. Measuring reward motivation in humans presents a series of challenges but, also, exciting avenues to investigate reward components (Haber & Knutson, 2010). In a review of naturalistic prospective studies, Study 1 examined the relationship between biological rhythms and positive affect (variously measured). To examine the deactivation of the reward system, Study 2 focused on lowered mood in the construction of a questionnaire designed to measure sleep quality, circadian functioning, and mood in a single self-report measure. Study 3 measured diurnal variation in reward motivation, paying particular attention to the three psychological components of reward. The BART was used to measure the unconscious experience of "wanting", IAPS images (arousal ratings) to measure wanting, the mDES and IAPS (pleasantness ratings) were used to examine the conscious experience of liking, and the IGT to measure learning. In a systematic literature review, Study 4 examined the evidence for circadian modulation of reward motivation in fMRI studies, including a focus on whether these effects are observed across reward anticipation and reward receipt. Study 5 explored the neural correlates of reward motivation in fMRI using a well-validated monetary reward task at three times of day.

Chapter 4: The Relationship Between Circadian Function and Reward Motivation

As reviewed in Chapter 2, the circadian system produces ~24-hour rhythms in a range of biological, psychological, and behavioural processes. From an evolutionary perspective, the circadian system has two major functions that maximise fitness in a survival context: it is adapted to optimally synchronise internal processes of the organism to the external world, and to optimally synchronise internal processes with each other (Watson, 2000b). Given these two functions, Wehr (1990) and Murray et al. (2009) have hypothesised that it may be evolutionarily advantageous to have a circadian rhythm in reward motivation. The reward potential of the environment is partially dependent on the light/dark cycle. For diurnal species such as humans, daylight, when vision is best, has high reward potential and low associated risks. This pattern is reversed at night: humans, with their poor night vision, have no biological advantage in seeking rewards at this time.

In setting up the present project that in part examines circadian modulation of reward motivation in healthy populations, this chapter briefly reviews three lines of evidence for circadian modulation of the reward system. Firstly, data from genetic and neural manipulations of the circadian system in the context of altered reward response in animal studies are reviewed (4.1). Secondly, the research into diurnal (4.2) and circadian rhythms (4.3) in relation to reward motivation in humans is reviewed, with an additional observed relationship between chronotypes and positive affect discussed (4.4). Finally, evidence of disrupted circadian rhythms and dysregulated reward motivation at the level of psychopathology is presented (4.5). The focus here is on bipolar disorder and the Reward and Circadian Dysregulation model proposed by Alloy, Nusslock, et al. (2015).

4.1   Evidence from Animal Studies for Circadian Modulation of Reward Motivation

Circadian modulation of reward motivation has been observed through circadian genotypes, SCN functioning and time of day regulating reward motivation in animals. Numerous studies have demonstrated that manipulation of circadian genes lead to abnormalities in the reward system: both in response to food rewards and drugs of abuse, and, in behaviour consistent with mood dysregulation (see McClung, 2007, 2013). For example, in one study, a mutation in the circadian *Clock* gene led to extreme hyperactivity in response to novelty across the entire light-dark cycle such as that seen in humans experiencing a manic episode (Roybal et al.,

2007). In addition, data from McClung et al. (2005) found a mutation to the *Clock* gene increased dopamine activation in response to cocaine in the VTA with lithium restoring VTA dopamine functioning. There is also evidence for *Per2* circadian gene involvement in the reward response. Monoamine oxidase A and B (MAO-A and MAO-B) metabolise dopamine in the VTA and striatum (Hampp et al., 2008). In *Per2* mutant mice, Hampp et al. (2008) found that MAO-A activity was reduced in the VTA leading to elevated dopamine levels in the caudate putamen and NAc to which the VTA projects. There is also data consistent with increased alcohol consumption (Spanagel et al., 2005), lack of food anticipation (Feillet et al., 2006), and a hypersensitive response to cocaine (Abarca, Albrecht, & Spanagel, 2002) in mice with *Per2* mutations. Speaking to a bi-directional relationship, in one study lesions to the mPFC in rats eliminated the diurnal rhythm in the NAc (core and shell) but did not affect the rhythmicity of the VTA (Baltazar, Coolen, & Webb, 2013).

Circadian rhythms in behavioural variables relating to the reward system have also been observed in animals. Baird and Gauvin (2000) showed that rats self-administer drugs of abuse during their active period. There is evidence that marmosets, golden hamsters, mice, and some rat strains exhibit a reward-conditioned circadian place preference at the circadian time of prior training (Abarca et al., 2002; Cain, Ko, Chalmers, & Ralph, 2004; Kurtuncu, Arslan, Akhisaroglu, Manev, & Uz, 2004; Valentinuzzi et al., 2008). Existing findings are not, however, unequivocal. One study did not find a conditioned place preference (Sleipness, Sorg, & Jansen, 2007a) and Storch and Weitz (2009) found circadian-driven food anticipation was not altered in mice lacking *Bmal1* (a core circadian clock gene). Data for circadian rhythmicity of reward motivation has also been observed in circadian clock gene expression. For example, Abarca et al. (2002) found that *Per2* mutant mice have a time-of-day dependent reward-response for when cocaine was administered. Not all outputs of the circadian system may affect the response to rewards. For example, Sleipness et al. (2007a) found that rats with a lesioned SCN had altered sensitisation to cocaine, acquiring the place preference at a quicker rate relative to sham rats; however this did not depend on the time of day. One mechanism by which SCN lesioning may alter reward learning may be through dopamine transporter levels in the NAc and mPFC (but not the caudate): One study found that rats ceased to exhibit diurnal variation when the SCN was lesioned (Sleipness, Sorg, & Jansen, 2007b).

4.2   Evidence from Human Studies of Diurnal Variation in Positive Affect

A range of evidence suggests that positive affect, most commonly measured by the PANAS, has an endogenous component causing it to vary systematically across the day. More than 25 years ago, Clark et al. (1989) demonstrated that positive affect was highest during daylight hours and lowest at night. As discussed above, positive affect is thought to be the subjective component of reward motivation, enhancing beliefs of capacity to achieve goals, efficacy that goals will be rewarded, and positive feelings once goals are achieved (see Section 3.5; Watson, 2000b; Watson et al., 1999). It has been argued that, in contrast to positive affect, negative affect would not display temporal variation as negative affect is activated to deal with acute threats. As environmental threats are unpredictable there is no biological reason this threat system would be primed for activation at particular times of day (Murray, Allen, & Trinder, 2002). As the probability of reward, but not risk, can be predicted in advance, it is hypothesised that positive affect, and not negative affect, may show an endogenous circadian rhythm (Murray, Allen, & Trinder, 2002; Murray et al., 2009). Despite this, some studies have found a diurnal rhythm in negative affect (M. A. Miller et al., 2015; Peeters, Berkhof, Delespaul, Rottenberg, & Nicolson, 2006; Stone et al., 2006); however, authors have suggested that an increased diurnal variation in negative affect may, in part, be driven by depressive symptoms (Peeters et al., 2006) and work-related emotional states (Stone et al., 2006) rather than the biological factors observed in the circadian positive affect rhythm.

Studies in naturalistic conditions have consistently found a diurnal rhythm of positive affect with a peak during daylight hours and nadir at night (Clark et al., 1989; Murray, Allen, & Trinder, 2002; Murray et al., 2009; Stone et al., 2006; Watson et al., 1999). In student samples, Clark et al. (1989) demonstrated that positive affect was highest during the day between midday and 9pm, while Watson et al. (1999) found that the peak of positive affect occurred at the mid-point between wake and sleep onset. One study by Steptoe, Leigh Gibson, Hamer, and Wardle (2007) found that lower individual ratings of happiness corresponded to higher levels of the circadian-controlled stress hormone cortisol earlier in the day and a heightened cortisol awakening response; however, no relationships between positive affect measured on the PANAS and cortisol variables were observed. In work moving

away from self-reported affect, in the first study of diurnal rhythms in neural reward activation, Hasler, Forbes, and Franzen (2014) found, as hypothesised, increased activation in reward circuitry (the striatum) in response to a monetary reward task in the afternoon relative to morning.

4.3   Evidence from Human Studies of Circadian Variation in Positive Affect

There is also empirical evidence that the diurnal variation in positive affect is at least partially of endogenous circadian origin. In the first study of diurnal variation in positive affect to use a recognised circadian unmasking protocol, Boivin et al. (1997) demonstrated in two multi-week forced desynchrony studies that subjective happiness interacted with the length of prior wakefulness, with decreases in happiness and cheerfulness close to sleep onset; simultaneously, the positive mood variables were highest at the peak of core body temperature, occurring about 8 hours after awakening in naturalistic conditions (the mid-afternoon for most people). Murray, Allen, and Trinder (2002) found that positive affect peaked at 3pm, aligning with the peak of the circadian controlled core body temperature in a constant routine protocol. Extending on these findings, Murray et al. (2009) demonstrated that a large proportion of variance in positive affect was attributable to the endogenous timing of the core body temperature rhythm in naturalistic (13%), constant routine (25%), and forced desynchrony (24%) protocols.

4.4   Chronotype and Positive Affect

As discussed in Chapter 2, chronotype is a self-report variable strongly related to circadian function (particularly circadian phase). A relationship has been observed between chronotype and various parameters of positive affect including the timing, amplitude, and mean levels of the diurnal rhythm in positive affect. A study by M. A. Miller et al. (2015) found that in healthy adults evening chronotypes had a lower circadian amplitude and experienced the peak of their positive affect at a later time on work days compared to morning and intermediate types. This pattern was also seen in a primary insomnia sample with evening types showing a blunted and delayed positive affect rhythm relative to morning types (Hasler, Germain, et al., 2012). Adding to these findings, Biss and Hasher (2012) found that both younger and older adult morning types experienced higher levels of positive affect and subjective health relative to evening types. In a large sample of high school children, morning, intermediate, and evening types showed the same diurnal pattern of

positive mood across the day with a progressive increase from the beginning of the school day (8:10h-8:30h) to late morning (10:20h-11:40h) to early afternoon (13:50h-14:10h). Even after controlling for time in bed, morning types experienced higher levels of positive mood followed by intermediate and evening types, respectively (Díaz-Morales, Escribano, & Jankowski, 2015). Higher levels of subjective wellbeing (Randler, 2008), and optimism and resilience (Antúnez, Navarro, & Adan, 2015) were observed in morning types as opposed to evening types. These results combined to emphasise a positive emotional tendency in morning types, and, a dampened positive experience for evening types.

4.5   Circadian Function and Reward Motivation in Bipolar Disorder

The aim of this section is to introduce Alloy, Nusslock et al.'s (2015) reward and circadian rhythm dysregulation model which is an integrated model of the reward hypersensitivity model (see Alloy & Abramson, 2010; Depue & Iacono, 1989; Johnson, 2005; Urošević, Abramson, Harmon-Jones, & Alloy, 2008) *and* the social/circadian rhythm disruption model (Ehlers, Frank, & Kupfer, 1988; Grandin, Alloy, & Abramson, 2006) of bipolar disorder. Although the current project focuses on healthy populations, deepening understanding of the processes between circadian function and reward motivation will improve understanding of the putative involvement of these systems in psychopathologies. There is growing support for the hypothesis that abnormal circadian rhythms are part of the pathogenesis of mood disorders (Malhi & Kuiper, 2013). As early as Halberg (1968), mood disorders have been associated with circadian rhythm dysregulation. The aetiological role of circadian disturbance in mood disorders has been attributed to two forms of circadian dysregulation. The endogenous circadian system may have disturbances, or the ability of the circadian system to entrain to zeitgebers might be disrupted (Alloy, Ng, Titone, & Boland, 2017).

4.5.1   Diagnostic criteria for bipolar disorder. Bipolar disorder is characterised by episodes of mania or hypomania (less functional impairment or shorter length than mania) which includes periods of elevated, euphoric, or, irritable mood accompanied by increased goal-activity, talkativeness, psychomotor activity, racing thoughts, distractibility, grandiosity, risky activities and decreased need for sleep, which last for at least one week (four days for hypomania) unless hospitalised (American Psychiatric Association, 2013). Major depressive episodes are typically

experienced over the course of bipolar disorders, and form part of the diagnostic criteria for Bipolar II (hypomania and depressive episodes). Depressive episodes also commonly co-occur in Bipolar I (but are not necessary for diagnosis). Major depressive episodes are defined as a period of at least two weeks of consistently depressed mood, or anhedonia, accompanied by at least four symptoms of: significant weight loss (or gain), insomnia or hypersomnia, psychomotor retardation or agitation, loss of energy, feelings of worthlessness or guilt, diminished ability to think or concentrate, or, suicidal thoughts or ideation (American Psychiatric Association, 2013).

4.5.2 **The reward hypersensitivity model of bipolar disorder.** In bipolar disorder, there are many lines of evidence that suggest a dysregulation of the reward system, largely operationalised as BAS. BAS is conditioned to be responsive to desired stimuli, modulating motivation and goal-directed behaviour in obtaining rewards (see Section 3.4; J. A. Gray, 1982, 1990). The presentation of the mood episodes in bipolar disorder is hypothesised to exist at the two poles of the BAS system: with low BAS activation in depression and high BAS activation in the hypomanic or manic phases of the disorder (Alloy, Olino, & Freed, 2016; Hayden et al., 2008). This model links basic science understandings of motivation to the defining states of bipolar disorder (Urošević et al., 2008). At a neurobiological level, the mesolimbic dopaminergic structures are linked to anticipation of desired events ("wanting"; Depue & Collins, 1999; Panksepp, 2005), which may be the driver of goal-pursuit emotions (Berridge & Robinson, 2003). Behaviourally, BAS activation has been associated with increased motor activity, goal-striving behaviours and positive emotions like hope, elation and happiness (J. A. Gray, van Goozen, Van de Poll, & Sergeant, 1994) and anger and irritability if goal-seeking behaviour is impeded (Carver, 2004; see Section 3.4.3); reflective of the clinical quale experienced by those in a manic or hypomanic state.

There is evidence that higher trait levels of BAS activation are related to the onset and course of bipolar disorder. This hypersensitive response is seen in the prodrome to development of bipolar disorder and remains present in interepisodic periods (Alloy et al., 2008; Alloy, Bender, et al., 2009; Alloy et al., 2012). Alloy et al. (2012) found that a high BAS score was related to an increased risk of developing a bipolar spectrum disorder and a shorter duration to bipolar disorder onset, relative

to those with a moderate BAS score. In this study, ambitious goal-striving partially mediated the relationship between trait BAS and bipolar disorder onset. This finding is consistent with the literature suggesting heightened goal-striving is a core feature in bipolar disorder symptomology. In bipolar disorder, high goal-striving features predict shortened time to disorder onset, and more severe symptomology. These goal-striving features remain present in bipolar disorder during interepisodic periods (Johnson, 2005; Johnson & Carver, 2006; Johnson, Carver, & Gotlib, 2012; Johnson, Eisner, & Carver, 2009; Johnson, Swerdlow, Treadway, Tharp, & Carver, 2017; Meyer, Johnson, & Winters, 2001; Stange et al., 2012). This higher trait vulnerability to BAS activation may have underlying neural mechanisms. In a neuroimaging study, Nusslock et al. (2012) found that individuals in a euthymic state of bipolar disorder had increased bilateral VS and right OFC activation during reward anticipation, but not reward receipt, relative to healthy controls.

Reward hypersensitivity to BAS-deactivating events may manifest in the depressive symptoms of bipolar disorder. A recent theoretical review by Nusslock and Alloy (2017) proposed that in the context of failure or loss, patients with bipolar disorder (or those vulnerable to the disorder) experience a hypersensitivity to reward deactivation which leads to excessive inhibition of reward motivation manifesting in motivational anhedonia (refer to Figure 1 of Alloy et al., 2016 for a schematic map of these vulnerability pathways). There is some evidence that individuals with bipolar disorder have *state* neural mechanisms that counteract the *trait* vulnerability for reward hypersensitivity (Alloy et al., 2016). For example, using fMRI Satterthwaite et al. (2015) found in a sample of unipolar and bipolar depressed patients and healthy controls, that relative to healthy controls the two depressed groups exhibited blunted reward receipt in the VS, anterior insula, and ACC. As these are dopamine-rich regions, this blunting may reflect behavioural withdrawal that occurs with lowered striatal dopamine availability (Depue & Collins, 1999; Depue & Iacono, 1989; Nusslock & Alloy, 2017). Despite similarities between unipolar and bipolar depression, Satterthwaite et al. (2015) went on to find in a Win > Loss contrast, individuals with bipolar depression had increased left VS activation relative to unipolar depression; and greater connectivity between the VS, anterior insula, VTA and thalamus in the bipolar group relative to the unipolar depression group. In sum, this work suggests that individuals with bipolar disorder have trait

and state level hypersensitivities of BAS that may relate to the behavioural symptoms and functional reward circuitry observed during manic and depressive episodes. This reward hypersensitivity may serve as a vulnerability to disorder onset and persist during interepisodic phases.

  4.5.3 The social / circadian rhythm model of bipolar disorders. On a range of measures, circadian rhythm disturbance is observed in individuals diagnosed with bipolar disorder (see Bellivier, Geoffroy, Etain, & Scott, 2015; Melo, Abreu, Linhares Neto, de Bruin, & de Bruin, 2017 for a review). Initially it was thought that individuals with bipolar disorder may have been hypersensitive to light (as measured by the light exposure needed for melatonin suppression) which may have contributed to circadian misalignment (Lewy et al., 1985; Lewy, Wehr, Goodwin, Newsome, & Rosenthal, 1981). Other studies implicated lower baseline levels of melatonin (Lam et al., 1990) and timing of circadian rhythms as more informative in accounting for circadian abnormalities in bipolar disorder (Ashman et al., 1999; Baek et al., 2016; Harvey, Schmidt, Scarnà, Semler, & Goodwin, 2005; Moon et al., 2016). Nurnberger et al. (2000), for example, showed that individuals with bipolar disorder had later melatonin onset times and lower melatonin levels (see also Robillard, Naismith, Rogers, Scott, et al., 2013; Salvatore et al., 2012). In addition, inconsistency in the timing of daily activities (e.g., timing of sleep and meals) across the week may lead to lowered circadian amplitudes (Schroeder & Colwell, 2013). Diminished circadian amplitude as measured by the 24-hour activity cycle has been observed in those with (Indic et al., 2011; Pagani et al., 2016; cf. De Crescenzo, Economou, Sharpley, Gormez, & Quested, 2017; Scott et al., 2016, for two recent reviews on altered activation in bipolar disorder) and at-risk for bipolar disorder (Alloy, Boland, Ng, Whitehouse, & Abramson, 2015; Bullock & Murray, 2014; J. Castro et al., 2015; Indic et al., 2011). In one study examining individuals at risk of developing bipolar disorder (Bullock & Murray, 2014), this altered activity pattern was found to be driven by both a decrease in daytime activity and heightened activity levels at night in those vulnerable to developing bipolar disorder relative to those at low risk. Pagani et al. (2016) found in a large-scale study of euthymic individuals with bipolar disorder reduced activity levels and interdaily variation in these activity levels were suggested to be phenotypically related to bipolar disorder. Strengthening the circadian signal to increase the amplitude may promote stronger

circadian rhythm alignment to the light-dark cycle and have a carry-over effect on mood stability (E. Frank, Swartz, & Kupfer, 2000; Murray, Allen, Trinder, & Burgess, 2002). For example, bright light therapy has been shown to ameliorate mood, circadian and sleep symptoms and are used in the treatment and management of mood disorders (Dallaspezia & Benedetti, 2011; Goodwin, 2009; Wirz-Justice et al., 2005). At a biological level, in mice that were treated pharmacologically with lithium, an increase in circadian amplitude in locomotor activity was found (J. Li, Lu, Beesley, Loudon, & Meng, 2012). One pathway through which lithium may affects circadian functioning is through inhibition of the GSK-3β gene, a central regulator of the circadian clock (see Malhi, Tanious, Das, Coulston, & Berk, 2013; Moreira & Geoffroy, 2016 for reviews).

A pair of systematic reviews (Melo et al., 2017; Melo et al., 2016) examined the evidence for circadian disturbances in those at-risk, and with bipolar disorder. Key findings suggest that individuals with bipolar disorder, relative to controls, had more unstable (variable) sleep-wake patterns, lower total activity across the 24-hour day, and a dampened circadian amplitude in activity levels. Melo et al. (2017) argue that higher evening activity and lower levels of daytime activity may in part explain the attenuated amplitude. Melatonin and cortisol profiles (circadian-controlled hormones) also appear to be altered in those with bipolar disorder (Melo et al., 2017). In those at-risk of bipolar disorder, Melo et al. (2016) found irregular circadian rhythms, lowered amplitude, and increased sensitivity to shifting circadian rhythms relative to control groups; while one reviewed study found no difference in chronotype between those at-risk and controls (Zanini et al., 2015). Polygenetic links were also suggested with numerous circadian genes associated with risk of bipolar disorder (Melo et al., 2016). Importantly, there is evidence that the circadian disruption observed in bipolar disorder is state-dependent and responsive to treatment. For example, Nováková, Praško, Látalová, Sládek, and Sumová (2015) found that melatonin profiles were significantly altered in manic patients with higher levels of melatonin in the afternoon, compared to relatively absent afternoon melatonin levels in patients with bipolar depression and healthy controls. Further, Moon et al. (2016) observed a phase advance of seven hours in 21 (out of 26) manic patients in cortisol rhythms and biochemical *ARNTL* and *PER1* gene expression, with mixed-mania and bipolar depression having delayed acrophases of 4-5 hours,

and >6 hours respectively. Importantly phase abnormalities in all groups normalised upon recovery. In recovering patients with mania, this was accompanied by an increase in the amplitude of *PER1/ARNTL* gene expression. In sum, a disturbed circadian system and desynchronization to the external environment may be one causal pathway to the onset of bipolar disorder.

The social zeitgeber theory posits that due to the weakened integrity of the circadian system, people with bipolar disorder are particularly sensitive to the loss of social zeitgebers (Ehlers et al., 1988; Grandin et al., 2006). That is, when positive (e.g., birth of a child or new job) or negative (e.g., loss of a spouse or job) life events occur, social rhythms are disrupted in an already weakened biological clock system (E. Frank et al., 2000). These social rhythm disruptions can alter exposure to other zeitgebers, particularly light, which in turn can affect the timing, length, and quality of the sleep-wake cycle (see Section 2.1.2). According to this model, changes to light zeitgebers and subsequent sleep perturbations might trigger affective episodes (refer to Figure 1 in Grandin et al., 2006). Hirschfeld, Lewis, and Vornik (2003) found in a sample of 600 patients with bipolar disorder that 78% reported erratic sleeping and 82% insomnia or hypersomnia as a prodrome to their first bipolar disorder episode.

4.5.4   Reward and circadian rhythm dysregulation model. Alloy, Nusslock, et al. (2015) propose that the reward hypersensitivity model of bipolar disorder and the social / circadian rhythm model of bipolar disorders might be integrated to assist understanding of the interplay between the circadian and reward systems in bipolar disorder. Reward hypersensitivity towards goal-enhancing events can increase goal-directed activity and energy (Johnson, Edge, Holmes, & Carver, 2012). This hyperactivation may then interfere with the low arousal state needed for sleep onset and increase social rhythm disruptions through excessive approach motivations to the detriment of stable social patterns (such as regular meal, work, and sleep times; Alloy et al., 2017; Alloy, Nusslock, et al., 2015). In the same way, excessive reward hypersensitivity should trigger excessive deactivation of the reward system following cues of failure or loss. These cues can lead to anhedonia, decreased energy, decreased activity levels and hypersomnia (clinical symptoms of depression; Alloy, Nusslock, et al., 2015). The behavioural correlates of reward deactivation further diminish exposure to zeitgebers and social rhythm regularity. Consistent with this model, Boland et al. (2015) found in teenagers without bipolar diagnoses, high

reward sensitivity (measured by high BAS and high sensitivity to reward scores) relative to moderate reward sensitivity levels, predicted greater levels of social rhythm disruptions following BAS-activating and BAS-deactivating life events. In moderated mediation analyses, excessive reward sensitivity and more social rhythm disruptions then predicted higher levels of manic and depressive symptoms from BAS-activating and BAS-deactivating life events, respectively.

4.6   Conclusion

Throughout this chapter, three lines of evidence were presented suggesting that the circadian and reward systems may have important interrelationships. Animal studies provide evidence that genetic manipulation of circadian clock genes or neural lesioning of the SCN can alter reward seeking behaviour, including the pattern of reward circadian rhythmicity (e.g., locomotor activity) in genetically modified animals. In humans, diurnal and circadian variation has been observed in positive affect. Consistent with the evolutionary hypothesis, there is some consensus that the peak of positive affect occurs in the mid-afternoon hours, indicating the reward system is activated during daylight. From an evolutionary lens, daylight promotes success in hunting and exploring reward behaviours for diurnal species. Finally, there is strong reason to believe that dysregulation of both circadian and reward systems may interact in the emergence and course of bipolar disorder. Hypersensitivity of the reward system during goal-striving events, and, the hypersensitivity towards cues of failure or loss, may disrupt social rhythms and circadian rhythms in a vulnerable circadian system thought to exist in bipolar disorder. The present project builds on the research summarised here to broaden the investigation of circadian modulation of reward motivation in healthy populations.

Chapter 5: Positive Affect and Biological Rhythms: Interactions in General Population and Clinical Samples

5.1   Study 1: Linking Section

Byrne, J. E. M., & Murray, G. (In Press). Positive affect and biological rhythms: Interactions in general population and clinical samples. In J. Gruber (Ed.), *Oxford Handbook of Positive Emotion and Psychopathology*: Oxford University Press. Reproduced by permission of Oxford University Press, https://www.oup.com.au/

Study 1 presented a book chapter that characterised the relationship between biological rhythms and positive affect. The book chapter that Study 1 presented is currently In Press with publishers at Oxford University Press as a chapter in the Oxford Handbook of Positive Emotion and Psychopathology (edited by June Gruber). In relation to the overarching aim to advance understanding of the relationship between biological rhythm function and reward motivation, Study 1 aimed to review naturalistic prospective studies of the relationships between biological rhythms and positive affect in humans.

Study 1 is relevant to the systematic review presented in Study 4 (see Chapter 9) that has examined circadian modulation of neural reward functioning. Relative to Study 4, that reviewed fMRI studies presenting data on circadian modulation of reward motivation, Study 1 presented a broader operationalisation of reward motivation to largely psychologically-derived reward measures (namely, positive affect). Additionally, Study 1 examined relationships between both circadian and sleep functioning in relation to reward motivation. Study 1 highlighted the important interactions among biological rhythms and positive affect. As there are important interrelationships between biological rhythms and positive affect, this led to considering how sleep quality, diurnal preference and mood can be investigated psychometrically, the aim of Study 2 (Chapter 6 and Chapter 7).

5.2 Introduction

It is well known that positive affect states are influenced by temperament and life events. Emerging from the disciplines of sleep science and chronobiology, the focus of the present chapter is an under-appreciated determinant of levels of positive affect, namely, biological rhythms. We use the term 'biological rhythm' to encompass both sleep and circadian rhythm processes that are adapted to work in unison to generate a consolidated sleep phase overnight, and to optimize daytime functioning. If we define positive affect as positive emotional activation and strong engagement with the environment, we might expect that the extent of positive affect depends partly on time of day. It is equally intuitive that poor sleep might be associated with alterations in positive affect the next day. We might also predict a priori that disturbance in the interaction between biological rhythms and positive affect could be etiologically important in disorders of mood and sleep. The overarching aim of this chapter is to review burgeoning empirical research into these three intriguing interdisciplinary propositions.

The chapter has five sections. First, we briefly characterize the three major biobehavioral systems addressed in the chapter (reward, circadian, sleep). Second, we critically review emerging evidence linking circadian function to positive affect, emphasising one particular pathway (the normative circadian rhythm in reward). Third, we critically review the wide range of evidence linking sleep to positive affect, highlighting sleep quality as both a determinant and a consequence of daytime positive affect. Fourth, we review circadian and sleep involvement in mood disorders, with a focus on bipolar disorder, a psychopathology characterised by circadian and reward diatheses. Finally, we outline conclusions and directions for research in this rapidly expanding interdisciplinary domain.

5.3 Reward, Circadian, and Sleep Systems

5.3.1 Reward function and positive affect. Positive affect is commonly understood as the subjective manifestation of activation of the biobehavioural reward system. This system appears to have an adapted temporal dimension, which coordinates rhythmic engagement with the temporally-varying environment.

A family of related theories proposes that human behaviour is influenced by two fundamental motivational systems: a reward system that underpins goal-oriented engagement with the environment, and a threat or aversive system that explains

withdrawal or vigilant inaction (e.g., Carver, 2004; Corr, 2004; Davidson et al., 2002; Depue & Collins, 1999; Fowles, 1994). The reach of this "two-system" paradigm is exceptionally broad, generating research into motivation, emotion, personality and psychopathology (see reviews by Carver, 2004; Urošević et al., 2008).

There is disagreement about the full affect-level implications of reward and threat activation (e.g., Carver, 2004; Perkins, Kemp, & Corr, 2007), but it is most commonly argued that activation of the reward system is experienced as the mood state positive affect , while activation of the threat system is experienced as negative affect (Knutson et al., 2014; Watson et al., 1999). Positive affect and negative affect are reliably measured by self-report, enabling practical assessment of reward and threat activation in humans (Watson et al., 1988). Theoretical and empirical issues in the definition and measurement of positive affect are addressed comprehensively elsewhere in this volume. Here, positive affect refers to the subjective facet of human reward activation as typically measured on the Positive and Negative Affect Schedule (e.g., Watson et al., 1988) in the circadian literature, with the sleep studies reviewed here using a wider range of questionnaires to measure positive affect.

Reward functioning is dynamic, and by recognising its temporal dimension, researchers have distinguished three aspects of reward: wanting (incentive salience, a motivation towards reward-related stimuli), liking (the hedonic impact of a reward), and learning (associatively reinforcing events related to reward; Berridge & Kringelbach, 2008; Byrne & Murray, 2017a). Of these three aspects of reward behaviour, the incentive salience or motivational aspect has been most reliably linked to biological rhythms (e.g., Byrne & Murray, 2017a; McClung, 2013; Murray et al., 2009).

The neural substrate of the incentive salience or motivational aspect of reward function is mesolimbic dopaminergic pathways (Berridge, 2007; Johnson, Edge, et al., 2012). The ventral tegmental area (VTA) and the nucleus accumbens of the ventral striatum (VS) are core to the reward system. Dopaminergic projections from the VTA to the nucleus accumbens release dopamine in response to reward-related stimuli, initiating reward-seeking behaviour (D'Ardenne, McClure, Nystrom, & Cohen, 2008; Haber & Knutson, 2010). Ascending dopaminergic pathways from the VTA also innervate the medial prefrontal cortex (mPFC), anterior cingulate

cortex (ACC), and limbic areas, indicating an important functional interaction between these brain regions and reward function (Carlson, Foti, Mujica-Parodi, Harmon-Jones, & Hajcak, 2011; Wacker, Dillon, & Pizzagalli, 2009; Yu et al., 2011).

5.3.2. Circadian and sleep-wake neurobiology. Human biology is built on a 24-hour rhythm, adapted to maximize fitness in the context of a seasonally-varying 24-hour light-dark cycle (Moore-Ede, 1986b). A complex network of biological clocks (the circadian system) drives and coordinates this 'predictive homeostasis', including the most visible daily rhythm in humans: the sleep-wake cycle (Roenneberg & Merrow, 2003).

The master oscillator of the human circadian system is located in the suprachiasmatic nucleus (SCN), a $\approx$ 20,000-cell structure with cells operating autonomously and as part of a network. Within cells, self-sustained rhythmicity of this 'clock' is generated by an autoregulatory transcriptional feedback loop involving the activators CLOCK and BMAL1, and their target genes *Per1*, *Per2*, *Cry1*, and *Cry2*, whose products form a core negative-feedback repressor complex (other feedback loops are interlocked with this core process, Mohawk et al., 2012). Electrical and biochemical output rhythms of the SCN (and robustness of the SCN oscillation) arise from nonlinear dynamic interactions between individual SCN cells which themselves oscillate with different period lengths (Herzog, 2007; A. C. Liu et al., 2007). In fact, most cells of the body contain the core clock machinery of SCN cells, but have different operating parameters and tissue-specific gene expression patterns (Dibner, Schibler, & Albrecht, 2010). These peripheral oscillators are moderated by the SCN via sympathetic and parasympathetic pathways (see Mohawk et al., 2012).

A critical feature of the circadian system is its sensitivity to exogenous cues (Reppert & Weaver, 2002). The period of the endogenous rhythm generated by the SCN is slightly different to 24 hours (on average it is >24 hours in humans; Duffy et al., 2011) and is entrained to a 24-hour rhythm via external *zeitgebers* (time-givers; Czeisler et al., 1986). Light is the most prominent zeitgeber in mammals, influencing the SCN via retinal transduction mediated through a network of retinal cones, rods, and melanopsin-expressing intrinsically photosensitive retinal ganglion cells (Paul, Saafir, & Tosini, 2009). Non-photic cues may also act as zeitgebers. For example,

feeding, exercise, exogenous melatonin and social cues are non-photic cues for humans (Mistlberger & Skene, 2005).
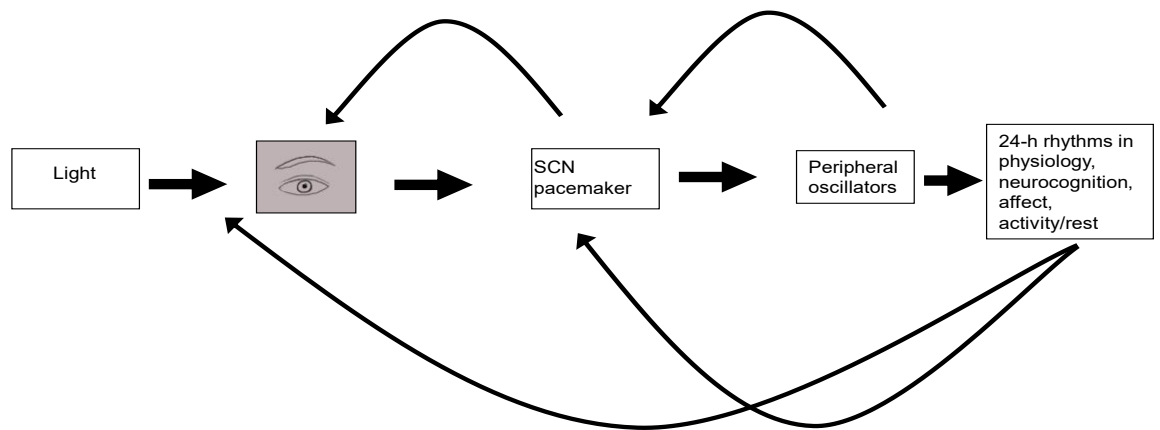
Figure 3. Schematic representation of the circadian system. SCN = suprachiasmatic nucleus. Reprinted from (Murray & Harvey, 2010) with authors' permission.

The circadian system is an archetypal multi-level biological system with multiple feedback loops (see Figure 3; Bechtel, 2013). For example, there is a feedback loop between the SCN and the pineal gland, whereby melatonin synthesis (during the subjective night in humans), is detected by receptors in the SCN (MT1 and MT2) that moderate clock resetting (Hunt, Al-Ghoul, Gillette, & Dubocovich, 2001). The SCN also sends signals that ultimately adjust its own input (Roenneberg & Merrow, 2003), for example by modulating the action of melanopsin in retinal ganglion cells (Rollag, Berson, & Provencio, 2003). Importantly for humans, volitional behaviour also feeds back into circadian function: individuals can intentionally modify their exposure to light and other environmental time cues, and thereby (at least theoretically) modify their circadian rhythms (Murray & Harvey, 2010). This fact is the basis for contemporary behavioral therapies designed to

redress circadian instability in mood disorders (e.g., Benedetti, Barbini, Colombo, & Smeraldi, 2007; Wirz-Justice et al., 2005). These therapies rely on modifying sleep and light exposure (inputs to the circadian system) to help stabilize and promote circadian realignment through a number of potential mechanisms (Duncan, 2016; Germain & Kupfer, 2008). Experimental data for this type of therapy is discussed below. Environmental factors can also modify zeitgeber information inadvertently, as seen in time zone travel, shift work and 'social jet lag' (Wittmann et al., 2006). There is growing interest in how to use behaviour to support clock function in the face of endogenous and exogenous challenges to circadian function (E. Frank et al., 2013; Juda, Vetter, & Roenneberg, 2013; Schroeder & Colwell, 2013; Serkh & Forger, 2014; Touitou, 2013).

Biological rhythmicity arising from the SCN provides an oscillatory foundation upon which the sleep system functions (L. P. Morin, 2013). Phylogenetically, sleep is a more recent and less ubiquitous adaptation than circadian rhythmicity (Rial et al., 2007). Although its specific adaptive function is debated, sleep has restorative and transformative effects on the brain and its functions (e.g., L. K. Brown, 2012; M. G. Frank, 2014; Jan et al., 2010; Verweij et al., 2014; Xie et al., 2013). Indeed, the synaptic homeostasis hypothesis proposes that sleep is necessary for brain plasticity (Tononi & Cirelli, 2014; G. Wang, Grone, Colas, Appelbaum, & Mourrain, 2011). Sleep is not a homogeneous state, but rather encompasses an organized set of stages across the night, which play different roles in sleep's restorative effects (e.g., Vyazovskiy & Delogu, 2014). For example, REM sleep is implicated in processing emotional memories (Perogamvros, Dang-Vu, Desseilles, & Schwartz, 2013; Van Der Helm et al., 2011; Walker & van der Helm, 2009).

5.3.3 **Interplay between circadian and sleep processes.** According to Borbely's widely-accepted two-process model of sleep regulation (Borbély, 1980, 1988; Borbély et al., 2016), the circadian system (Process C) regulates sleep timing and architecture in a bidirectional interaction with sleep homeostasis (Process S). Sleep homeostasis increases with wake time and dissipates with sleep. The mechanisms guiding sleep homeostasis are not well characterized, but various sleep-promoting substances, including adenosine and cytokines are implicated (R. E. Brown, Basheer, McKenna, Strecker, & McCarley, 2012; Lazarus, Chen, Urade, & Huang, 2013). Widely distributed cell groups in the brainstem, hypothalamus and

basal forebrain participate in arousing the cerebral cortex and thalamus (Saper, Scammell, & Lu, 2005; Szymusiak & McGinty, 2008). Highlighting the multifaceted interplay of circadian and sleep factors, clock genes have been consistently implicated in sleep homeostasis (Dijk & Archer, 2010; P. Franken, 2013; P. Franken, Thomason, Heller, & O'Hara, 2007).

Circadian function moderates timing of the sleep/wake cycle, but there is strong evidence that changes to sleep also impact circadian function (L. P. Morin, 2013). For example, six hours of sleep deprivation in rats decreases SCN neuronal activity (Deboer, Detari, & Meijer, 2007), advancing sleep wake schedules in young adults alters circadian gene expression (Y. Zhu et al., 2013), and SCN firing rates reliably alter with sleep stage (Deboer, Vansteensel, Detari, & Meijer, 2003). Most strikingly, Moller-Levet and colleagues (2013) used blood transcriptome analysis to demonstrate that one week of insufficient sleep moderates the circadian expression profile of numerous genes, including canonical clock genes (see also comparable conclusions by Archer et al., 2014; S. K. Davies et al., 2014). Brain regions subserving homeostatic influences on circadian function include the medial preoptic area anterior hypothalamus ('suprachiasmatic area'), and orexin/melanin concentrating hormone areas in the posterior lateral hypothalamus (Deurveilher & Semba, 2005; Gaggioni, Maquet, Schmidt, Dijk, & Vandewalle, 2014).

In sum, periodicity in humans is primarily orchestrated through a system of endogenous self-sustained ≈ 24-hour rhythms. The sleep-wake cycle is a highly visible output rhythm of the circadian system, but sleep disruption can also affect core circadian function. Although the system's master oscillator is located deep in the brain, biological rhythms are highly responsive to the person's volitional behaviour and environmental influences.

5.4   Circadian Modulation of Reward Function and Positive Affect

Both circadian function and reward function are grounded in complex systems operating across multiple levels, with significant reach into brain, mind and behaviour (Cromwell & Panksepp, 2011; P. S. Davies, 2011; Panksepp, Asma, Curran, Gabriel, & Greif, 2012). Consequently, mechanisms linking circadian and reward function are legion (McClung, 2013), and disciplines from molecular biology (e.g., Chung et al., 2014) to behavioral psychology (e.g., Bullock et al., 2017) have been involved in their investigation. Even at the level of predictors of self-reported

positive affect, it is important to appreciate that the circadian system has been demonstrated to impact positive affect *traits* (e.g., Biss & Hasher, 2012; DeYoung, Hasher, Djikic, Criger, & Peterson, 2007; Grierson et al., 2016), as well as positive affect *states* (e.g., circadian amplitude and state wellbeing, Schroeder & Colwell, 2013). We will review some of those mechanisms below when considering the impact of circadian rhythms and sleep on mood disorders. Here, we focus on one specific pathway that has received substantial attention in human research and speaks directly to an under-appreciated determinant of *momentary* positive affect.

5.4.1 **The circadian reward rhythm.** The reward potential of the environment varies with the light/dark cycle, and being primed to engage with the environment when the likelihood of reward is high (daytime for diurnal species) enhances an organism's fitness (Murray et al., 2009). In all species, the endogenous circadian system is adapted for this purpose. It has therefore been hypothesised that the human reward system is not only reactive to external cues, but is also moderated by timing information from the circadian system (Clark et al., 1989). We briefly review animal research consistent with this circadian rhythm in reward (or Circadian Reward Rhythm, Murray et al., 2015) before summarising human research demonstrating a circadian rhythm in positive affect.
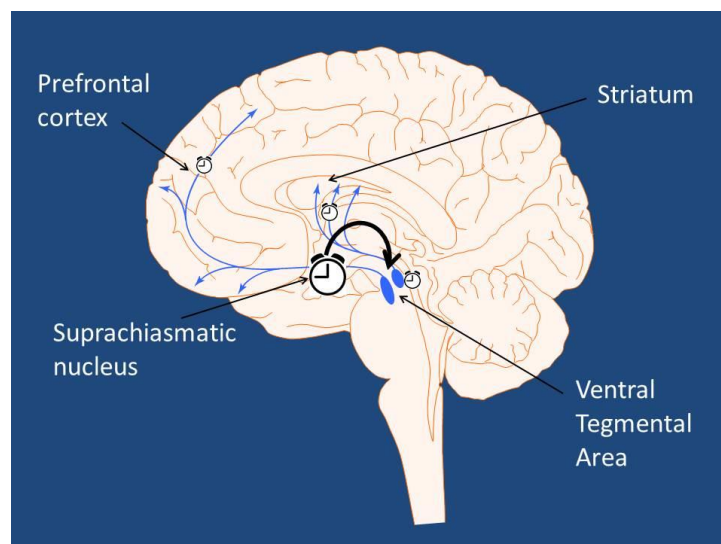
Figure 4. Circadian modulation of reward via indirect pathways from SCN to VTA (black arrow) and via gene expression in reward centres (small clock icons). Ascending dopaminergic pathways shown in blue.

In mammals, real-time reward-related behaviour varies in a daily rhythm. For example, rats and primates self-administer drugs of abuse at a greater rate during their typical active period (Baird & Gauvin, 2000). In golden hamsters, reward-conditioned place preference is observed only when it is investigated at the same time of day as prior training (Cain, McDonald, & Ralph, 2008). Key reward centres have also been shown to exhibit diurnal or circadian rhythms in dopamine transporters, clearance, synthesis and metabolites (Sleipness et al., 2007b). At the level of genotype, a range of circadian gene mutations generates abnormal reward phenotypes in drosophila and mice (McClung, 2011).

Animal research suggests that the circadian system impacts dopaminergic reward motivation via two types of mechanism (Figure 4). First, mesolimbic circuitry is under local regulation by circadian gene expression. Circadian gene expression in reward pathways is a mediator of diurnal changes in dopaminergic transmission and daily patterns of cocaine-seeking behaviour (Webb, Baltazar, Lehman, & Coolen, 2009), and circadian rhythmicity of clock gene expression has been demonstrated in the striatum, VTA, amygdala and PFC (Ángeles-Castellanos, Salgado-Delgado, Rodríguez, Buijs, & Escobar, 2008; Webb, Baltazar, Wang, et al., 2009). Second, timing information from the SCN reaches the VTA through indirect pathways, including the medial preoptic nucleus and orexinergic neurons in the hypothalamus (Deurveilher & Semba, 2005).

5.4.2 Circadian rhythm in positive affect. It has been known for some time that positive affect exhibits daily changes under naturalistic settings, a normative diurnal rhythm (e.g., Clark et al., 1989; Murray, Allen, & Trinder, 2002). Under naturalistic conditions, positive affect peaks in the early afternoon, plateaus, and then declines in the late evening (Stone et al., 2006; Watson et al., 1999). Of course a measured daily rhythm in behaviour may not be of endogenous circadian origin – an observed pattern could be a reaction to rhythmic features of the social and physical environment (Moore-Ede, 1986b).

Our group used a series of linked investigations to test whether the daily rhythm in positive affect has an endogenous circadian component (Murray et al.,

2009). Under naturalistic conditions, a 24-hour sinusoidal curve with a peak in the early afternoon explained 13.0% of variance in positive affect. In a constant routine laboratory protocol (controlling for exogenous impacts on core body temperature for 30 hours), 25.0% of positive affect variance was explained by the unmasked circadian rhythm in core body temperature. In a novel forced desynchrony study (which dissociates the endogenous 24-hour rhythm from an enforced 28-hour lifestyle in an 8-day laboratory protocol), positive affect aligned with core body temperature to exhibit circadian periodicity independent of the 28-hour sleep/wake cycle, as did a psychophysiological measure of reward system activation (Figure 5). Significantly, circadian variation is not limited to the arousal components of positive affect, as a circadian rhythm has been demonstrated in self-report measures of happiness/positive valence (Boivin et al., 1997; Murray et al., 2009). The project provides strong evidence for circadian priming of the human reward system, extending on animal research by demonstrating the moderation effect in subjective positive affect and related positive mood states.
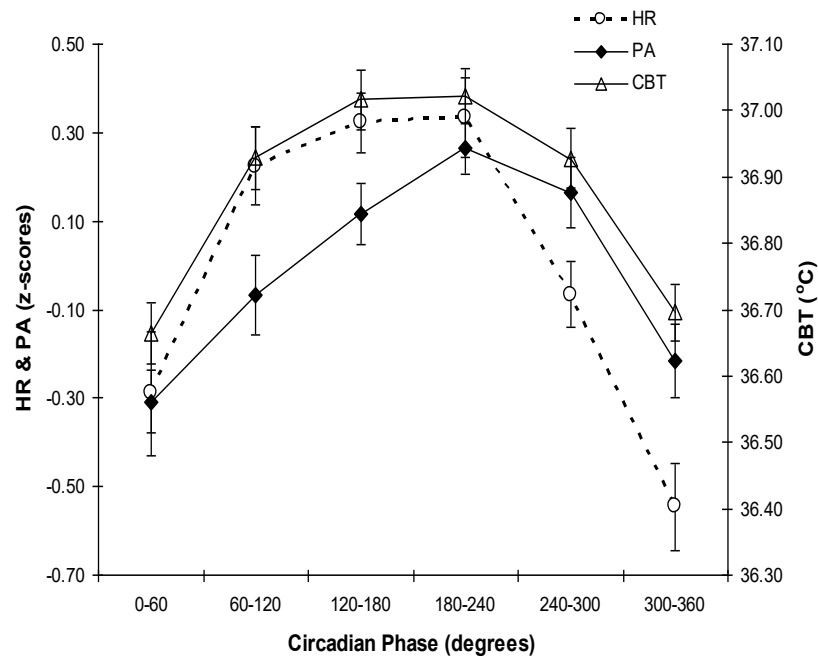
Figure 5. Mean (SEM) positive affect (PA), heart rate during a gambling task (HR), and core body temperature (CBT) plotted against circadian phase. Reprinted from Murray et al. (2009) with authors' permission.

Reliable evidence for a circadian component to positive affect variation in humans is consistent with the notion of a Circadian Reward Rhythm. Hasler and colleagues (2014) conducted a pilot fMRI study of the neural basis of the hypothesised circadian rhythm in reward, finding support for a daily rhythm in activation of the striatum to a reward task. Relative to the morning scan, in the afternoon participants had a stronger neural response to reward stimuli in the ventral striatum. This study offers novel findings into the neural mechanisms of diurnal changes in reward seeking; consistent with evidence for a circadian rhythm in positive affect. The notion of a circadian rhythm in reward with positive affect variation as a primary index, is currently being explored in models of mood psychopathology. Hasler and colleagues, for example, have shown that individual differences in circadian phase may influence psychopathology via moderation of the Circadian Reward Rhythm (Hasler, Allen, Sbarra, Bootzin, & Bernert, 2010; Hasler, Germain, et al., 2012; Hasler, Smith, Cousins, & Bootzin, 2012; M. A. Miller et al., 2015).

5.5   Sleep and Positive Affect

This section considers the many ways that sleep and daytime positive affect may be related with potential mechanisms for this relationship discussed. Measurement is a key issue in this multidisciplinary area, and is briefly reviewed before moving on to evidence for various types of relationship between sleep and positive affect.

In the sleep literature, sleep is objectively measured through polysomnography (in sleep laboratories) or through wearable devices (actigraphy) (Ancoli-Israel et al., 2003; Kushida et al., 2005). These methods generate data on a variety of sleep parameters including: total sleep time; sleep latency (time taken to fall asleep); REM sleep latency; wake after sleep onset; sleep efficiency; sleep architecture; and, night-time movements (Kushida et al., 2005). More commonly in the literature reviewed here, sleep has been subjectively measured through questionnaires. Studies have largely measured subjective sleep through sleep quality and / or sleep duration. Sleep quality has been measured through either single-item questions (often recorded in daily sleep diaries) or as a composite score on questionnaires. Commonly used self-report questionnaires such as the Pittsburgh Sleep Quality Index derive a single score of sleep quality from an amalgamation of

sleep parameters: subjective sleep quality; sleep latency; sleep duration; sleep efficiency; sleep disturbances; daytime dysfunction; and, medication use (Buysse, Reynolds III, Monk, Berman, & Kupfer, 1989). Sleep duration is subjectively reported as an estimate of total hours slept, or recorded in sleep diary logs where participants list daily bed and wake times. Self-reported sleep diaries often include other estimates of objectively measured sleep such as sleep latency, wake after sleep onset, and variability of sleep times (Carney et al., 2012); however these individual facets are not widely considered in their relationship with positive affect.

The majority of studies to date have attended to sleep's putative moderation of daytime positive affect. We will focus largely on cross-sectional and prospective studies that have used self-report ratings for measuring sleep quality, sleep duration, and positive affect. In addition, a handful of experiments have investigated how restricting sleep (either partial or full sleep deprivation), increasing sleep (extended sleep periods and napping), and how sleep disorders (particularly insomnia) may moderate positive affect. Next, the possible influence of daytime positive affect on night-time sleep quality is considered with particular reference to nonclinical groups showing high positive affect (intense romantic love) and also experimental studies aimed at increasing positive affect before sleep. Finally, we review the small number of prospective studies directly testing for bi-directional relationships between sleep and positive affect.

5.5.1 Sleep as a moderator of positive affect. Several studies have examined the effects of sleep on positive affect using cross-sectional self-report, naturalistic prospective, and experimental (sleep restriction and nap) protocols (see Table 2). Broadly, findings across a range of methods and populations align with the common sense expectation that poor sleep is associated with low positive affect the next day.

Table 2

Key Studies Examining Sleep's Impact on Positive Affect

Study	Study type	Sample demographic				Measure used		Main findings in relation to positive affect
		Clinical/non-	Gender	N	Age	Positive affect	Sleep/ circadian	
ECOLOGICAL MOMENTARY ASSESSMENT STUDIES								
Bower et al. (2010)	3 days, 10 x daily measures	Major depressive disorder, *n*=35 Minor depression *n*=25, controls *n*= 36	75.3% F	96	28.2 (9.24)	Rating adjectives 1-100: talkative, enthusiastic, confident, cheerful, energetic, satisfied, happy	PSQI	Individuals with depression had worse sleep quality (overall PSQI score) and lower daytime PA. Of the PSQI components subjective sleep quality and daytime dysfunction were the best predictors of PA. Aside from habitual SEf, all PSQI components related to PA.
Buysse et al. (2007)	1 week, 4x per day measures (wake-up, noon, 6pm, bedtime)	Clinical and controls: primary insomnia (PI) *n*=47, good sleep controls (GSC), *n*=18	PI: 25 F GSC: 15 F	65	PI: 35.9 (9.6) GSC: 27.2 (7.9)	Daytime insomnia symptom scale: positive mood subscale (relaxed, energetic, calm, happy, efficient)	PSQI, ESS; Pittsburgh Sleep diary (scored 0-100)	PI had lower means scores on positive mood compared to GSC. Positive mood was negatively related to PSQI score, and positive related to sleep diary sleep efficiency.
Fortier et al. (2015)	2 weeks, once daily	Working mothers	100% F	63	42.6 (5.61)	PANAS	Overall sleep satisfaction 7-point	Higher levels of sleep satisfaction was related to higher levels of next day PA (only contributed 1.4% of variance). When physical exercise was included in the model sleep became non-significant.
Lemola et al. (2013)	1 week (mood measured retrospectively looking once in past week)	Non-clinical, looking at white (W) and African American (AA) well-being in Midlife in US	55.3% F (white sample) 72.7% F (AA sample)	441	57.65 (11.8, W) 54.89 (10.28, AA)	Satisfaction with life Scale, high PA on Mood and Anxiety Symptom Questionnaire (MASQ)	Actigraphy, PSQI	Poor subjective sleep quality predicted lower subjective wellbeing. Variability of TST was negatively related to subjective well-being (as measured by satisfaction of life and MASQ), after Bonferroni correction this was non-significant. Variability in sleep duration and well-being was partially mediated by subjective sleep quality.
Levitt et al. (2004)	1 week 4x per day (morning, midday, 5pm, bedtime)	Insomnia and age-matched controls	PI (6F) control (7F)	15 (7PI)	PI 24.1 Control 23.3	Daytime symptom diary 20 VAS (mood, subjective	PSQI	The control group reported significantly higher mood, subjective alertness, energy and concentration in the morning compared to insomnia group. The control group also reported higher subjective alertness and energy at

Study	Study type	Sample demographic				Measure used		Main findings in relation to positive affect
		Clinical/non-	Gender	N	Age	Positive affect	Sleep/ circadian	
						alertness, energy & concentration)		midday, but this was non-significant (study had a small sample size; correlations had large correlation coefficients (~.6) but were not significant)
McCrae et al. (2008)	2 weeks, once daily each morning	Older adults		103	72.81 (7.12)	PANAS (completed each morning)	Actigraphy, Sleep diaries (total wake time and subjective sleep quality)	Higher sleep quality and lower subjective wake time (but not objective) was associated with higher PA within individuals. Less subjective wake time was associated with higher PA across individuals.
Tavernier & Willoughby (2015)	Survey once annually for three years	Enrolled, university students	71.5% F	942	19.01 (.90)	Difficulties with emotion regulation scale, student adaptation to college questionnaire (social ties)	ISI, self-report sleep duration for weekday and weekend, weekend delay, and oversleep (calculated from bed and wake-times)	Sleep problems at T1 and T2 were related to social ties at T2 and T3 respectively; and, social problems at T1 and T2 were related to sleep problems at T2 and T3 respectively. No other sleep variables were significant. A significant mediating effect of emotional regulation was found with a significant indirect path found between sleep problems (T1) and social ties (T3) through emotional regulation (T2), and, between social ties (T1) and sleep problems (T3) through emotional regulation (T2).
Scott & Judge (2006)	3 weeks daily survey (Monday-Friday) near end of work day	Employees	36 F	45	34.9 (11.8)	PANAS-X	Insomnia scale (Jenkins) 5-point scale, measuring problems with sleeping	Insomnia was positively related to fatigue, and negatively related to joviality and attentiveness.
Zohar et al. (2005)	3x per day for 3 days	Non-clinical medical residents	33% F	78	26-39	PANAS, POMS (fatigue)	Actigraphy for sleep duration and sleep diary for sleep fragmentation during night shifts	Longer sleep duration lead to elevated PA following goal-enhancing events. Short sleepers were not significantly affected by goal-enhancing events. Shorter sleep had a higher PA level than long sleep.
CROSS-SECTIONAL STUDIES								
Bixler et al. (2005)	Cross-sectional	General population, oversampled people with sleep disordered breathing	1000 F	1741	20-100	Diagnosis or treatment for depression	1 night PSG, excessive daytime sleepiness	Report of depression treatment is the most significant risk factor in reporting excessive daytime sleepiness. The effect of depression on daytime sleepiness was more pronounced in younger individuals.

Study	Study type	Sample demographic				Measure used		Main findings in relation to positive affect
		Clinical/non-	Gender	N	Age	Positive affect	Sleep/ circadian	
Fortunato & Harsh (2006)	Cross-sectional	Non-clinical undergrad students	347 F	467	21.3 (5.15)	Positive affectivity (Sociability-free PA scale)	Sleep quality (CSWS)	High PA correlated with ease of falling asleep, maintaining sleep, reinitiating sleep and waking up. For individuals low on PA the ability to fall asleep and return to sleep decreased with increasing interpersonal conflict, for those high in PA increases in job ambiguity made it more difficult to wake up.
Fredman et al. (2014)	Cross-sectional	Non-clinical 92 caregivers, 137 non-caregivers over 60	69% F	229	60-97 73.8 (7.9)	PA (CES-D), categorized into high and low PA, and depressive symptoms	Sleep quality and duration (PSQI)	In caregivers, PSQI scores were an average of 4.48 for individuals with high PA, 5.59 for those with low PA, and, 6.79 for those with depressive symptoms. In non-caregivers there was no relationship between PA and sleep problems.
Garcia et al. (2012)	Cross-sectional	Non-clinical, high school students	121 F	304	17.34 (1.16) 16-19	PANAS	Sleep problems (Uppsala Sleep Inventory)	Individuals who were self-fulfilling (high PA and low NA) had less sleep problems and difficulties falling asleep compared to those high affective (high PA and NA), and self-destructive (low PA and high NA) individuals. Those who were low affective (low PA and NA) had more sleep problems than self-fulfilling.
Gray & Watson (2002)	Cross-sectional	Non-clinical, first year college	213 F	334	19.2 (1.8) 18-21	General temperament survey, PANAS	Sleep quality and duration (PSQI, sleep questionnaire, retrospective sleep log, sleep log)	Subjective sleep inefficiency and PSQI were negatively related to PA and positive temperament. Positive temperament was also negatively related to rise time.
Jackowska et al. (2012)	Cross-sectional, 2 days sleep and mood data (one leisure, one work day), sessions started at 5pm	Non-clinical employed (mainly at the university)	100% F	199	33.8 (9.3) 18-65	Positive affect (self-report items)	Sleep problems (Jenkins Sleep Problems Scale)	Positive affect in the evening and on workdays was negatively related to sleep problems.
Jackowska et al. (2011)	Cross-sectional, 2 days sleep and mood data (one leisure, one work day), sessions started at 5pm	Non-clinical employed (mainly at the university)	100% F	199	33.8 (9.3) 18-65	Happiness scale (four items)	Sleep efficiency, actiheart monitor	There was a higher self-reported sleep efficiency among happier people, with no relationship between objective sleep efficiency and happiness.

Study	Study type	Sample demographic				Measure used		Main findings in relation to positive affect
		Clinical/non-	Gender	N	Age	Positive affect	Sleep/ circadian	
Kelly (2002)	Cross-sectional	Non-clinical undergraduate students	86 F	135	18-57 23.9 (8.1)	Humor (MSHS)	Sleep disturbance (SAW)	Negative relationship between sleep disturbance attributed to worry and humor production
MacDonald & Kormi-Nouri (2013)	Cross-sectional, asked to recall autobiographical memories coded as positive, negative or neutral	Non-clinical college students	63% F	313	23.28 (4.27) 19-46	PANAS	Insomnia (ISI)	PA was negatively associated with the ISI. High PA and low NA was associated with lower insomnia symptoms than low PA and NA, and, low PA and high NA individuals.
Ng & Wong (2013)	Cross-sectional	Clinical – chronic pain	57% F	224	45.66 (9.84) 19-61	Gratitude (GQ-6)	Sleep quality and duration (PSQI)	Higher gratitude was significantly related to better sleep. Poorer sleep quality was associated with more depressive symptoms
Norlander et al. (2005)	Cross-sectional	41 stress-related patients, 50 non-clinical	74 F	91	10% <30, 61.5% 31-50, 28.5% >50	PANAS	Sleep quality (self-report)	High PA and low NA individuals had better sleep quality than high NA and low PA individuals.
Ryff et al. (2004)	Cross-sectional	Non-clinical	100% F	135	61-91	Eudaimonic wellbeing (positive r/ships, purpose in life, environmental mastery, self-acceptance personal growth)	REM sleep, sleep duration (Nightcap eye sensor)	More body movement was related to less positive relationships and lower life purpose for >75year olds. More time in bed, longer sleep duration and more REM sleep was positively related to scores on environmental mastery (>65 year olds) and shorter time to first REM period was related to more environmental mastery in >75 year olds. Positive relationships were related to more REM sleep in >75 year olds.
Stewart et al. (2011)	Cross-sectional	Non-clinical college students	75%	224	23.4 (6.1)	PANAS (PA)	Sleep quality and duration (PSQI)	Higher PSQI scores were related to lower levels on PA. When anger, anxiety and depression were controlled for, the path between PA and sleep quality was not significant.
Sunderajan et al. (2010)	Cross-sectional	Clinical – adult outpatients with non-psychotic MDD,	With insomn ia sympto	3743	18-75	IDS-C$_{30}$ – has items pertaining to pleasure, energy, involvement,	IDS-C$_{30}$ – insomnia symptoms over past week	85% of MDD sample had insomnia symptoms, 27% of people with insomnia symptoms had sleep onset, mid-sleep and early morning insomnia symptoms. Patients with insomnia symptoms were more sad, irritable, anxious,

Study	Study type	Sample demographic				Measure used		Main findings in relation to positive affect
		Clinical/non-	Gender	N	Age	Positive affect	Sleep/ circadian	
		ms 61% F, without 63% F				outlook for self and future		reactive mood, and experienced less pleasure, energy and involvement compared to MDD without insomnia symptoms. After Bonferroni correction only anxious mood was significantly related to insomnia symptoms.
Troxel et al. (2009)	Cross-sectional	Non-clinical mid-life women	100% F	1938	45.8 (2.71)	Marital happiness (DAS)	Sleep disturbance (Women's Health Initiative Insomnia Rating Scale)	Higher marital levels were associated with fewer sleep disturbances after controlling for other covariates (e.g., social roles, sexual activity).
EXPERIMENTAL SLEEP DEPRIVATION								
Alfarra et al. (2015)	Experimental sleep restriction, baseline testing session two days later with SD or without SD	Non-clinical, healthy right-handed	40% F in control 50% F in SD	20, 10 in SD	23 (3.97) 21 (2.80)	EEG (testing between 7-9am), valence ratings to IAPS images	Overnight sleep deprivation protocol (from 7pm until testing following morning)	From the EEG results, positive and negative images elicited larger late positive potential (LPP) amplitude (outside of SD). LPP amplitude decreased after SD to emotional pictures (non-significant), and significantly increased LPP amplitude to neutral images. Negative images were rated as significantly less negative following SD.
Baum et al. (2014)	Randomized, cross-over study experimental sleep restriction, 3-week sleep study (baseline, 6.5 hrs for 5 nights, 10 hrs for 5 nights)	Non-clinical, healthy adolescents	50% F	50	14-17.9	POMS, Emotion Control subscale of the parent- and self-report Behavior Rating Inventory of Executive Functioning	Sleep manipulation Monday-Friday with a two-day weekend washout before cross-over (sleep restriction 6.5 hours, and healthy sleep 10 hours). Also completed 5-night sleep baseline	Compared to healthy sleep, participants during the restricted sleep experienced higher levels of irritability, lower levels of vigor, and more emotion regulation problems.
Cote et al. (2014)	Experimental sleep restriction, random assignment to sleep or 31.5h wakefulness	Non-clinical, good sleepers, with consistent sleeping pattern	12 F control, 13 F SD	49, 25 in SD	18-30 ~19.24 control, ~19.85 SD	Face processing tasks of happy, sad, angry and fearful faces at 100% emotional intensity or morphed faces; event-related potentials (N170)	Overnight sleep deprivation	No differences between SD and control in accuracy for the full intensity face task or morphed face task for happy faces. No difference in RTs between groups for full intensity, but RTs to happy faces were slower for SD group compared to controls. When a mistake was made on recognizing sad, fearful, or angry faces for full intensity, SD participants were significantly more likely than controls to incorrectly categorize it as a happy face; for

Study	Study type	Sample demographic				Measure used		Main findings in relation to positive affect
		Clinical/non-	Gender	N	Age	Positive affect	Sleep/ circadian	
								morphed faces incorrectly categorizing as happy was present when making a mistake on angry or fearful trials. N170 responses were not different between groups in response to happy faces.
Dinges et al. (1997)	Experimental, sleep restriction ~5 hrs per night for 7 nights, baseline 2 nights, 1 recovery	Non-clinical, healthy young adults	50% F	16	22.9	POMS, VAS	MSLT, SSS, PVT	Vigor declined from baseline to day 7 of sleep restriction after adjusting for tiredness. Higher scores were seen on all POMS subscales except for anger and depression with 7-day sleep restriction.
Guadagni et al. (2014)	3 groups randomly assigned (SD, sleep, and day) all tested twice	Non-clinical, healthy volunteers	22 F	37 (13 SD)	22.05 (4.08)	Multifaceted emotional empathy test created using IAPS images; interpersonal reactivity index	Sleep deprivation, SD group tested 9pm and 8am, sleep group 6pm and 10am, day group 10am and 6pm	Those in SD group had less capacity to share emotional experiences following sleep deprivation compared to those in the day or sleep group, in both direct (how strong is the emotion you feel about this person) and indirect (how calm/aroused does the picture make you feel). Ratings of valence of images did not differ between groups.
Haack & Mullington (2005)	Experimental SD, 10 night study, 8 hr sleep or 4 hr sleep (11pm-3am)	Non-clinical	14 F	40, 22 in SD	26.3 (4.9)	Deactivation Activation check list and POMS	Actigraphy in controlled sleep conditions	A linear decrease was seen in the optimism-sociability factor across the nine experimental days, following a night of recovery sleep this was not significantly different to the sleep control.
Kahn-Greene et al. (2006)	Experimental SD including baseline. NB: caffeine administered as part of larger study	Healthy military volunteers	5 F	26	25.3 (4.1)	Responses to Rosenzweig picture-frustration study and bar-on emotional quotient inventory (completed before and after SD)	55-hours continual wakefulness	Following SD participants tended to be more punitive (directing blame or hostility) relative to rested baseline. Post-SD there were less attempts to solve interpersonal problems in the picture variables. Trait emotional intelligence factors altered resilience to SD. Those with lower happiness were less accepting of blame following SD, and higher trait optimism were more likely to deny the presence of frustrating situations following SD.
Killgore et al. (2008)	Experimental SD including baseline. NB: caffeine administered as	Healthy military volunteers	5 F	26	25.3 (4.1)	Constructive thinking inventory, bar-on emotional quotient inventory (completed before and after SD)	55-hours continual wakefulness	Following SD participants declined in levels of self-regard, assertiveness, independence, self-actualization (Intrapersonal subscale of bar-on), empathy, and interpersonal relationships (Interpersonal subscale of bar-on). No differences were found between baseline and SD between Happiness and Optimism subscales of the bar-on.

Study	Study type	Sample demographic				Measure used		Main findings in relation to positive affect
		Clinical/non-	Gender	N	Age	Positive affect	Sleep/ circadian	
	part of larger study							Higher scores during SD conditions on the Defensive subscale of the Constructive thinking inventory suggests tendency to present an unrealistically positive self-description. The decline in Behavioral Coping during SD was driven largely by decreases in Positive Thinking and Action Orientation components. No difference in Emotional Coping, Categorical Thinking or Naïve Optimism subscales.
Maccari et al. (2014)	Experimental, SD, baseline and following SD counter-balanced	Non-clinical, (7.5-8.5h sleepers, 7.30 +/- 60 mins wake time)	15 F	18	24.28 (2.30)	Face (4 negative and 4 positive facial expressions) and word stimuli (4 negative and 4 positive words)	24 hours of wakefulness	No differences in RTs to positive facial expressions between SD and baseline. Following SD, participants were significantly slower to respond to positive words compared to baseline. More errors were present in recognizing positive faces and words following SD.
Motomura et al. (2013)	Experimental, 5 days of SD (4 hrs sleep), 5 days 8 hrs sleep, fMRI imaging on last day of each condition	Non-clinical	100% M	14	24.1 (3.3)	POMS, different valence faces	PSG (days 4 and 5 of each session), SSS	Restricted sleep increased activity of left amygdala to facial expression and a decrease in connectivity between amygdala and ventral anterior cingulate cortex as a function of degree of sleep debt (as measured by PSG). No effects of sleep condition was seen on POMS scores but more tension-anxiety and confusion was related to less connectivity between the amygdala and ventral anterior cingulate cortex
Paterson et al. (2011)	Experimental, 1 night SD, 2 night SD and 1 or 2 night normal sleep control	Non-clinical healthy young adults	25 F	62 (23, 2 night SD, 20 1 night SD, 19 control)	22.4 (18-33)	Mood Scale II (Walter Reed Performance Assessment Battery); 36 mood related adjectives	Sleep restriction paradigm (sleep diaries were used week prior to ensure bedtime between 2200-2400 and wake between 7-9am	Within subjects, there were lower happiness, activation levels and greater fatigue compared to baseline for both SD groups.
Talbot et al. (2010)	Experimental, (maximum 6.5 hours sleep night 1, max. 2 hours sleep night 2, rest	Non-clinical looking at sleep in different ages, young and mid-	Early ad. 10 F, mid ad. 9 F,	64	20 (10-13) 24 (13-16) 20 (30-60)	PANAS-C	SSS, actigraphy	Participants reported lower PA when sleep deprived. All PA items were significant at the item level except for calm, when multiple comparison corrections were applied joyful and lively were also non-significant. There was no effect of age-group.

Study	Study type	Sample demographic				Measure used		Main findings in relation to positive affect
		Clinical/non-	Gender	N	Age	Positive affect	Sleep/ circadian	
	night 3 & 4 (7-8 hours sleep)	adolescents, and adults	adults 10 F					
Taub & Berger (1973)	Experimental, 5 different sleep conditions, each condition separated by one week of normal sleep	Non-clinical, healthy	100% M	10	19.6, 19-24	AD-ACL	Sleep conditions: Habitual sleep (12-8am), 5 hours (3-8am), 11 hours (9pm-11am), advanced sleep (9pm-5am), delayed sleep (3am-11am)	Mood was more depressed after sleep deprivation than sleep extension. Anger and hostility was higher after sleep extension and deprivation than advanced and delayed sleep.
Tempesta et al. (2015)	Imaging – emotional memory	Poor sleepers (PS); good sleepers (GS), GS divided into SD one night total sleep deprivation and sleep as normal	GS 16F, PS 8F, SD 12F	PS= 21, GS= 31, SD= 23	GS 21.68 (.93)	IAPS 90 images (divided into 30 of each stimulus type), at recall 1 & 2, 45 'old' images shown, 30 new images (10 of each type), rated valence, arousal and memory for image	Actigraphy	After SD the valence for positive images was lower compared to GS. Valence for neutral images was lower for both PS and SD compared to GS, indicating images were evaluated more negatively.
van der Helm et al. (2010)	Experimental, sleep control or total sleep deprivation	Non-clinical	21F	37	19.7 (.91) 18-25	Neutral to positive emotion faces with increasing intensity of emotion	Sleep deprivation	Following sleep deprivation there was significant impairment in ability to recognize happy facial expressions, this was particularly for the mid-range emotionally ambiguous faces. With increasing intensity or neutrality difference between sleep deprivation and control are no different.
Yoo et al. (2007)	Experimental fMRI, sleep deprivation, 35 hours of SD	Non-clinical healthy	13 F	26, 14 Sleep dep	24.1 (2.3)	Neutral to increasingly negative stimuli	Sleep deprivation	Amygdala activation was 60% greater in SD condition, significantly stronger connectivity in rested condition between the amygdala and medial pre-frontal cortex.
EXPERIMENTAL NAP STUDIES								
Berger et al. (2012)	Experimental, within: Nap and No-nap with 5	Non-clinical, healthy children	7 F	10	30-36 months old	IAPS images, solvable and unsolvable task –	Nap / No-nap condition from 3-4pm, actigraphy to	In the solvable puzzle condition, during the no-nap condition children displayed 34% less positive emotions (joy and pride) and more confusion than when rested.

Study	Study type	Sample demographic				Measure used		Main findings in relation to positive affect
		Clinical/non-	Gender	N	Age	Positive affect	Sleep/ circadian	
	days strict sleep schedule (>12.5 hrs sleep, p/ 24hrs) in between conditions (11 day study)					coding of children's facial expression	confirm sleep compliance	Children had a non-significant trend (p=.051) towards a more positive response towards positive pictures.
Birchler-Pedross et al. (2009)	Experimental: 2, 40 hr constant routine protocol 1-3 weeks apart in dim light, condition 1: total sleep deprivation, condition 2: multiple naps	Non-clinical, healthy younger and older	50% F	32	Young: 25.0 (3.3) 20-31 Older: 65.0 (5.5) 57-74	Mood, tension and physical comfort on VAS, at 30 min intervals	8-hr PSG, constant routine protocol	Wellbeing was lower in older participants during sleep deprivation than in the nap condition. There was an age x gender interaction with young men's subjective wellbeing not affected by rising sleepiness but young and older women having lower mood in the evening. Subjective wellbeing had the highest correlation with subjective sleepiness, explaining 20% of variance in wellbeing.
Luo & Inoué. (2000)	Experimental: daytime nap	Non-clinical healthy young adults	50% F	8	29.5 (2.6), 27-35	Emotion spectrum analysis method (cross correlation coefficients of multichannel EEG)	Nap condition – max 60 minutes	Anger, joy and relaxation were significantly higher post-nap. Joy was significantly higher post-nap compared to pre-nap, stage 1 and stage 2 sleep. Relaxation was higher post-nap than during stage 1 sleep.

Note. Abbreviations: AD-ACL = Activation-Deactivation Adjective Check List; CES-D = Center for Epidemiological Studies Depression Scale; DAS = Dyadic

Adjustment Scale; EEG = Electroencephalogram; ESS = Epworth Sleepiness Scale; F = Female; GSC = Good sleep control; GQ-6 = Gratitude Questionnaire Six-

Item Form; IAPS = International Affective Picture System; IDS-C_{30} = Inventory of Depressive Symptomatology–Clinician-rated; ISI = Insomnia Severity Index;

MDD = Major depressive disorder; MSHS = Multi-Dimensional Sense of Humor Scale; MSLT = Multiple Sleep Latencies Test; PA= Positive affect; PANAS =

Positive and Negative Affect Scales; PI = Primary insomnia; POMS = Profile of Mood States; PVT = Psychomotor Vigilance Test; PSG = Polysomnography;

PSQI = Pittsburgh Sleep Quality Index; REM = Rapid eye movement; RTs = Reaction times; SAW = Sleep Disturbance Ascribed to Worry Scale; SD = Sleep

deprivation; SSS = Stanford Sleepiness Scale; VAS = Visual analogue scale

A large number of cross-sectional studies point to a positive correlation between poor sleep quality and lowered indices of positive mood, including gratitude (Ng & Wong, 2013; Wood, Joseph, Lloyd, & Atkins, 2009), eudaimonic wellbeing (Ryff, Singer, & Love, 2004), life satisfaction (Pilcher, Ginter, & Sadowsky, 1997), humour (Kelly, 2002) and more specific positive affect scales (Buysse et al., 2007; Fuligni & Hardway, 2006; Lemola, Ledermann, & Friedman, 2013). Correspondingly, better night-time sleep quality has reliably been shown to predict positive affect the following day (de Wild-Hartmann et al., 2013; F. Jones & Fletcher, 1996; Kalmbach, Pillai, Roth, & Drake, 2014; Kouros & El-Sheikh, 2015; Simor, Krietsch, Köteles, & McCrae, 2015; Totterdell, 1994; van Zundert, van Roekel, Engels, & Scholte, 2015). In sum, there is strong support for sleep quality moderating next day positive affect.

It should be noted that half of these studies used a single time-point of data collection for both sleep and mood measures, a potentially important confound. Some of the authors acknowledge this limitation may bias findings through the issue of shared method variance (F. Jones & Fletcher, 1996; Kalmbach et al., 2014; McCrae et al., 2008). In McCrae and colleagues' (2008) study, for example, better subjective sleep quality and fewer night-time awakenings predicted higher levels of positive affect in an older adult sample. This finding was not mirrored in objective markers of sleep quality using actigraphy, perhaps an artefact of this single time-point collection for the self-report data. To account for this confound, other studies have used more rigorous experience sample methodologies (de Wild-Hartmann et al., 2013; Totterdell, 1994; van Zundert et al., 2015) collecting multiple measures of positive affect each day.

Likewise, sleep deprivation studies have consistently found that next day positive affect is lowered by ongoing partial sleep deprivation. For example, compared to an 8-hour sleep schedule control group, a chronic partial sleep deprivation schedule (4-hour sleep period from 11pm-3am) was found by Haack and Mullington (2005) to generate decreased levels of optimism-sociability across 12 days, even after controlling for group differences in tiredness. Restricting sleep to four hours over 7-8 days, Dinges and colleagues (1997) found that ratings of vigour were significantly lower on Day 7 compared to the other days of sleep restriction with a quick rebound of vigour following recovery sleep.

Consistent with partial sleep deprivation altering positive affect, a number of studies have found a positive association between daytime napping and various measures of positive emotion. In a within-subjects design, Kaida and colleagues (2007) found participants reported higher levels of pleasantness, satisfaction and relaxation on the nap day compared to the no-nap day. Likewise Luo and Inoué (2000) found that, following a daytime nap, participants exhibited higher levels of joy and relaxation, with no changes to sadness levels.

Particularly relevant to positive affect as a facet of reward functioning, a number of studies suggest that sleep loss hinders normal affective processing through a dampened response to positive emotional cues the next day. Zohar and colleagues (2005), for example, used a naturalistic study to investigate the effects of sleep loss on medical students' affective responses to goal-enhancing events (stimuli that are interesting or relevant to the students' professional development). Compared to those with longer sleep durations, students with shorter sleep durations did not exhibit an increased level of positive affect following goal-enhancing events. Likewise, van der Helm and colleagues (2010) examined the effect of a total night of sleep deprivation on the identification of happy facial expressions. Faces that were more ambiguous (i.e., the facial expression had lower emotional intensity) were rated as less happy following sleep loss compared to the sleep as usual group. In a sample of pre-school children (30-36 months), Berger and colleagues (2012) found a significant decrease in subjective 'joy' and 'pride' when solving puzzles in a group deprived of a single afternoon nap. Finally, a seminal meta-analysis by Pilcher and Huffcutt (1996) examined the impact of partial and total sleep loss on behavioural outcomes. Studies that examined the effects of chronic partial sleep deprivation affected motor, cognitive and mood domains more than short-term (<45 hours) and long-term (>45 hours) total sleep deprivation, with mood more affected by sleep loss than motor or cognitive domains.

Convergent data indicates that sleep loss can result in a host of interpersonal problems, closely related to the positive affect experience. Both sleep quality and sleep duration may be relevant to social functioning (Baum et al., 2014; Christian & Ellis, 2011; Kahn-Greene, Lipizzi, Conrad, Kamimori, & Killgore, 2006; Tavernier & Willoughby, 2015) and empathy (Guadagni, Burles, Ferrara, & Iaria, 2014; Killgore et al., 2008). Guadagni and colleagues' (2014) investigation found that

participants who had been sleep deprived exhibited less emotional empathy than those that had been tested following sleep or a daytime control that had been tested twice in the same day. Similarly, Kahn-Greene et al. (2006) found that 55 hours of continual wakefulness resulted in higher levels of interpersonal frustration and aggression relative to baseline; this was mirrored in a study that showed higher levels of work-place deviance and lower self-control when sleep deprived (Christian & Ellis, 2011).

The clinical condition of insomnia (C. M. Morin, Savard, Ouellet, & Daley, 2003) provides an additional perspective on relationships between sleep and positive affect. Not surprisingly, patients with insomnia symptoms have lowered positive mood states (e.g., Buysse et al., 2007; Levitt et al., 2004). Even within a depressed population, Sunderajan et al. (2010) found that those with insomnia symptoms had lower levels of pleasure and general quality of life than those without sleep disturbances. In a workplace study, individuals with high levels of insomnia were found to experience less joviality than those with less sleep symptoms (B. A. Scott & Judge, 2006).

5.5.1.1   REM abnormalities and next day mood: a hypothesised mechanism linking sleep disturbance to positive affect. A prominent explanation for sleep's role in next day positive affect is provided by Walker and van Der Helm's (2009) model for sleep dependent emotional processing (van der Helm & Walker, 2012). These authors propose a 'sleep to forget, sleep to remember' hypothesis that posits that 'effective' REM sleep strips the emotion from emotional memories, transforming an "emotional memory into a memory of an emotional event" (p. 781). In psychopathologies such as depression or post-traumatic stress disorder that have known REM abnormalities and emotional hyperarousal, the emotional tone may not be successfully decoupled in the REM period due to disturbed adrenergic pathways (van Bemmel, 1997; van der Helm & Walker, 2012). Van Der Helm et al.'s (2011) study offers some support for this model. Compared to a sleep deprivation condition, the authors found decreased reactivity of the amygdala following sleep with greater ventromedial prefrontal cortex connectivity. This study also found that the largest overnight decrease in emotional reactivity was observed in those with lower REM-gamma power, a validated proxy for adrenergic activity.

It has been argued by the same researchers that properties of REM sleep may alter the capacity to learn and encode positive memories. Walker and van der Helm (2009) report on unpublished data suggesting that encoding of positive valence words is reduced following a night of sleep deprivation. Importantly, this reduction was not observed for negative words, and was a non-significant trend for neutral words, suggesting a bias for a negative learning tendency following sleep loss. Some support for this prediction comes from a study showing increased ratings to positive and happy stimuli in a group that entered REM sleep during a 90-minute nap compared to a no-nap group and individuals that did not enter REM sleep (Gujar, McDonald, Nishida, & Walker, 2010).

5.5.1.2 An intriguing qualification. While the lay prediction that poor sleep decreases positive affect the next day is broadly supported, there is one important caveat: under some paradigms, sleep deprivation has been found to acutely increase positive affect. For example, Gujar and colleagues found that participants rated more images as positive and fewer images as neutral following a night of total sleep deprivation (Gujar, Yoo, Hu, & Walker, 2011). Greater positive bias towards stimuli was related to greater activation of reward regions of the brain such as the ventral tegmental area and ventral striatum.

Clinically, a link between decreased sleep and increased positive affect is used in sleep deprivation as a treatment for depression. Sleep deprivation has been found to lead to remission in up to 80% of patients, with particularly positive findings for individuals with melancholic depression or bipolar disorder (Dallaspezia & Benedetti, 2011; Dallaspezia & Benedetti, 2015; Wirz-Justice et al., 2005). Indeed, in people with bipolar disorder, mania – a pathology of elevated positive affect/reward activation – can occur as a side-effect of sleep deprivation therapy (Dallaspezia & Benedetti, 2015). Despite the rapid antidepressant effect of sleep deprivation, it remains rarely used in practice, as 80% of cases relapse following the next sleep episode (Dallaspezia & Benedetti, 2015). To prevent relapse after sleep, antidepressants (Benedetti, Colombo, Barbini, Campori, & Smeraldi, 1999; Colombo et al., 2000) and light therapy (Neumeister et al., 1996) have been used in clinical trials to augment and sustain therapeutic effects (Dallaspezia & Benedetti, 2015). Energised responses to insomnia have also been discussed in the context of the link between decreased sleep and manic relapse in bipolar disorder (Wehr, Sack, &

Rosenthal, 1987). How this pattern of findings relates to the flattening of positive affect reliably associated with decreased sleep in other protocols is not understood, but clearly speaks to still open questions about the relationship between affect and arousal (Kuppens et al., 2013).

      5.5.2   Positive affect as a moderator of sleep. A range of designs have been used to explore the possible influence of daytime positive affect on night-time sleep variables (Table 3). While cross-sectional and prospective studies indicate some relationship between daytime positive affect and night-time sleep variables, the stronger experimental designs have not generated convincing evidence of a causal relationship.

Table 3

Key Studies Examining Positive Affect's Impact on Sleep

Study	Study type	Sample demographic				Measure used		Main findings in relation to positive affect
		Clinical/non-	Gender	N	Age	Positive affect	Sleep/ circadian	
PROSPECTIVE STUDIES								
Brissette & Cohen, (2002)	Prospective, baseline training session and 7-day follow-up (phone call between 6-10pm)	Non-clinical community volunteers	29 F	47	34 (10.7)	PANAS	Sleep quality and duration (PSQI, self-report)	PA was unrelated to subsequent sleep disturbance.
Fisher et al., (1994)	10 week, daily checklist for sleep and mood	Non-clinical sleep habits near Christmas Parents (P) *n*=60, children (C) *n*=29	13 F	P=60 C=29	8-10	Excitement (self-report items)	Sleep behavior (parent CSBS), sleep quality (child self-report)	Child ratings for excitement and tiredness was positively related to child's sleep behavior. Parent's rating of child's excitement and tiredness was associated with parent and child's rating of sleep.
Lawson et al. (2014)	Prospective, nightly interviews with mother and youth for 8 days	Non-clinical working mother and youth	53 % F (for youths)	174 mothers	9-17 13.02 (2.22) (youth)	PANAS	Sleep quality (PSQI) and duration (self-report)	Mother's mood after work was related to youth's sleep quality and duration. Youth's positive mood was positively correlated with both sleep quality and duration. When modelled only between subject difference in mother's positive mood after work predicted sleep duration, with a non-significant trend towards sleep quality.
Loft & Cameron, (2014)	Prospective, 9 days daily measures completed between 3pm and end of workday	Non-clinical employees	48 F	73	21-65	Work-related positive emotions (Job Emotions Scale)	Sleep quality and sleep duration and global PSQI at follow-up (day 10)	No correlation between positive emotions and sleep measures on Day 1 or global PSQI at Day 10. Positive work-related emotions lead to higher levels of sleep quality but not longer sleep durations.
Pilcher et al. (1997)	7-day prospective study. Study 1 was one day before exams, Study 2 was at a less stressful time	Healthy college students	Study 1: 22 F Study 2: 62	Study 1: 30 Study 2: 87	Study 1: 20.9 (.98) Study	Positive affect balance, general satisfaction with life, POMS, Cornell Medical	Self-report sleep logs, PSQI, ESS, SSS	Both studies: Satisfaction with life were health and wellbeing better related to sleep quality than duration. Study 1: When sleep duration was controlled for PSQI score related to more psychological health complaints, lower levels of

Study	Study type	Sample demographic				Measure used		Main findings in relation to positive affect
		Clinical/non-	Gender	N	Age	Positive affect	Sleep/ circadian	
					2: 18.9 (1.1)	Index (psychological health complaints)		satisfaction with life and less vigor on POMS. Study 2: when sleep duration was controlled for daily ratings of sleep quality predicted better scores on all psychological health related outcomes (except for ESS). When sleep duration was controlled for PSQI was related to all psychological health outcomes except for satisfaction with life and vigor.
Song et al (2015)	Prospective, 3x per day (1st hour of waking, between 2-4pm, bedtime), 22 days	Knee osteoarthritis and partners, 50+ year olds who share house with partner/ spouse	58% F	143	65.5	Positive mood (self-report items)	Sleep quality (PSQI, self-report)	Daily positive mood was associated with feeling refreshed following sleep; an increase of one standard deviation of positive mood corresponded to a 20% increase in refreshing sleep quality. Receiving empathy from their partner significantly interacted with positive mood and sleep quality; however these were very small magnitudes.
Tavernier et al., (2016)	Prospective 3 days 2x per day (within 30 minutes of waking and bedtime)	High-school	42.9% F	77	14.37	High-arousal PA (HAPA) (excited, happy, energetic); calm	Actigraphy	Higher levels of calm and lower levels of the HAPA had reduced sleep onset latency. This was significant for the high arousal PA within participants; a non-significant trend that higher levels of calm was associated with longer total sleep time. Trends for higher calm being related to higher sleep efficiency, and, lower sleep efficiency being related to higher HAPA. Trend for shorter wake bouts being related to higher levels of calm.
von Kanel et al (2014)	Longitudinal, up to four years, assessments at 3, 15, 27 and 39 months after transition (spouse placed in care of deceased)	Non-clinical caregivers of Alzheimer's disease	~70% F	126	74.2 (7.9) at baseline	PANAS	Sleep quality and duration (PSQI, actigraphy)	PA was subjectively related to PSQI sleep quality but not actigraphy measures of sleep quality (total sleep time, wake after sleep onset, and sleep percentage). Higher mean levels of PA and greater positivity ratio (PA divided by NA) over the study lead to higher sleep quality,

Study	Study type	Sample demographic				Measure used		Main findings in relation to positive affect
		Clinical/non-	Gender	N	Age	Positive affect	Sleep/ circadian	
								but the PA-sleep quality relationship was not significant when NA was controlled for. Increases in PA and positivity ratio over the study period (within subject) had a significant improvement with sleep quality. Even when NA was controlled for no objective measures of sleep were significant.

CROSS-SECTIONAL STUDIES

Study	Study type	Sample demographic				Measure used		Main findings in relation to positive affect
Bajoghli et al., (2011)	Cross-sectional (daily sleep log 7 days)	Non-clinical adolescents (41 in romantic love)	100%F	86	17.97 (1.09)	Romantic love (self-report items), hypomania (HCL-32)	Sleep quality (daily sleep log questionnaire	Morning ratings had no difference in sleep variables between groups. Those in love reported better mood and concentration during the day for the evening rating. Better sleep quality was related to better mood in the morning and evening.
Bajoghli et al., (2013)	Cross-sectional (sleep diary 7 days, morning and evening ratings)	Non-clinical adolescents. In romantic love (81, 48F), control (120, 65F)	91% F	201	17.73 (1.06)	Romantic love (self-report items), hypomania (HCL-32)	8-point Likert Sleep quality (daily sleep log questionnaire	Morning sleep ratings had no difference between love groups; evening ratings for those in love had higher concentration, better mood and less tiredness.
Brand et al., (2015)	Cross-sectional	Healthy, in love	75.8% F	844	24.79 (5.72)	Romantic love (Y-BOCS), hypomania (HCL-32)	Sleep quality and duration (retrospective sleep log), insomnia (ISI)	Higher scores for being in love was associated with higher quality sleep (less awakenings, shorter sleep onset latency), and decreased sleepiness during the day. Higher scores of dark side hypomania were related to more sleep disturbances and more nighttime awakenings, and, less concentration and more tiredness during the day.
Brand et al., (2011)	Cross-sectional	Non-clinical divided into low hypomanic,	639 F	862	24.67 (5.91)	Hypomania (HCL-32)	Insomnia (ISI), dysfunctional thoughts	Individuals high on risk-taking hypomania had more sleep complaints on the ISI and more dysfunctional beliefs compared to those higher

Study	Study type	Sample demographic				Measure used		Main findings in relation to positive affect
		Clinical/non-	Gender	N	Age	Positive affect	Sleep/ circadian	
		active/elated, and risk-taking/ irritable						on active/elated hypomania and those with a low hypomania score.
Brand et al., (2007)	Cross-sectional, 7 days, daily sleep log completed twice including mood ratings	Divided into recent intense love (*n*=65), longer term relationships (*n*=11) and not in love (*n*=37) (last 2 categories combined for analyses)	72	107	17.95 (1.34)	Romantic love (Y-BOCS), hypomania (HCL-32). Mood ratings asked on 8-point Likert morning and evening	Sleep quality and duration (daily sleep log questionnaire)	Intense love group had higher sleep quality, improved mood higher relaxation and shorter total sleep time (over the whole week), compared to the long-term relationship and no relationship control group. No differences in sleep onset latency.
Steptoe et al., (2008)	Cross-sectional, 4x for one day (2.5, 8, 12 hours after waking and bedtime)	Non-clinical mid-older adults	250 F	736	58-72	PA ("how happy, excited or content do you feel at this moment" 4-point scale), eudaimonic wellbeing	Sleep problems (Jenkins Sleep Problems Scale)	Sleep problems were 47% higher in those reporting no PA across the day, compared to people reporting PA at all four time points. Compared to the highest eudaimonic wellbeing quintile, those in the lowest quintile had a 141% increase of reported sleep problems.
EXPERIMENTAL STUDIES								
Emmons & McCullough (2003)	Experimental: Study 2: 16 days, 1x p/day gratitude, hassles and downward social comparison Study 3: 21 days 1x p/day – gratitude or just mood questions	Study 2: Non-clinical, undergraduate students Study 3: neuromuscular disease	Study 2: 125 F Study 3: 44 F	Study 2: 157 Study 3: 65	Study 2: does not say Study 3: 22-79	Gratitude (self-report items)	Sleep quality and duration (self-report)	Study 2: No relationship between gratitude, PA and sleep. Study 3: Gratitude condition report getting more hours of sleep than participants in the control condition and reported feeling more refreshed upon awakening.
Fredrickson et al., (2008)	Experimental (meditation workshops), completed daily mood for nine weeks	Non-clinical full time employees of a computer company	66% F	139	41	Life satisfaction completed daily	Sleep duration	Life satisfaction not related to sleep duration.

Study	Study type	Sample demographic				Measure used		Main findings in relation to positive affect
		Clinical/non-	Gender	N	Age	Positive affect	Sleep/ circadian	
Jackowska et al., (2015)	Experimental, gratitude, everyday events, control, 4 week study, 2 weeks, 3x per week of a writing task for gratitude and everyday events	Non-clinical, working or studying women	100% F	119	26	Hedonic well-being (Positive emotional style scale)	Sleep quality and duration (PSQI, self-report)	Daily sleep quality was slightly improved in the gratitude condition but not significantly different to the everyday condition. No changes were observed in PSQI score. Increases in positive emotional style was associated with improvements in daily sleep quality.
Schmidt & Van der Linden (2013)	Experimental, evening diary describing a regret, pride or neutral event, morning diary about sleep quality	Non-clinical college students	155 F	176	17-45, 20.94 (4.18)	Pride (BCPQ-extended)	Sleep disturbance (ISI), sleep diary in morning (total sleep time, sleep onset latency, total wake time in bed)	Experimentally induced pride did not alter sleep parameters compared to neutral or regretful events. When trait anxiety and ISI were controlled for, the pride condition had shorter sleep latencies, but this was not significant. Sleep onset latency was longer in regret condition than neutral condition.

Note. Abbreviations: BCPQ = Bedtime Counterfactual Processing Questionnaire; CSBS = Children's Sleep Behaviour Scale; ESS = Epworth Sleepiness Scale; F = Female; HCL-32 = Hypomania Check List-32; ISI = Insomnia Severity Index; NA = Negative affect; PA= Positive affect; PANAS = Positive and Negative Affect Scales; POMS Profile of Mood States; PSQI = Pittsburgh Sleep Quality Index; SSS = Stanford Sleepiness Scale; Y-BOCS = Yale-Brown Obsessive Compulsive Scale

Cross-sectional studies have offered some evidence that higher levels of positive affect precede better night-time sleep. In two studies of romantic relationships in adolescents, Brand and colleagues (2015; 2007) adolescents in love had higher levels of sleep quality. Bajoghli and colleagues (2013; 2011) also examined adolescents in love finding that there were no significant differences in sleep quality between love groups; however better mood in the morning and evening was related to sleep quality, and less tiredness in the evening. In a mid-older adult sample (58-72 years of age), Steptoe and colleagues (2008) assessed positive affect at four times of day and eudaimonic wellbeing were both independent predictors of good sleep. Importantly this study found that results were maintained after controlling for age, gender income, employment status and self-rated physical health. In sum, this data suggests that the experience of positive affect during the day is linked to night-time sleep quality.

Some, but not all prospective studies have found that levels of positive affect influence a variety of sleep parameters. Prospective studies have indicated that positive mood is positively related to shorter sleep latencies (Tavernier, Choo, Grant, & Adam, 2016), sleep continuity (Fisher, Ross, & Wilson, 1994), feeling refreshed following sleep (Song, Graham-Engeland, Mogle, & Martire, 2015), and more general sleep quality and duration (Lawson, Davis, McHale, Hammer, & Buxton, 2014; Tavernier et al., 2016; von Känel et al., 2014). Several studies suggest that positive mood may affect sleep quality more than sleep duration (Loft & Cameron, 2014; Pilcher et al., 1997; von Känel et al., 2014), suggesting the sleep-positive affect relationship may be largely independent of the duration of sleep. Finally, two studies (Brissette & Cohen, 2002; Loft & Cameron, 2014) found that positive affect was not related to sleep quality or duration. Loft and Cameron (2014) found that prioritising sleep and positive work-related emotions predicted better sleep quality that night; however, positive work-related emotions were not correlated to sleep quality, sleep latency, total sleep time, night-time arousal the same night nor global sleep quality across the 9-day study. In sum, this there is ambiguous evidence of a relationship between higher levels of positive affect and night-time sleep quality, but more work is clearly required.

Four experimental studies have sought to investigate the effect of artificially increasing positive affect on night-time sleep quality. In a within subjects study

requiring participants to write about daily experiences of gratitude Jackowska, Brown, Ronaldson, and Steptoe (2015) did not find significant changes in daily sleep quality. However, the trait characteristic of positive emotional style, was significantly associated with higher levels of daily sleep quality. A similar multi-study experiment of journaling gratitude events (Emmons & McCullough, 2003) found no relationship between gratitude, positive affect and sleep in one study, but found gratitude levels were related to increased sleep duration and feeling more refreshed upon awakening in another study. In a diary study, college students who wrote at night-time about events during the day when they felt proud exhibited no changes in sleep quality compared to those who wrote about neutral or regretful events (R. E. Schmidt & Van der Linden, 2013). Concurrently, Fredrickson and colleagues (2008) found that meditation workshops over nine weeks did not influence the sleep duration of employees; however sleep quality more broadly defined was not measured in this study. Overall, existing limited research does not provide a strong signal of the ability to improve sleep variables by manipulating daytime positive affect.

5.5.3 Evidence for a bi-directional relationship between positive affect and sleep. A small number of studies have used multi-wave longitudinal panel designs to directly test the putative bi-directional relationship between sleep quality and positive affect states.

Table 4

Prospective Studies Examining a Bi-directional Relationship Between Sleep and Positive Affect

Study	Time sampling	Sample demographic				Measure used		Main findings in relation to positive affect
		Clinical/non-	Gender	N	Age	Positive affect	Sleep/ circadian	
Armon et al. (2014)	3 time periods 18 months between T1-T2, 17 months between T2-T3	Non-clinical	30% F	1414	46.6 (9.5) 21-71	Vigor (SMVM)	Insomnia (AIS-5)	**PA to S:** Higher levels of vigor at T2 predicted less insomnia at T3. **S to PA:** Levels of insomnia at T1 and T2 predicted levels of vigor at T3.
Cousins et al. (2011)	8 days across 2 weeks	Clinical (anxiety (ANX) and major depressive disorder (MDD)), controls	MDD 63% F ANX 35% F control 58% F	94	11.73 (12 MDD, 10 ANX, 12 control)	PANAS-C happy, joyful, excited, energetic	Actigraphy (time in bed, total sleep time, sleep onset latency, wake after sleep onset, sleep efficiency)	**PA to S:** For individuals with MDD ratings of more daytime PA and higher PA/NA ratios was associated with less time in bed, less total sleep time. **S to PA:** A longer sleep latency was related to lower PA levels the following day for MDD patients; longer time in bed was associated with higher next-day PA. Compared to low-risk controls, MDD group had longer sleep latency, lower PA next day, more wake after sleep onset, longer total sleep time, and lower sleep efficiency.
De Wild-Hartmann et al. (2013)	5 days 2x per day (morning and evening)	Non clinical (577 twins, 44 non-twin)	100% F	621	27.77 (7.86)	7-point Cheerful, content, energetic, enthusiastic	Sleep diary: sleep quality, sleep onset latency, number of awakenings, bed and wake time, total sleep time	**PA to S:** Sleep quality was negatively associated with prior day PA. **S to PA:** Higher levels of sleep quality and total sleep time linearly increased PA. More awakenings and longer sleep latencies decreased PA.
Doane & Thurston (2014)	3 day, 5x per day	Non-clinical (high-school to university students)	77% F	78	18.05 (.41)	PANAS	Actigraphy (time in bed, sleep efficiency, sleep onset latency, time in bed, bedtime)	**PA to S:** Prior day PA had no relationship with sleep duration, efficiency or latency. **S to PA:** Prior day sleep had no relationship to next day affect (NB: participants slept 5.88(1.06) hours).
Galambos et al. (2009)	2-14 days (89% >10 days), 1x per day	Non-clinical, full-time first year students	60% F	191	17.3-19.9 18.35 (.47)	PANAS	Self-reported sleep quality (single item) and duration (sleep onset and offset)	**PA to S:** Daytime PA predicted night-time sleep quality (higher PA, higher sleep quality). **SA to P:** For every one unit increase in sleep quality, PA went up by .1 (5-point scale).
Garcia et al. (2014)	2-13 days 4x per day	Adolescent Latinas	100%	19	M=15 (14-17)	PANAS 4-point (happy, excited, relaxed)	Self-report sleep duration and sleep quality	**PA to S:** When PA was less than the mean level, sleep hour increases .24 with one unit increase in PA, when PA greater or equal than the mean sleep hour decreases by .13 with a one-unit increase in PA (both relationships non-significant).

Study	Time sampling	Sample demographic				Measure used		Main findings in relation to positive affect
		Clinical/non-	Gender	N	Age	Positive affect	Sleep/ circadian	
								Higher positivity ratio increased odds ratio by 2.41 of chance of having a good night's sleep. **S to PA:** Sufficient sleep lead to .48 higher PA and .04 higher positivity ratio (not significant).
Jones & Fletcher (1996)	3 weeks, 1 per day	Non-clinical couples	50% F	20 pair	Does not say	9-item bipolar i.e., alert – lethargic; dejected-cheerful	4-point measure sleep quality	**PA to S:** Partner's daytime mood positively correlated to night-time sleep for men and women, women's mood was positively associated with night-time sleep. **S to PA:** Night-time sleep quality was positively associated with next day mood for men and women. Women's sleep the night before was correlated to their partner's next day mood.
Kalak et al. (2014)	3 time periods, baseline, 6 months and 12 months	Non-clinical adolescents	51.8% F	1601	10-15 13.05 (1.49)	Subjective psychological wellbeing (SPW) (BFW/J)	Sleep duration (self-report)	**PA to S:** SPW did not predict sleep duration at any time point **S to PA:** Longer sleep duration at T1 higher SPW at T2 (small effects).
Kalmbach et al. (2014)	2 weeks, 1x per day	Non-clinical	100% F	171	20.07 (3.32)	PANAS-X (joviality; self-assurance; serenity subscales)	PSQI (total sleep time, sleep onset latency, sleep quality every 24-h)	**PA to S:** Greater PA (specifically joviality and serenity) predicted shorter sleep onset latency and higher sleep quality; PA (specifically serenity) predicted longer total sleep time. **S to PA:** Higher sleep quality (specifically joviality and self-assurance) predicted PA (but not sleep onset latency or total sleep time).
Kouros & El-Sheikh, (2015)	7 days mood reported 1 x nightly by mother	3rd grade healthy children	57% F	142	10.69 (.56)	5-point happy-sad, calm-jittery, carefree-worried, easygoing-irritable, even-tempered-mood swing, relaxed-tense	Actigraphy (sleep minutes, sleep efficiency, sleep activity, sleep onset latency)	**PA to S:** When participants reported worse mood than usual they tended to have higher levels of sleep activity and longer sleep onset latency **S to PA:** Longer sleep onset latency leads to lowered next day PA.
Simor et al. (2015)	7 days 2x per day (sleep upon awakening, mood 8 hours later)	Non-clinical university students	60% F	75	22.15 (2.98)	PANAS	Gronigen Sleep Quality Scale	**PA to S:** PA did not explain within person differences in sleep quality. Lower PA was associated with poorer sleep quality, but did not vary daily as a function of PA. **S to PA:** Poorer sleep was associated with lower ratings of PA; poorer sleep than average lead to lower PA ratings than average.

Study	Time sampling	Sample demographic				Measure used		Main findings in relation to positive affect
		Clinical/non-	Gender	N	Age	Positive affect	Sleep/ circadian	
Takano et al. (2014)	7 days 8 x per day (between 8am-12am, every 2 hours)	Non-clinical university students	38 F	49	19.4 (1.3)	PANAS (7-point): only used active, proud and strong	Actigraphy (sleep onset latency, efficiency, total sleep time)	**PA to S:** No significant relationship was found. **S to PA:** Higher sleep efficiency and *lower* total sleep time were related to higher levels of PA.
Totterdell et al. (1994)	2 weeks (ratings every two hours except during sleep)	Healthy, working full-time	16 F	30	31.6	VAS – mood adjective checklist: energetic arousal, hedonic tone, tense arousal & involved (engaged with environment)	Sleep diary (subjective)	**PA to S:** More cheerful rating were related to more sleep awakenings, more calm were related to shorter sleep onset latency, **S to PA:** Shorter sleep onset latency, earlier sleep onset and higher sleep quality were related to more cheerfulness. Earlier sleep onset, less night-time awakenings, and higher sleep quality were related to higher alertness. Earlier sleep offset, less night awakenings and higher sleep quality were related to more involved. Later sleep onsets were associated with less cheerfulness across the entire day; later sleep onset was associated with alertness but only in the morning.
van Zundert et al. (2015)	6 day 9x per day	Non-clinical	59% F	286	14.19 (.54)	PA Adjectives 7-point joyful, satisfied, happy, energetic, cheerful	Single item 7-point sleep disturb: how many times awoken, sleep quality: "I sleep well"	**PA to S:** Higher PA during the day lead to better sleep quality and *more* sleep disturbance at night. **S to PA:** controlling for PA of day before sleep quality was related to higher PA next day. Sleep disturbances were not related to PA.
Wrzus et al., (2014)	9 days 6x day every 2 hours, first assessment between 6am-midday	79 12-17 years, 82 18-29 years, 50 30-39 years, 55 40-49 years, 46 50-59 years, 55 60-69 years, 33 70-88 years	48% F	397	39.86 (20.48)	Happy, enthusiastic, even-tempered, content, relaxed	Sleep duration self-report	**PA to S:** Affect balance (PA divided by NA) did not predict amount of sleep the following night. **S to PA:** Less sleep compared to average resulted in lower affect balance in morning. Having more than average sleep duration lead to lower affective balance for middle and older adults, while adolescents had higher affect balance with more sleep than their average amount.

Note. Abbreviations: AIS-5 = Athens Insomnia Scale; ANX = Anxiety; BFW/J = Bern Well-being Questionnaire for Adolescents; F = Female; MDD = Major depressive disorder; NA = Negative affect; PA = Positive affect; PANAS = Positive and Negative Affect Scales; S = Sleep; SMVM = Shirom-Melamed Vigor Measure; VAS = Visual Analogue Scale

The naturalistic prospective studies examining a bi-directional relationship between sleep quality and positive affect are presented in Table 4. As reviewed in the previous sections a reliable link has been demonstrated between sleep quality and next day positive affect. Less evidence of a link between daytime positive affect and night-time sleep quality was observed. This section finds (as the reader might expect) that prospective multi-day studies also find evidence of a stronger relationship between night-time sleep and positive affect the following day, than vice versa.

All studies investigating a bi-directional relationship have found a significant relationship between sleep quality and next day positive affect (e.g., de Wild-Hartmann et al., 2013; Galambos, Dalton, & Maggs, 2009; Simor et al., 2015; van Zundert et al., 2015). The links between other components of sleep (sleep latency, sleep duration and sleep disturbances) were somewhat more inconsistent. Generally, shorter sleep latencies were related to higher next-day levels of positive affect (Cousins et al., 2011; de Wild-Hartmann et al., 2013; Kouros & El-Sheikh, 2015; Totterdell, 1994); however Kalmbach et al. (2014) found that sleep latency did not predict next day positive affect. Some studies found that increased total sleep time increased positive affect (de Wild-Hartmann et al., 2013; Garcia, Zhang, Holt, Hardeman, & Peterson, 2014; Kalak, Lemola, Brand, Holsboer–Trachsler, & Grob, 2014; Wrzus, Wagner, & Riediger, 2014). Other studies have found that sleep duration did not affect next-day positive affect (Doane & Thurston, 2014; Kalmbach et al., 2014) with one study (Takano, Sakamoto, & Tanno, 2014) finding that shorter total sleep time increased next day positive affect in a university sample. It should be noted that the university samples used in Doane and Thurston (2014) and Takano et al.'s (2014) sample slept for mean times of 5.88 hours and 5.4 hours respectively, far below the recommended 9 hours for this age group. In the studies examining sleep efficiency or night-time disturbances, more disturbances generally lead to lower positive affect (de Wild-Hartmann et al., 2013; Takano et al., 2014; Totterdell, 1994) with van Zundert et al. (2015) finding no relationship between sleep disturbances and next day positive affect.

In the bidirectional studies conducted to date, some have found that higher levels of daytime positive affect predict poorer sleep quality (e.g., de Wild-Hartmann et al., 2013), while others have found higher levels of daytime positive affect predict

better sleep quality (e.g., Kouros & El-Sheikh, 2015; Simor et al., 2015). Adding further complexity, van Zundert et al. (2015) found that higher daytime positive affect led to better self-reported sleep quality, but also more night-time awakenings. Totterdell (1994) reports similar findings with more cheerfulness predicting more sleep awakenings, but higher levels of calm predicting shorter sleep latencies. Some of these discrepancies may be accounted for by attending to the different facets of positive affect. Positive affect can be conceptualised as a multi-faceted construct, taking into account both the arousal and valence of positive affect terms (Kuppens et al., 2013; Russell & Carroll, 1999a, 1999b; Watson & Tellegen, 1985). Kalmbach et al. (2014) found that joviality and serenity predicted higher self-reported sleep quality and shorter sleep onset latency; however only serenity predicted longer sleep times. Other studies have also found that *high arousal positive affect items* may index a factor detrimental to sleep quality, while *low arousal positive affect items* such as calm may capture a factor associated with improved night-time sleep (Tavernier et al., 2016).

While most of the studies reviewed here have examined sleep and positive affect in short sampling periods (days and weeks), two longer-term prospective studies have examined the bi-directional relationship between sleep and positive affect; with one study examining sleep quality and the other sleep duration. These studies allows us to suggest an interpretation of the nature and strength of this bi-directional relationship across time (Armon, Melamed, & Vinokur, 2014). In a 3-year study, self-reported vigor predicted levels of insomnia 17 months later, and insomnia predicted levels of vigor at 17 *and* 35 months later; however each of these paths had very small effect sizes (Armon et al., 2014). In a second prospective study, Kalak et al. (2014) found a positive correlation between levels of positive affect and sleep duration six and twelve months later in adolescents aged 10-15. While longer sleep duration predicted greater psychological wellbeing six months later, the modeled path was not strong (β=0.07-0.08); and no relationship was observed between psychological wellbeing at any time point and sleep for any adolescent age groups. Initial findings therefore suggest that any long-term relationship between sleep and positive affect is not strong. In sum, a limited set of studies modelling pathways from sleep to positive affect and vice versa, suggest that the former path is stronger. To investigate this relationship further, increased time sampling over more

frequent intervals could help to provide greater insight into the longitudinal relationship between sleep and positive affect. Increased time sampling might help to assess for a potential circadian influence in this dynamic relationship.

Beyond a bi-directional relationship, there is growing interest in the synergistic relationship between sleep quality and positive affect. Referred to by Rofey and colleagues (2013) as 'negative spirals', a negative mood may lead to night-time rumination delay resulting in poor sleep quality. The next day this may make an individual more irritable, sedentary, socially volatile, and isolated leading to worsened sleep quality in subsequent nights. This work posits that this negative spiral process between sleep and positive affect may go beyond a bi-directional relationship and may progress to a synergistic relationship where sleep and mood progressively impact each other, and both worsen, over time (Rofey et al., 2013). No empirical research has yet tested this face-valid 'vicious cycle' hypothesis linking poor sleep quality and disturbed mood.

5.5.4   Limitations of the existing literature. For the present review, the studies reviewed in the preceding three subsections tend to share some important limitations. Three are particularly noteworthy. Firstly, the relationship between positive affect and night-time sleep quality may not be independent of daytime levels of negative affect. There is some evidence that 'the positivity ratio', the ratio of positive affect to negative affect, is more important in predicting night-time sleep quality than positive affect alone (Garcia et al., 2014). Secondly, it is important to note that subjective reports of sleep quality may only be modestly related to objective measures of sleep quality (namely actigraphy in the current review), a methodological consideration raised in the sleep literature (e.g., Baker, Maloney, & Driver, 1999; Jean-Louis, Kripke, & Ancoli-Israel, 2000). Only three of the studies in the current review (Lemola et al., 2013; McCrae et al., 2008; von Känel et al., 2014) have taken concurrent subjective and objective measures of sleep quality and sleep duration. All three found associations between subjective sleep quality and positive affect with no relationship (McCrae et al., 2008; von Känel et al., 2014), or a partially mediated relationship (Lemola et al., 2013), between objective sleep parameters and positive affect. A final consideration is that sleep duration may have an age-dependent relationship with positive affect (Birchler-Pedross et al., 2009; Wrzus et al., 2014). Wrzus et al. (2014) found that sleep duration had a quadratic

relationship with next day positive affect. Adolescents had improved mood when they slept longer than usual, but when older adults slept longer than normal they reported lower positive mood the next day. These examples highlight the complexity of accurate assessment in the bidirectional relationship between sleep and positive affect.

5.6 Circadian and Sleep Involvement in Bipolar Disorder

Having considered relationships between positive affect and circadian function (Section 2), and positive affect and sleep (Section 3), the final topic of this chapter is biological rhythm involvement in pathologies of positive affect/reward.

Recent years have seen an explosion of interest in the circadian etiology of mood disorders (Malhi & Kuiper, 2013), addictions (Logan, Williams III, & McClung, 2014; Parekh, Ozburn, & McClung, 2015), and other debilitating pathologies of dysregulated reward (Landgraf et al., 2016; Landgraf, McCarthy, & Welsh, 2014a). Here, we focus specifically on bipolar disorder, a diagnosis sitting at the intersection of reward, circadian and sleep processes (Harvey et al., 2011; Murray & Harvey, 2010). Longstanding evidence that bipolar disorder emerges partly from a diathesis in the reward system is presented (i.e., bipolar disorder involves dysregulation of positive affect), before we review evidence for biological rhythm involvement in the disorder. Finally, we introduce growing research into the hypothesis that bipolar disorder arises from an interacting circadian X reward diathesis – one manifestation of which might be abnormalities of the Circadian Reward Rhythm.

Abnormalities in positive affect and reward sensitivity are well-documented in bipolar disorder. Contemporary research has shown bipolar disorder to be predictably associated with neurobiological (e.g., Dutra, Cunningham, Kober, & Gruber, 2015), behavioral (e.g., Giovanelli, Hoerger, Johnson, & Gruber, 2013), affective (e.g., Gruber, Kogan, Mennin, & Murray, 2013) and cognitive (e.g., Alloy, Abramson, et al., 2009; Johnson & Jones, 2009) facets of reward. Building on earlier models of positive affective functioning in bipolar disorder (Depue, Krauss, Spoont, & Arbisi, 1989; Johnson, Edge, et al., 2012; Urošević et al., 2008), Alloy and colleagues have used a large prospective study to provide support for a fundamental diathesis to bipolar diagnosis through behavioral activation system sensitivity (e.g., Alloy et al., 2012).

In parallel, multiple lines of evidence strongly suggest the involvement of biological rhythms in the etiology of bipolar disorder. For example, sleep and circadian abnormalities are seen in mania, depression and euthymia (A. J. Bradley et al., 2017; Harvey, 2008; S. H. Jones, 2001), and biological rhythm abnormalities are present in at-risk populations (e.g., Bullock, Corlass-Brown, & Murray, 2014; Bullock, Judd, & Murray, 2011; Bullock & Murray, 2014; Murray, Allen, Trinder, et al., 2002). Naturalistic studies show that changes in sleep and zeitgeber exposure predict symptoms (e.g., Asarnow, Soehner, & Harvey, 2014; Bauer et al., 2006; Shen, Alloy, Abramson, & Sylvia, 2008), and experimentally induced sleep deprivation temporarily relieves bipolar depression and can induce hypomanic or manic switching in some 11% of cases (Benedetti & Colombo, 2011; Colombo, Benedetti, Barbini, Campori, & Smeraldi, 1999). Effective pharmacotherapy also acts through biological rhythm mechanisms: lithium affects circadian rhythms through the GSK-3β gene, a central regulator of the circadian clock (Beaulieu et al., 2004; Fornaro et al., 2013; Gould & Manji, 2005; Malhi et al., 2013; Moreira & Geoffroy, 2016; Yin, Wang, Klein, & Lazar, 2006).

Further, consistent with a biological rhythm etiology in bipolar disorder, Ehlers and colleagues' (1988) Social Zeitgeber Theory, proposes that life events may alter exposure to social cues thereby disrupting biological rhythms through photic and non-photic zeitgebers. In individuals vulnerable to, or diagnosed with a mood disorder, sleep and circadian disruptions may be more pronounced following social rhythm disruption (Germain & Kupfer, 2008), and in general, social rhythms may have less regularity compared to non-vulnerable counterparts (Alloy, Nusslock, et al., 2015).

Mechanisms underpinning biological rhythm involvement in bipolar disorder have been partly elucidated in animal models (see, for a review, Landgraf, McCarthy, & Welsh, 2014b). For example, the circadian nuclear receptor REV-ERBα (encoded by the NR1D1 gene, in turn linked to bipolar disorder onset and lithium response) in mice is associated with mania-like behaviour and hyperdopaminergic state through its activity in the ventral midbrain and its role in circadian expression of tyrosine hydroxylase (Chung et al., 2014).

A number of authors have noted that reward and circadian diatheses to bipolar disorder may interact (Johnson, Edge, et al., 2012; Murray et al., 2009). Most

recently, Alloy and colleagues have reviewed supporting data and formulated an integrated reward and circadian rhythm dysregulation model of bipolar spectrum disorders (Alloy, Nusslock, et al., 2015). As flagged above, the prediction of 'interaction between chronobiological and reward systems in bipolar disorder' is complex and multifaceted: To put the prediction in its proper scientific context, it is worth remembering that it speaks to interplay between two (Positive Valence and Arousal/Regulatory) of the five multi-level systems identified in the NIMH Research Domain Criteria matrix (Insel, 2014). Its adequate investigation will require networks of researchers working in a multi-disciplinary framework, with progressively iterated models. Strategically, it will be useful to tie this endeavour to ongoing attempts to understand the role of activation in the course of bipolar disorder (J. Scott et al., 2016).

Bipolar disorder may therefore be an exemplar of pathological interaction between chronobiological and reward systems, a conclusion with important clinical implications (Alloy, Nusslock, et al., 2015; A. J. Bradley et al., 2017; Murray et al., 2009). A key feature of circadian function is its open nature, and consequent malleability through volitional behaviour (see Figure 3). Important clinical insights into circadian modulation of reward may therefore arise from deliberate manipulation of the clock (through light, sleep, activity scheduling, etc., Schroeder & Colwell, 2013). Likewise, better understanding of the chronobiology of reward may help refine treatments operating partly through reward pathways. For example, biological oscillations exhibit phase response curves (PRCs: systematic variability depending on the phase at which a perturbation is applied, see Efimov, 2011). Existing treatments targeting reward activation (behavioral activation, transcranial magnetic stimulation and deep brain stimulation for depression, for example) could take advantage of a potential PRC for reward.

5.7   Conclusions and Future Directions

Positive affect can be understood as the subjective facet of the reward system, responsible for guiding positive affect, motivation, and behaviour in the context of incentive cues (Depue & Collins, 1999; Knutson et al., 2014). Many authors have argued for the importance of considering factors that moderate reward system function (Cromwell & Panksepp, 2011; P. S. Davies, 2011; Panksepp et al., 2012). The present chapter has considered a wide range of data and theory which, in

total, suggest chronobiology (the study of adapted biological timing) provides a fruitful new perspective (e.g., Alloy, Nusslock, et al., 2015; McClung, 2013; Murray et al., 2009). The present review was structured around the two foundational biological rhythm processes in humans: circadian function and sleep.

In relation to circadian function and positive affect, this chapter has three primary take-home messages. First, there is robust evidence for daily variation in positive affect. Second, there is emerging evidence that this variation is partly of endogenous circadian origin. Finally, apparent interactions between reward and circadian systems (particularly the Circadian Reward Rhythm model) have potential to generate novel hypotheses about normal and abnormal regulation of affect/ reward motivation. There is growing interest in 'bottom-up' affective regulation (Cromwell & Panksepp, 2011), and the circadian reward rhythm constitutes a uniquely well-characterised target for such research. One aspect of this investigation is the growing interest in circadian-mediated nonlinear dynamic features of activity (Hadaeghi, Hashemi Golpayegani, Jafari, & Murray, 2016; Hadaeghi, Hashemi Golpayegani, & Murray, 2015), and parallel interest in actigraphy itself as a key method in this area (J. Scott et al., 2016).

In relation to sleep, three major conclusions are warranted. First, empirical studies have supported the lay assumption that, under most circumstances, poor sleep quality and shorter sleep duration are associated with decreased positive affect the next day. This relationship is strongest when sleep is assessed by self-report. Experimental manipulations have confirmed that this association is likely to be causal. The qualification that imposed sleep deprivation can under some circumstances increase positive affect acutely is clinically important because of the potential antidepressant (and manicogenic) effect of sleep deprivation. Second, some studies suggest that daytime positive affect does influence night-time sleep. However this influence may depend on whether the positive affect variable under investigation is high or low arousal: evidence suggests that low arousal positive affect improves sleep quality, whereas high arousal positive affect may lead to worse sleep quality (Tavernier et al., 2016). Finally, the small number of longitudinal studies investigating bi-directional relationships between sleep and positive affect suggest, again, that average sleep quality predicts average positive affect across time (the inverse relationship is less strong).

The reviews above clearly point to pressing research issues yet to be addressed. In relation to sleep and positive affect, it will be important for imaging technology to investigate mechanisms linking lowered sleep quality to next day positive affect. Whereas experiments in this area have largely employed total sleep deprivation studies, examining poor sleep quality may be more ecologically valid, with the 'all-nighter' relatively rare compared to problems with sleep quality. In a recent national survey of 1011 Australian adults, Adams and colleagues (2017) found that 48% of the sample reported two or more problems with their sleep; highlighting sleep quality as a high prevalence issue in need of urgent attention. More prospective studies are needed to directly test the predictive effects of sleep quality on next day positive affect and vice versa. Investigation into these areas can help us to understand the trajectory of sleep and mood problems and to support research into targeted sleep and mood clinical interventions. To this end, targeted sleep and mood treatments have already shown promise in treating and sustaining mood remittance in both depression (Manber et al., 2008) and bipolar disorder (Harvey et al., 2015; Kaplan & Harvey, 2013).

Research into the putative Circadian Reward Rhythm requires replication, particularly through attention to underpinning neural mechanisms. Future studies should also be fully situated in more sophisticated models of positive affect/reward: our group has started to explore daily rhythms in the three recognised facets of reward (Byrne & Murray, 2017a) but many questions remain. Whether disturbance in this Circadian Reward Rhythm is a primary form of interaction between circadian and reward functions in psychopathology remains an open question.

Finally, the present review has overlap with another major stream of current research, namely, temporal patterns of *activation* in mood disorders. Interest in these issues arises from the recent elevation of activation to a cardinal symptom of mania (J. Scott et al., 2016). Using actigraphy, there is a growing theoretical and clinical interest in objectively quantified activity rhythms across the day (understood as diurnal, circadian) and the complex system investigations using the high-resolution data available with actigraphy (Hadaeghi et al., 2016; Hadaeghi et al., 2015).

In conclusion, positive affect is a fundamental aspect of human experience, rooted in our evolutionary past via the biobehavioral reward system. As such, we should expect that positive affect has multiple and complex relationships with other

important adaptive functions, including circadian processes and sleep itself. Investigating these interactions may have important clinical implications through refining interventions for mood disorders. Moving forward, this may also re-double efforts into understanding mechanisms behind sleep deprivation's antidepressant effects. Finally, this work prompts other lines of inquiry into the 'vicious cycle' of what may be an ongoing, synergistic relationship between sleep and positive affect – testing this hypothesis, with possible extension to the circadian context, will also be critical in understanding the course of mood disorders. One key approach to this examination will involve prospective collection of sleep (objectively and subjectively assessed), circadian, and positive affect parameters. There is a growing array of methods, technologies and analytic approaches to support this complex time-linked research (Trull & Ebner-Priemer, 2013). Indeed, the substantial literature on the interplay between biological rhythms and positive affect constitutes a fertile source of theoretically-grounded hypotheses for a more dynamic clinical psychological science in the 21st Century.

Chapter 6: Development of a Measure of Sleep, Circadian Rhythms, and Mood:

The SCRAM Questionnaire

6.1   Study 2a: Linking Section

Byrne, J. E. M., Bullock, B., & Murray, G. (2017). Development of a measure of sleep, circadian rhythms, and mood: The SCRAM Questionnaire. *Frontiers in Psychology, 8*(2105). doi:10.3389/fpsyg.2017.02105

In the first of the project's empirical studies, Study 2 aimed to quantitatively separate the three interrelated processes of sleep quality, diurnal preference, and mood. This generated a useful and novel self-report tool. The final Sleep, Circadian Rhythm, and Mood (SCRAM) questionnaire is comprised of three, five-item scales: Good Sleep, Morningness, and Depressed Mood (see Appendix B).

This work built on the reviewed literature of Study 1 (see Chapter 5) that highlighted a putative relationship between circadian function, sleep parameters and positive affect. Given that dysregulation of these systems may be implicated in clinical reward disorders (most notably discussed in this project, bipolar disorder) the preliminary step was taken in this project to advance how sleep quality, diurnal preference, and lowered mood could be measured in the general population using a single questionnaire, designed to select items with minimal cross-loadings. This work is also the first stage of a program of research to develop this questionnaire further, notably in Study 2b (see Chapter 7) additional validation is provided for the SCRAM questionnaire.

6.2   Abstract

Sleep quality, circadian phase, and mood are highly interdependent processes. Remarkably, there is currently no self-report questionnaire that measures all three of these clinically significant functions: The aim of this project was to address this deficit. In Study 1, 720 participants completed a set of potential items was generated from existing questionnaires in each of the three domains and refined to follow a single presentation format. Study 2 used an independent sample (N=498) to interrogate the latent structure. Exploratory factor analysis was used to identify a parsimonious, three-factor latent structure. Following item reduction, the optimal representation of sleep quality, circadian phase, and mood was captured by a questionnaire with three 5-item scales: Depressed Mood, Morningness, and Good Sleep. Confirmatory factor analysis found the three-scale structure provided adequate fit. In both samples, Morningness and Good Sleep were positively associated, and each was negatively associated with the Depressed Mood scale. Further research is now required to quantify the convergent and discriminant validity of its three face-valid and structurally replicated scales. The new sleep, circadian rhythms, and mood (SCRAM) questionnaire is the first instrument to conjointly measure sleep quality, circadian phase, and mood processes, and has significant potential as a clinical tool.

Keywords: sleep; circadian phase; mood; depression; measure; questionnaire; chronotype; circadian rhythm

6.3 Introduction

A range of evidence in normative and clinical populations demonstrates that sleep quality, circadian phase, and mood are highly interdependent (Mason & Harvey, 2014; Soehner et al., 2016; Soehner, Kaplan, & Harvey, 2014). In clinical settings this generates a common problem: When a patient presents with some combination of sleep quality, circadian phase, and mood problems, where should treatment be targeted (Harvey, 2015)? At least in part, this clinical problem arises from the fact that, while well-validated measures of sleep quality, circadian phase, and mood exist, there is no self-report instrument that quantifies function in all three domains. Such an instrument would provide a quantum advance over existing single-construct measures that, while validly capturing the individual construct of interest, pay no attention to independent and overlapping variance arising from the mechanistic interplay between the three processes. The aim of this project was to take the first step towards addressing this problem by developing a novel self-report questionnaire to measure sleep quality, circadian phase, and mood processes.

There are strong reasons to consider the interaction of sleep quality, circadian phase, and mood problems in treatment. Circadian phase refers to the timing of endogenous circadian rhythms relative to 24-hour clock time (Czeisler et al., 1989; Kripke, Elliott, Youngstedt, & Rex, 2007). Circadian phase has reliable associations with diurnal preference of activity and rest, or chronotype (Duffy et al., 2001; Mongrain, Lavoie, Selmaoui, Paquet, & Dumont, 2004). Chronotype is anchored by extremes of 'morningness' and 'eveningness'. Morningness being the preference for earlier activity and sleep times, eveningness the preference for later activity and sleep times (Baehr et al., 2000; Duffy et al., 1999). Sleep quality involves a subjective assessment of total sleep duration, sleep latency, wake after sleep onset, and qualitative interpretation of the depth and restfulness of the sleep period (Buysse et al., 1989). Sleep quality and circadian phase are interdependent processes with individuals high on morningness reporting better sleep quality (Barclay, Rowe, O'Leary, Bream, & Gregory, 2016, 2016; Wittmann et al., 2006). Moreover, a stable circadian phase, i.e., having regular sleep times, has been found to improve sleep quality (Gruber et al., 2011; Harvey et al., 2011), and the circadian system regulates antidepressant and mood stabilising medication pathways in the brain (McClung, 2013). Data suggests that cognitive behavioural therapy for insomnia can

alleviate symptoms of depression (Manber et al., 2008), and in turn Chan et al. (2014) found high levels of eveningness and insomnia were independent risk factors of non-remitting depression. It is clear therefore, that comprehensive consideration of all three processes has the potential to improve case formulation and treatment planning.

Clinical interactions between sleep quality, circadian phase, and mood processes limit current self-report measures. For example, self-report measures of sleep quality (such as the Pittsburgh Sleep Quality Index) may have difficulty in reliably differentiating individuals with depression from primary insomnia (Buysse et al., 1989). Grandner, Kripke, Yoon, and Youngstedt (2006) hypothesised that self-report measures of sleep quality may in part reflect negative cognitive processes and pessimism rather than sleep quality alone. Similarly, individuals with insomnia scored in the mild symptomology bracket of the Beck Depression Inventory-II (Carney, Ulmer, Edinger, Krystal, & Knauss, 2009). In a study by Abe et al. (2011), 64% of individuals who had a delayed circadian phase (as measured by the Morningness-Eveningness Questionnaire, J. A. Horne & Östberg, 1976) had moderate to severe depressive symptoms. Suggesting a bidirectional link, Robillard, Naismith, Rogers, Ip, et al. (2013) observed that a delayed evening sleep phase is common in those with both unipolar and bipolar depression. Finally, shifts in circadian phase (such as those experienced in jetlag and shift-work) leads to sleep quality complaints (Rajaratnam & Arendt, 2001), and poor sleep quality can also impact circadian function (L. P. Morin, 2013).

The overarching aim of this project was to develop a single questionnaire to measure the three interconnected processes of sleep quality, circadian phase, and mood. Such a questionnaire has the potential to guide assessment and treatment given the important clinical conundrum that arises when a client presents with a combination of complaints in the three domains. The present project is a critical first step in an ongoing program of research. The aim of Study 1 was to develop a brief three-factor self-report measure that provides maximal measurement separation between the domains of sleep quality, circadian phase and mood. Depressed mood in physical illnesses is common and leads to an increased mortality rate (Katon, 2003); autonomic function (Grimaldi, Carter, Van Cauter, & Leproult, 2016) and obesity (Haus et al., 2016) have both been associated with sleep and circadian disruption.

These processes may be linked by fundamental physiological dysregulation (see, for example, Beauchaine & Thayer, 2015; Gruber, Mennin, Fields, Purcell, & Murray, 2015; Kemp & Quintana, 2013). As part of a preliminary external validation of the measure, we predicted that scale scores from the new instrument would demonstrate intelligible patterns of convergent and divergent validity with single-item measures of sleep, physical, and mental health problems. Study 2 aimed to confirm the measure's theoretical three-factor structure using confirmatory factor analysis.

6.4   Study 1: Method

6.4.1   Study design and data analysis. Instrument development was guided by the PROMIS standards (Cella et al., 2007). Item generation involved drawing items from existing questionnaires in the three domains, standardizing them to the same response format and making small changes to wording where necessary. Item reduction was achieved by conducting an Exploratory Factor Analysis (EFA) on responses from a predominantly student sample to this draft set of items. Preliminary investigation of external validity was conducted via associations with self-reported physical and mental health outcomes.

6.4.1.1   Item generation. To develop a comprehensive list of items measuring the three domains we examined relevant topic areas from which we could generate newer items. Draft items were identified from highly cited self-report measures of sleep quality, circadian phase, and pathological mood (symptoms of depression and also hypo/mania). Nine sleep scales (e.g., PSQI [Buysse et al., 1989] and Insomnia Severity Index [Bastien, Vallières, & Morin, 2001]); five circadian rhythm questionnaires (e.g., Munich Chronotype Questionnaire [Roenneberg, Wirz-Justice, et al., 2003] and Morningness-Eveningness Questionnaire [J. A. Horne & Östberg, 1976]), and 20 mood questionnaires (e.g., BDI-II [Beck, Steer, & Brown, 1996], Centre for Epidemiological Studies Depression Scale [Radloff, 1977], and The Hospital Anxiety and Depression Scale [Zigmond & Snaith, 1983]) were used. As part of this generative process we created items that had purified wording, with the specific aim of decreasing overlap between the three domains. Items were selected for being face-valid as relatively pure measures of only one of the three processes. Draft items were then reworded to permit a shared response format (below) and/or to improve clarity and brevity. The preliminary item pool contained 170 items, $n = 58$ measuring sleep quality, $n = 60$ measuring circadian phase, and $n =$

52 measuring problems with mood (full list included in the Supplementary Materials).

The given question prompt was: "The following questions ask about your sleep, mood and timing of daily activities. Pick the answer which best describes you **over the past two weeks**". A 2-week timeframe was deemed appropriate, given the nature of the processes under investigation (e.g., two weeks is the minimum timeframe required for DSM-5 diagnosis of Major Depressive Episode (American Psychiatric Association, 2013). A 6-point Likert-type response scale (*Strongly Disagree* to *Strongly Agree*) was selected for the new questionnaire. We chose not to have a middle response option to avoid ambiguity, as middle response options can reflect socially desirable responding, indifference, uncertainty, or non-applicability (Garland, 1991; Nowlis, Kahn, & Dhar, 2002). Six response categories was considered an optimal balance between the higher validity associated with increasing response options and participant response burden (Chang, 1994; Preston & Colman, 2000).

6.4.1.2   Exploratory factor analysis. The expected three factor structure was forced onto the item set. For completeness, a range of empirical methods was also used to explore the number of factors to extract (B. P. O'Connor, 2000). The scree plot (Tabachnick & Fidell, 2013), minimum average partial test (Velicer, 1976), parallel analysis (Horn, 1965), and Kaiser-Guttman's criteria (Tabachnick & Fidell, 2013) were all examined. Using an orthogonal rotation (varimax), the adequacy of all factor solutions was compared against the following criteria: item communality magnitudes of over .40, cross-loadings less than .32 and at least five strongly loading (>.50) items on each factor (Costello & Osborne, 2005).

6.4.1.3   Item reduction. To generate the three scale questionnaire, two item reduction steps were applied. First, items were removed if they failed to load with sufficient strength (<.32) on any factor, had low communalities (<.2), or had high cross-loading (>.3; Tabachnick & Fidell, 2013). The item content of the final three-scale questionnaire was developed from the remaining 98 items using the following principles: (1) each scale should have the minimum number of items for internal reliability, (2) each scale should contain reverse-coded items, and equal numbers of reverse-coded items were required for each scale, and (3) heterogeneity of meaning across items was sought to cover the breadth of the domain being measured. When

items with comparable loadings were semantically similar, brevity and face validity were preferred.

      6.4.1.4 Preliminary investigation of external correlates. Participants completed standard demographic questions including age and gender, and were asked dichotomous (Yes/No) questions about physical and mental health problems. For example, "Have you ever been diagnosed with a mental disorder"? Affirmative responses were followed by a request for participants to describe the mental disorder in an open response format. Age, gender, physical health problems, history of mental illness, and self-reported difficulties sleeping were investigated as external correlates of the final questionnaire.

      6.4.2 Participants. A predominantly university student sample (18 years or older) was recruited. A total of 890 individuals commenced the questionnaire package online, with 783 (88%) complete responses recorded (see Table 5 for sample characteristics). Participants were largely first-year university students who were participating in a research experience program (which included on-campus and online students). Other recruitment methods included advertisements on social media and through contacts of the researchers.

Table 5

Demographic Characteristics for Study 1 and Study 2

	Study 1 (*n* =720)	Study 2 (*n* = 462)
	n (%)	n (%)
Age (years, M ± SD)	33.32 (10.11)	33.82 ± 11.19
Gender (% Women)	593 (82.4)	366 (79.2)
Employment		
Full-time	256 (35.6)	158 (34.2)
Part-time/ Casual	285 (39.6)	173 (37.5)
Not working	179 (24.9)	131 (28.4)
Studying		
Full-time	313 (43.5)	212 (45.9)
Part-time	362 (50.3)	243 (52.6)
Not studying	45 (6.3)	7 (1.5)
Relationship status		
Single	305 (42.4)	186 (40.3)
De facto	192 (26.7)	118 (25.5)
Married	223 (31.0)	158 (34.2)
Living in Australia	689 (95.7)	449 (97.2)
Current sleep problems	259 (36.0)	189 (40.9)
History of mental illness	221 (30.7)	160 (34.6)
Current physical problems	94 (13.1)	73 (15.8)

NB. De facto relationships is used in Australia to refer to a couple who lives together but are not married

6.4.3   Materials and procedures. A questionnaire package was developed and delivered online using Qualtrics software (https://www.qualtrics.com.au), Version 15. Participants were given a direct link to the survey. Order of items in the 170-item pool was randomised prior to participant administration. A single item measuring mindless responding was included: "Some participants don't read questionnaires carefully, please select 'agree' for this question". Ninety-two percent of participants selected the correct response for this item. The 62 incorrect responses were excluded leaving a final sample of 720 participants for item reduction analyses (adequate for an EFA of 170 items [Tabachnick & Fidell, 2013]). The university's internal ethics review board approved study procedures.

6.5   Study 1: Results

6.5.1   Exploratory factor analysis. Preliminary analyses showed the data were amenable to factor analysis. Inspection of the correlation matrix at the item generation stage showed numerous correlations >.3 with sampling adequacy meeting

criteria (Kaiser-Meyer-Olkin = .94). Bartlett's test of sphericity indicated that the observed correlation matrix deviated significantly from the identity matrix (χ^2 (14365) = 84692.54, p < .001).

The enforced orthogonal three-factor solution (explaining 30% of the total variance) was robust against Costello and Osborne's (2005) criteria. Inspection of item content and factor loadings in the forced 3-factor solution generated three robust factors with item content of depressed mood, morningness, and sleep quality.

Data-driven approaches to factor extraction generated a wide range of number of factors to extract. Inspection of the scree plot indicated five factors, the minimum average partial test indicated 26 factors, parallel analysis indicated 26 factors, and Kaiser-Guttman's criteria indicated 35 components with eigenvalues greater than 1. None of the empirically derived solutions were robust against the criteria of Costello and Osborne (2005). The 35-factor solution had five stable factors, the 26-factor solutions had four stable factors and the five-factor solution had three stable factors all explored for item content. All factor solutions indicated factor content of: depressed mood, morningness, and sleep quality; the fourth factor in the 26- and 35-factor solution included item content of value and beliefs about sleep, and the 35-factor model had a fifth stable factor with items pertaining to hypomania.

6.5.2   Item reduction. After initial item removal using the above criteria, 36 items remained on a provisional depressed mood scale, 24 items on a provisional sleep quality scale, and 38 items on a provisional morningness scale. Applying the principles outlined above to select the final items, the scales could be unambiguously named Depressed Mood, Morningness, and Good Sleep on the basis of their item content.

The 15-item Sleep, Circadian Rhythm and Mood (SCRAM) questionnaire had three 5-item scales (one reverse-scored item per scale; see formatted questionnaire in Appendix B). As shown in Table 6, these items had moderate-large loadings on their respective factors, and the resultant scales had adequate internal reliabilities, and interpretable intercorrelations in this sample (Table 7).

Table 6

Items and Factor Loadings for Morningness, Good Sleep, and Depressed Mood Scales

Scale		Item	Factor Loading
Morningness	M1	People talk about 'morning' and 'evening' people, I'm a morning person	.86
	M2	I work most efficiently before midday	.75
	M3	Waking up at 7am or earlier works really well for my natural body clock	.70
	M4	I get very tired by 11pm	.54
	M5	I wake up at least two hours later on a day off compared to a work day*	-.42
Good Sleep	GS1	I get the amount of sleep that I need	.79
	GS2	I sleep soundly through the night	.68
	GS3	I wake up feeling refreshed, like I've had enough sleep	.66
	GS4	If I slept better at night my life would be drastically different*	-.54
	GS5	I fall asleep within 30 minutes of trying to sleep	.49
Depressed Mood	DM1	Everything is going from bad to worse	.76
	DM2	All I want to do is cry	.72
	DM3	I have lost interest in things that I used to enjoy	.65
	DM4	I can't let things go, I find I ruminate a lot	.50
	DM5	I can laugh and see the funny side of things*	-.44

Note. * = reverse-scored item
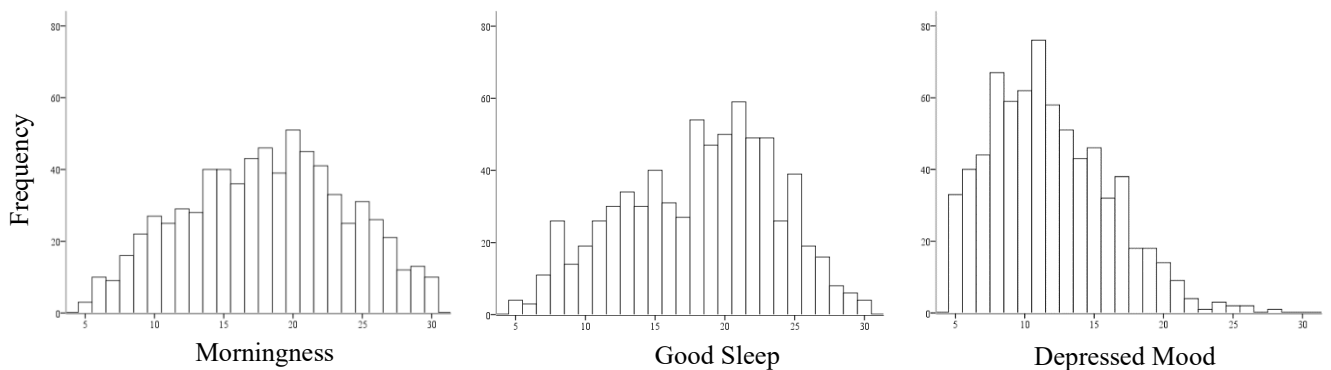
Figure 6. Distribution of scores on factors of Morningness, Good Sleep and Depressed Mood

Table 7

Correlations, Descriptive Statistics and Cronbach's Alpha for the Morningness, Good Sleep and Depressed Mood Scales

Scale	Morningness	Good Sleep	Depressed Mood
Morningness	-	.33***	-.17***
Good Sleep		-	-.45***
Depressed Mood			-
Mean	18.05	18.11	11.78
SD	5.82	5.51	4.29
Skew	-0.06	-0.25	0.59
Kurtosis	-0.73	-0.69	0.06
Cronbach's α	.79	.81	.77

Note. $N = 720$, relevant items reverse scored prior to reliability analysis, theoretical range on each scale is 5 – 30, ***$p<.001$

Figure 6 shows that scores on the SCRAM Morningness and Good Sleep scales were relatively normally distributed, while a non-significant positive skew was observed for scores on the Depressed Mood scale.

6.5.3   External correlates. Women scored significantly higher on scores of Morningness than men (t (717) = 2.77, p = .005, Hedge's g = .27); and a non-significant trend was observed for women reporting lower levels of Good Sleep (t (717) = 1.78, p = .075). Scores on Depressed Mood did not differ by gender (t (717) = .053, p = .96). Age was associated positively with Morningness (r (719) = .21, $p <$ .001), and negatively with Depressed Mood (r (719) = -.13, p = .001).

6.5.4   Preliminary external validation of the SCRAM factors. Independent samples t-tests were performed to investigate differences in Morningness, Good Sleep, and Depressed Mood in dichotomous self-reported health outcomes for mental illnesses (31% of the sample), reported physical complaints (13%) and sleep problems (36%) (see Table 8).

Table 8

Differences in Mean Good Sleep, Depressed Mood and Morningness Scores Across

Self-Reported Mental Illness Status, Physical Complaints, and Sleep Problems

	Mental Illness (31%)	No Mental Illness (69%)	*df*	*t*	Hedges' *g*
Morningness	17.24 (6.03)	18.41 (5.70)	719	2.51**	.20
Good Sleep	16.22 (5.69)	18.94 (5.21)	389.60	6.07***	.51
Depressed Mood	12.95 (4.44)	11.26 (4.12)	719	4.97***	.40
	Physical Complaints (13%)	No Physical Complaints (87%)			
Morningness	16.89 (5.59)	18.22 (5.84)	719	2.07*	.23
Good Sleep	15.64 (6.17)	18.48 (5.31)	114.58	4.23***	.52
Depressed Mood	12.22 (4.47)	11.71 (4.26)	719	1.08	.12
	Problems Sleeping (36%)	No Problems Sleeping (64%)			
Morningness	16.98 (6.14)	18.66 (5.55)	493.47	3.64***	.29
Good Sleep	13.90 (4.67)	20.48 (4.42)	719	18.82***	1.46
Depressed Mood	13.20 (4.55)	10.98 (3.92)	473.81	6.61***	.53

Note. Standard deviations presented in parentheses, adjusted degrees of freedom were used when the homogeneity of variance assumptions was violated, *p<.05, **p<.01, ***p<.001

Self-reporting a diagnosed mental illness was associated with lower scores on Morningness (t (718) = 2.55, p =.011, Hedge's g = .21) and Good Sleep (t (390.22) = 6.07, p <.001, Hedge's g = .51), and higher scores on Depressed Mood (t (718) = 4.97, p <.001, Hedge's g = .40). Self-reported presence of physical complaints was associated with lower scores on Good Sleep (t (114.65) = 4.23, p <.001, Hedge's g = .52) and Morningness (t (718) = 2.10, p =.036, Hedge's g = .23), but was unrelated to Depressed Mood (t (718) = 1.07, p = .28). Finally, self-reported problems sleeping were associated with lower scores on Good Sleep (t (718) =18.84, p <.001, Hedge's g = 1.46) and Morningness (t (491.89) = 3.57 p <.001, Hedge's g = .29) and higher scores on Depressed Mood (t (470.83) = 6.62, p <.001, Hedge's g = .54).

6.6   Study 2: Method

6.6.1   Participants, materials, and procedure. A predominantly student population was recruited with 498 complete survey responses (95% completion rate). A further 36 participants incorrectly answered the validity question (see Study 1 Method) and were deleted from further analyses. Administration of the questionnaire was identical to Study 1 with participants answering demographic questions and then the draft item pool. From these items the 15 items selected in

Study 1 for the SCRAM questionnaire were screened for univariate outliers with 32 participants deleted across the scales to leave a final sample of 430 for the CFA (see Table 5 for sample characteristics).

      6.6.2   Data analyses. Using Mplus version 7.11 (Muthén & Muthén, 2013), a CFA with a maximum likelihood estimation was used to investigate the three-factor model found in Study 1. Multiple methods were used to assess model fit (Hu & Bentler, 1999) including: the chi square test of model fit (divided by the degrees of freedom given the sensitivity to sample size), root mean square error of approximation (RMSEA), standardized root mean square residual (SRMR), comparative goodness-of-fit index (CFI), and Tucker-Lewis index (TLI). The chi square statistic divided by the degrees of freedom should be less than 3 for an acceptable fit (Schermelleh-Engel, Moosbrugger, & Müller, 2003), RMSEA scores less than .05 reflect a good fit, scores less than .08 an adequate model fit; and if the upper limit of the 90% confidence interval is .08 this adds additional support of model adequacy (Browne & Cudeck, 1992). SRMR scores should be below .08 (T. A. Brown, 2015; Hu & Bentler, 1999). CFI and TLI values should preferably be above .95, however indices in the range of .90-.95 are acceptable (Hu & Bentler, 1999).

6.7   Study 2: Results

      The results of the CFA are displayed in Figure 7.
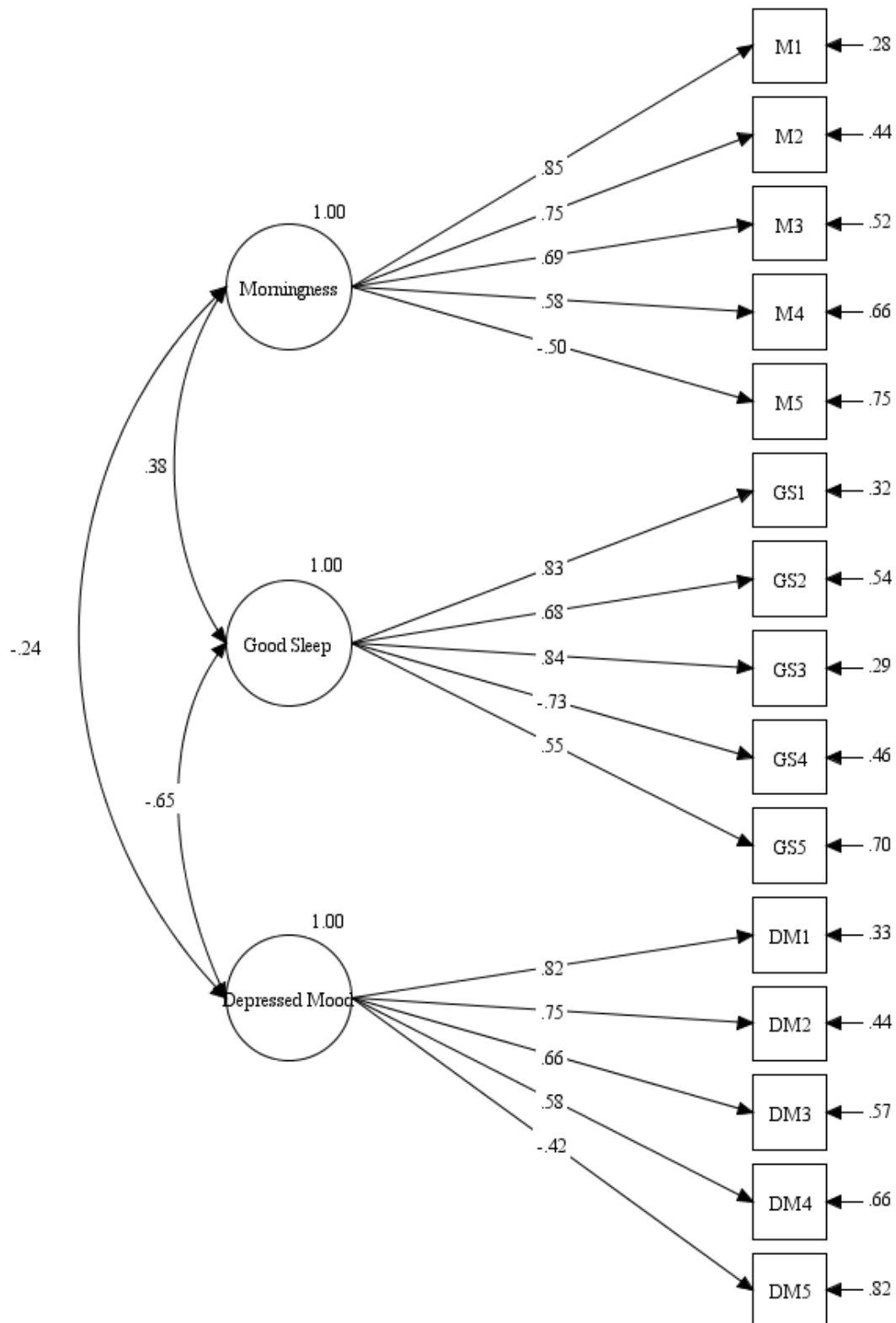
Figure 7. Multiple measurement model of the three-factor model

The analyses indicated the following fit indices: χ^2/df = 2.93, CFI = .93, TLI = .92, RMSEA =.067 (90% CI [.058, .077]), and SRMR = .052. Given the reference criteria, model fit was acceptable across all fit indices. As displayed in Figure 7, the resultant model supported the latent structure of the SCRAM as scored. In each case, the five items of the SCRAM scale loaded significantly on a single latent variable. The Morningness scale had a moderate positive relationship to Good Sleep (r = .38) and a weak negative association with Depression (r = - .24); Good Sleep and Depression had a strong negative relationship (r = - .65).

6.8 General Discussion

The aim of this project was to develop the first self-report instrument to reliably measure individual differences in sleep quality, circadian phase, and mood. Three distinct but correlated latent factors of Depressed Mood, Good Sleep and Morningness were identified using exploratory factor analyses. Data-driven factor structures supported the theoretically-based three-factor solution, and systematic item reduction led to the 15-item SCRAM questionnaire – a face-valid instrument maximally separating the measurement of sleep quality, circadian phase and mood. The three-factor latent structure of the SCRAM was confirmed in a second large student sample.

6.8.1 Relationship between Morningness, Good Sleep and Depressed Mood scales. Relationships amongst the three SCRAM scales were found to be congruent with existing literature. First, Study 1 and Study 2 data showed that Depressed Mood was correlated with lower levels of Good Sleep. Sleep disturbances affect mood (Pilcher & Huffcutt, 1996), and mood problems have been associated with lowered sleep quality through increased rumination and subsequent arousal at night (R. E. Schmidt, Harvey, & Van der Linden, 2011). The negative correlation between Morningness and Depressed Mood aligns with data suggesting that evening-type individuals are more likely to experience depression, and report more severe depressive symptomatology (Abe et al., 2011; Chan et al., 2014). Morningness and Good Sleep had a moderate positive correlation, consistent with evidence that eveningness is associated with higher levels of insomnia complaints (Barclay et al., 2016; Chan et al., 2014; Wittmann et al., 2006). Consistent with some previous research (e.g., Roenneberg, Wirz-Justice, et al., 2003), Morningness on the SCRAM questionnaire was positively associated with older age and female

gender (cf. Merikanto et al., 2012, for evidence that men may have higher levels of morningness relative to women).

In a preliminary assessment of convergent and divergent validity (Study 1), the SCRAM scales showed interpretable relationships to self-reported medical, sleep and psychiatric diagnoses. Previous or current mental illness were associated with lower scores on Morningness and Good Sleep scales, and higher scores on the Depressed Mood scale, consistent with evidence for sleep and circadian rhythm disturbances in a range of mental health disorders, (e.g., Gershon, Ram, Johnson, Harvey, & Zeitzer, 2015; Gershon et al., 2012; Harvey et al., 2011; Pritchett et al., 2012; Soehner et al., 2016; Wong, Brower, & Craun, 2016). Self-report of mental illness was associated with higher levels of Depressed Mood; aligning with previous data showing mood complaints to be common in mood and anxiety disorders, and schizophrenia (Levinson, Umapathy, & Musthaq, 1999; Ohayon & Roth, 2003; Pritchett et al., 2012; Taylor, Lichstein, Durrence, Reidel, & Bush, 2005). Finally, consistent with links between physical illnesses and biological rhythm function (e.g., Ancoli-Israel et al., 2006; Grimaldi et al., 2016; Haus et al., 2016; Katon, 2003; Musiek, Xiong, & Holtzman, 2015), self-reported physical illness was associated lower scores on the Good Sleep and Morningness scales.

The potential clinical significance of distinguishing between sleep quality, circadian phase, and mood is underscored by the SCRAM scores of participants who self-reported sleeping problems in Study 1. Self-reported sleep problems, not surprisingly, were associated with lower scores on the SCRAM Good Sleep scale but were also associated with higher scores on the SCRAM Depressed Mood scale. This is consistent with sleep disturbance being part of the diagnostic constellation of mood disorders in the DSM-5 (American Psychiatric Association, 2013) and higher negative mood levels observed following sleep disturbance in healthy individuals (Raniti et al., 2016; Tempesta, De Gennaro, Natale, & Ferrara, 2015). Self-reported sleep problems were also associated with lower scores on the SCRAM Morningness scale, consistent with an association between morningness and better sleep quality (e.g., Wittmann et al., 2006). The significance of this is that when a patient presents with sleep complaints mood problems and circadian phase alignment are critical in both the remittance of sleep problems and maintenance of sleep quality (Carney et al., 2009; Crowe, Beaglehole, & Inder, 2016; Harvey et al., 2005). Sleep quality

may be effectively treated but if the patient continues to have a delayed sleep cycle or depressed mood these may serve as independent risk factors for future problems with sleep quality, circadian phase, and/or mood.

6.8.2   The SCRAM questionnaire as a clinical and research tool. With additional validation (see below) the SCRAM questionnaire could improve clinical assessment of symptomatology across the three domains. By distinguishing these three strongly interrelated processes, the SCRAM questionnaire may also be a useful research tool. Malhi and Kuiper (2013) highlight that the substrates of sleep quality, circadian phase, and mood are likely to have different configurations and relationships across psychopathologies. The well-recognised biobehavioural interplay between sleep, circadian function and mood may speak to an under-appreciated superordinate construct or biobehavioural process that could be measured by the SCRAM questionnaire: Murray and colleagues have proposed the Circadian Reward Rhythm as a fundamental motivational process with circadian, sleep and mood manifestations (see also Alloy et al., 2017; Murray et al., 2009).

6.8.3   Limitations. A number of limitations should be noted. The samples of both studies were predominantly women (82% and 79% for Study 1 and 2 respectively) and students (94% and 98%), so findings may not generalise to the general population. Test-retest reliability was not investigated here, and the SCRAM's sensitivity to change in clinical settings is unknown.

6.8.4   Conclusions. The present project is a necessary first step in an ongoing program of research. Here, we have developed a psychometrically sound, face-valid brief measure that separates three intrinsically correlated processes for measurement/assessment purposes – the SCRAM questionnaire. To confirm the expected clinical utility of the instrument, more research is required. A critical next phase is to develop SCRAM profiles (pre- and post-treatment) for clinical samples with primary presenting problems in the sleep, circadian phase or mood domains. Subsequently our core prediction – that use of such profiles to drive treatment decisions is superior to current practice based on single-construct instruments – can be tested. With further investigation, the SCRAM questionnaire holds promise as a tool for assessing clinically-significant patterns of disturbance across these three processes.

Chapter 7: A Psychometric Investigation of the SCRAM Questionnaire

7.1   Study 2b: Linking Section

Contributing to the overarching aim of advancing knowledge of the relationship between biological rhythms and reward motivation, Study 2b (Chapter 7) aimed to investigate preliminary validity and reliability of the SCRAM questionnaire developed in Study 2a (see Chapter 6).

Chapter 7 has built upon the development and confirmatory structure work in the preceding Chapter 6. A subsample of participants from Study 3 (see Chapter 8) were used in Study 2b. The Study 3 sample wore an actiwatch for a week to measure sleep-wake behaviours. Approximately 18 months after collecting actigraphy data, participants were recontacted and asked to fill out the SCRAM questionnaire from which the correlations between the SCRAM scales and sleep-wake behaviours in Study 2b were analysed.

7.2 Abstract

The SCRAM questionnaire (Byrne, Bullock, & Murray, 2017) was designed to concurrently measure individual differences in three clinically important functions: diurnal preference, sleep quality, and mood. The 15-item questionnaire consists of three 5-item scales named Morningness, Good Sleep, and Depressed Mood. The overarching aim of the current project was to investigate the validity and reliability of the questionnaire. Here we report on associations investigated in three data sets. Study 1 (N=70, 80% females) was used to examine the test-retest reliability of the questionnaire, finding strong test-retest reliability of the three scales over a 2-week period (r's ranging from .73 to .86). Study 2 (N=183, 80% females) enabled us to examine the construct validity of the SCRAM scales against well-validated self-report measures of diurnal preference, sleep quality, and depression. Strong correlations were found between each SCRAM scale and their respective measure in bivariate analyses, and associations were robust after the inclusion of the remaining two SCRAM scales as predictors in regression analyses. Data from Study 3 (N=42, 100% males) were used to measure the extent to which SCRAM scores correlated with objective measures of sleep-wake behaviour using actigraphy. Morningness was found to be related to earlier sleep onset and offset times, and Good Sleep was related to higher sleep efficiency but to no other measures of sleep quality; Depressed Mood was not related to actigraphy measures. The findings provide provisional support for construct validity and reliability of the SCRAM questionnaire as a measure of diurnal preference, sleep quality, and depressed mood. Future research into the psychometrics of SCRAM should test the questionnaire's discriminant and predictive validity in clinical samples.

7.3   Introduction

Sleep quality, circadian function and mood, are interconnected biobehavioural processes. This reality can be observed in well-known associations between the three processes: Evening types, for example, report poorer sleep quality than morning types (Bakotic, Radosevic-Vidacek, & Koscec Bjelajac, 2017; Vollmer et al., 2017) and higher levels of depression (Abe et al., 2011; Kitamura et al., 2010; Merikanto et al., 2013). At the level of psychometrics, there is a long tradition of assessing key parameters from each of these processes via self-report questionnaires. These self-report measures assess timing of daily behaviours (e.g., Munich ChronoType Questionnaire [MCTQ], Till Roenneberg, Wirz-Justice, et al., 2003), sleep (the Pittsburgh Sleep Quality Index [PSQI], Buysse et al., 1989), and depression (Center for Epidemiologic Studies Depression [CES-D], Radloff, 1977) have arisen independently and do not account for covariation between the three processes. To address this limitation in the measurement literature, our group recently designed the SCRAM questionnaire (Byrne, Bullock et al., 2017) with the intention of creating a brief, clinical tool with two aims: 1) to have a questionnaire that optimally discriminates between self-reported diurnal preference, sleep quality, and mood, and, 2) to alert clinicians to consider all three processes in the presenting clinical picture. The development is motivated by the potential clinical utility of identifying whether patients are presenting with sleep complaints, mood symptoms, or phase disturbances, or some combination of disturbances in these three processes. We postulate that the SCRAM, in explicitly reminding clinicians to attend to all three processes, may improvement management of common multi-faceted presentations in primary care.

Byrne, Bullock et al. (2017) examined the latent structure of items generated from existing measures of diurnal preference, sleep quality, and depressed mood. Item content of existing questionnaires measuring diurnal preference, sleep quality, and mood was reviewed to ensure content coverage, and to suggest item content for the new questionnaire.   New items (none of which contained identical wording to items from existing questionnaires) were given a Likert-type 6-point response format ranging from Strongly Disagree to Strongly Agree (further distinguishing the new items from the items reviewed from existing instruments). Using an exploratory factor analysis with an orthogonal rotation, only a three-factor solution was an

adequate fit to the data. During item-reduction, only items with low cross-loadings on the other two factors were selected. The final three, 5-item scales measured different aspects of sleep quality (Good Sleep scale), diurnal preference (Morningness scale), and mood (Depressed Mood scale). Byrne et al. (2017) found correlations between the three scales consistent with previous research – Morningness and Good Sleep were positively associated, and Depressed Mood was negatively associated with both Morningness and Good Sleep (e.g., Barclay et al., 2016; Chan et al., 2014; Fernandez-Mendoza et al., 2015). A subsequent confirmatory factor analysis supported the three-factor latent structure (Byrne et al., 2017).

The present report compiles data from three studies, using different samples to investigate different psychometric properties of the SCRAM. The first data set examined internal consistency and test-retest reliability of the three scales over two weeks. High test-retest reliability (correlations of ~.8) is commonly observed for diurnal preferences and sleep quality in two-week time-frames (Backhaus, Junghanns, Broocks, Riemann, & Hohagen, 2002; Mollayeva et al., 2016; Randler, 2009). Test-retest reliability is also present in commonly-used mood scales, however the two week test-retest reliability is usually more modest (correlations of ~.5 at two weeks, Radloff, 1977), but with higher levels of test-retest reliability observed in nonclinical populations (Smarr & Keefer, 2011).

In the second sample, construct validity was examined by comparing well-validated self-report measures of diurnal preference (MCTQ), sleep quality (PSQI), and mood (CES-D) with the three SCRAM scales. The MCTQ focuses on the actual timing of sleep between work days and schedule-free days, light exposure and subjective ratings of morningness-eveningness throughout the lifespan (Till Roenneberg et al., 2003). The variable of mid-sleep on free days on the MCTQ has strong convergent validity with other measures of diurnal preference (Zavada et al., 2005) and is stable over periods of months and years (Kantermann & Eastman, 2018). The PSQI is the most commonly used measure of sleep quality, with demonstrated validity and reliability in separating good and poor sleepers in clinical and research settings (Buysse et al., 2008; Buysse et al., 1989; Mollayeva et al., 2016). The CES-D is a widely used measure for screening depression with sound convergent validity, and sensitivity and specificity in distinguishing clinical

depression from non-clinical populations (Chin, Choi, Chan, & Wong, 2015;
Cuijpers, Boluijt, & van Straten, 2008; Yang, Jia, & Qin, 2015).

Studies of self-report measures consistently find associations between sleep
quality, diurnal preference, and depressed mood. For example, Grandner et al. (2006)
found that higher global scores on the PSQI were associated with greater CES-D
scores (a finding that is robust to the removal of the sleep item on the CES-D, Ji et
al., 2017). More recently, C. M. Horne, Watts, and Norbury (2018) found that higher
levels of eveningness (as measured on the revised Morningness-Eveningness
Questionnaire) were associated with higher PSQI and CES-D scores, and a meta-
analysis by Au and Reece (2017) found a small association between evening
preferences and more severe mood symptoms in different mood disorders. In a
population study, Merikanto et al. (2015) found an increased odds ratio in the
incidence of depression in evening types relative to intermediate types, and in
intermediate types relative to morning types, even after controlling for self-reported
sleep sufficiency. In this sample, sleep sufficiency was also found to be related to
chronotype, with 47% of morning types reporting that they nearly always sleep
enough relative to 31% of intermediate, and 21% of evening chronotypes.

In assessing the construct validity of the new SCRAM questionnaire, we
wanted to assess how the three scales relate to objective measures of sleep-wake
behaviour. Sleep and activity can be objectively measured using actigraphy (Berger
et al., 2008). Actigraphy is associated with changes in the timing of sleep onset and
offset between free and work days (Korsiak, Tranmer, Leung, Borghese, & Aronson,
2018; Valomon et al., 2014), with evidence for a strong correlation in the expected
direction between these actigraphy parameters and self-report measures of diurnal
preference (Montaruli et al., 2017; Roveda**,** Vitale**,** et al., 2017). Actigraphy-
measured sleep efficiency, wake after sleep onset, and sleep latency are able to
distinguish between good and poor sleepers on the PSQI (Buysse et al., 2008).
Additionally, Keller, Grünewald, Vetter, Roenneberg, and Schulte-Körne (2017)
found that actigraphy measured sleep duration was related to subjective reports of
sleep length and poorer sleep quality when there are no next-day commitments.
Others have found that risk for (Bullock & Murray, 2014) and duration of (Grierson
et al., 2016) mood disorders is related to a reduced amplitude in actigraphically-

measured 24-hour activity rhythms; although contrary findings have also been reported (Robillard et al., 2015).

7.3.1   The present project. The present project sought to investigate reliability and construct validity for the SCRAM questionnaire. Data for the project were drawn from three studies enabling us to address three psychometric questions. We hypothesised that the scales would show strong internal consistency and test-retest reliability over a 2-week period (Study 1). In Study 2, we assessed the relationship between the SCRAM scales and well-validated measures of the same constructs. We predicted that each SCRAM scale would be associated with, and the strongest predictor of, their well-validated counterpart measure. Study 3 utilised an existing dataset with actigraphy data to assess external correlates of the new SCRAM scales. Higher scores on Morningness were hypothesised to be associated with earlier sleep onset and offset times. Good Sleep was hypothesised to be positively associated with sleep efficiency (SE), total sleep time (TST), and, negatively associated with sleep onset latency (SOL) and wake after sleep onset (WASO). Parameters of average daily activity, relative amplitude (RA), interdaily variability (IV), and intradaily stability (IS) have been examined in clinical populations but there is insufficient evidence in non-clinical populations to form hypotheses for the current study. As such, these variables were explored for potential relationships with the SCRAM scales.

7.4   Study 1: Test-Retest Reliability and Internal Consistency of the SCRAM Scales

7.4.1   Method: Study 1.

7.4.1.1   Participants. The sample for Study 1 ($N = 70$, 80% females, $M = 34.87$, $SD = 10.84$, age range 18 – 57 years) was predominantly drawn from the local university's pool of online and on-campus students who participated for course credit. The remainder of participants came from the researchers' social networks.

7.4.1.2   Materials. The SCRAM questionnaire (Byrne, Bullock, et al., 2017) contains three 5-item scales measuring sleep quality (Good Sleep, e.g., "I get the amount of sleep that I need"), diurnal preference (Morningness, e.g., "People talk about 'morning' and 'evening' people, I'm a morning person"), and mood (Depressed Mood, e.g., "Everything is going from bad to worse"). Each scale contains one reverse scored item. All items are measured on a 6-point Likert-type

scale ranging from 1 (Strongly Disagree) to 6 (Strongly Agree). A scale score is derived by summing ratings after reverse scoring. The theoretical range for each scale is 5-30. The item content of the Good Sleep scale includes sleep quantity, sleep latency, sleep continuity, restorative quality of sleep, and daytime dysfunction, with higher scores indicative of better sleep quality, and lower scores poorer sleep quality. The Morningness scale reflects self-reported diurnal preference, sleep onset and offset preferences, change in sleep between work days and free days, and time of day work preferences. While higher scores are indicative of someone with a stronger morning orientation, lower scores are indicative of stronger evening preferences. Unlike the bipolar Good Sleep and Morningness scales, the Depressed Mood scale reflects higher depressed mood at one end of the scale, and a relative absence of depressed mood with low scores (rather than high levels of positive mood). The Depressed Mood scale includes items reflecting anhedonia, crying, pessimism, rumination, and lowered mood.

7.4.1.3 Procedure. A large sample was recruited for the first two studies. Due to technical difficulties only 38 participants had valid scores for both studies and the two samples were separated into Study 1 and Study 2. For Study 1, the SCRAM questionnaire was completed online at two time-points, separated by two weeks. Participation was voluntary and anonymous. The local university ethics board approved study procedures.

7.4.2   Results: Study 1. Questionnaire responses were screened for missing data, duplicate records, univariate outliers, and invalid responses. One univariate outlier on the Depressed Mood scale at Time 1 was excluded from the analyses, leaving a final sample of 69.

Table 9

Means, Standard Deviations, Correlations, and Internal Consistency between the

SCRAM Scales at Time 1 and Time 2 for Study 1

	Mean (SD) T1	Mean (SD) T2	Morningness (T2)	Good Sleep (T2)	Depressed Mood (T2)	Cronbach's alpha T1	Cronbach's alpha T2
Morningness	17.86 (6.42)	18.09 (5.81)	.86***	.42***	-.28*	.85	.77
Good Sleep	17.01 (5.71)	17.00 (5.46)	.40**	.81***	-.30*	.81	.82
Depressed Mood	11.91 (4.43)	12.03 (4.02)	-.10	-.30*	.73***	.76	.77

Note. T1= Time 1, T2 = Time 2 (two weeks following Time 1); * *p*<.05, ** *p*<.01, *** *p*<.001

As shown in Table **9**, the test-retest reliability is strong across the two-week retest period. Morningness had the highest test-retest reliability, followed by Good Sleep, and Depressed Mood. Cronbach's alpha at Time 1 and Time 2 suggests all scales have acceptable internal consistency. Using paired t-tests, no significant differences were found for Morningness (*p* = .57), Good Sleep (*p* = .97), or Depressed Mood (*p* = .76) between Time 1 and Time 2.

7.5   Study 2: Predictive validity of the SCRAM scales for well-validated measures

7.5.1   Method: Study 2.

7.5.1.1   Participants. Participants were 183 undergraduate psychology students (147 females, *M* = 32.18, *SD* = 9.79, age range 18-57 years, 38 participants also took part in Study 1) who participated as part of the local university's research experience program and for which they earned course credit. A key variable needed to calculate PSQI scores was inadvertently not included on the online survey. Before this error was discovered some participants had already completed the SCRAM at Time 1 and Time 2 as part of Study 1. After the online questionnaire was corrected, 38 of the 183 participants were included in both Study 1 and Study 2.

7.5.1.2   Materials.

7.5.1.2.1   Munich ChronoType Questionnaire. The Munich ChronoType Questionnaire (MCTQ; Roenneberg, Wirz-Justice, et al., 2003) quantifies time of day preference through reports of the timing of sleep on work days and schedule-free days, light exposure and subjective ratings of morningness-eveningness throughout the lifespan (Roenneberg, Wirz-Justice, et al., 2003; Zavada et al., 2005). In contrast to instruments like the commonly-used Morningness-Eveningness questionnaire (J.

A. Horne & Östberg, 1976), the MCTQ is designed to measure actual timing of daily behaviours, rather than the individual's preferred timing. Morningness may be a self-report proxy for sleep phase, and diurnal preference measures have been found to correlate strongly with sleep timing measures (e.g., Zavada et al., 2005). Mid-sleep time on free days is considered to be a measure of chronotype, which is often corrected for sleep duration (Roenneberg & Merrow, 2007); however this sleep correction may introduce bias. Jankowski (2015, 2017) has argued that the sleep corrected mid-sleep time on free days may be biased by sleep duration on both free days and work days. As such, the MCTQ outcome variable used in the current study was mid-sleep time on schedule-free days (calculated as the mid-point between sleep onset and sleep offset in minutes relative to midnight, MSF; Roenneberg, Wirz-Justice, et al., 2003).

7.5.1.2.2   Pittsburgh Sleep Quality Index. The PSQI (10 items; Buysse et al., 1989) measures the quality and pattern of sleep over the past month, through seven domains: subjective sleep quality; sleep latency; sleep duration; habitual sleep efficiency; sleep disturbances; use of sleeping medication, and daytime dysfunction, using both free-response (quantitative sleep parameters) and forced choice questions (Buysse et al., 1989). The outcome variable is a global score derived from these component scores.

7.5.1.2.3   Center for Epidemiologic Studies Depression Scale (CES-D). The CES-D (20 items; Radloff, 1977) is a self-report measure of depressive symptomatology. Depressive symptoms are measured on a scale ranging from 0 (*symptom experienced "rarely or none of the time / 1 day"*) to 3 (*symptom experienced "most or all of the time [5–7 days]*")." Four items are reverse-scored (Radloff, 1977). The CES-D has shown adequate test-retest reliability and internal consistency across multiple samples (Chin et al., 2015; Cuijpers et al., 2008; W. C. Miller, Anton, & Townson, 2008; Yang et al., 2015). Total CES-D score was used as the outcome variable here.

7.5.1.3   Procedure. Participants completed the SCRAM questionnaire (see Study 1 method), MCTQ, PSQI, and CES-D, through an online survey on the Qualtrics platform. The order of presentation of questionnaires was randomised, with the full survey battery taking approximately 20-30 minutes to complete.

7.5.1.4 Data analytic approach. Participants were screened for implausible and invalid responding. Univariate outliers (*z*-scores > 3.29) were also identified for each variable. Participants who reported sleeping more than 12 hours per day were considered implausible responses, and those who reported spending more time asleep than in bed on the PSQI were invalid responses, and were excluded from analyses. In the data cleaning for the MSF one participant's responses were missing, there were 23 implausible responses, and one univariate outlier was excluded from later analyses. For the PSQI, seven participants' scores were excluded: four for implausible responding, one for invalid responding, and two for being univariate outliers. All responses were complete on the CES-D, two univariate outliers were identified and excluded from later analyses.

The distribution of scores on the Good Sleep, Morningness, MSF scales were approximately normal. Slight positive skews for PSQI global score, Depressed Mood, and CES-D did not warrant transformation.

Prior to the regressions, correlations and t-tests were performed between age and gender, respectively, to assess whether they were significantly related to the variables under investigation. Additionally, correlations were performed between the three SCRAM scales and the well-validated measures to examine their associations. Three standard multiple regressions were conducted to assess the ability of the three SCRAM scales to predict well-validated self-report measurement of chronotype (MSF), sleep (PSQI), and depression (CES-D) in each regression.

7.5.2 Results: Study 2. Significant correlations were found between Morningness, MSF, and CES-D and Age. There was a significant difference between men and women on Morningness, $t(180) = -2.08$, $p = .039$ such that women had significantly higher Morningness relative to men. This led us to control for Age and Gender in Step One of the regressions.

Table 10

Descriptive Statistics and Intercorrelations of SCRAM Scales and CES-D, PSQI, and MSF for Study 2

	(1)	(2)	(3)	M	SD	n
(1) Morningness	-	.30***	-.04	17.74	5.96	183
(2) Good Sleep	-	-	-.45***	17.64	5.53	183
(3) Depressed Mood	-	-	-	12.01	4.63	183
MSF	-.65***	-.08	-.05	229.35	88.67	158
PSQI	-.15*	-.70***	.51***	6.54	2.92	175
CESD	-.17*	-.48***	.81***	15.16	10.49	181

Note. * $p<.05$, ** $p<.01$, *** $p<.001$, MSF = Mid-Sleep on Free Days (expressed as minutes past midnight), PSQI = Pittsburgh Sleep Quality Index, CES-D = Center for Epidemiologic Studies Depression Scale.

Table 10 shows no significant association between Morningness and Depressed Mood. A significant moderate positive correlation was found between Good Sleep and Morningness. Good Sleep and Depressed Mood had a strong negative association. The PSQI and CES-D were significantly related to all three SCRAM scales, while MSF was only related to Morningness.

Table 11

Standard Multiple Regression using Morningness, Good Sleep, and Depressed Mood SCRAM Scales as Predictors of MSF, PSQI, and CES-D for Study 2

	MSF, n=158			PSQI, n=175			CES-D, n=181		
	B	β	R^2	B	β	R^2	B	β	R^2
Step 1	393.91		.18	6.83		.003	23.49		.06
Age	-3.80	-.41***		-.02	-.05		-.26	-.24**	
Gender	-24.35	-.11		.13	.02		.05	.002	
Step 2	442.44		.49	10.26		.53	6.06		.69
Age	-2.30	-.25***		-.01	-.03		-.13	-.13**	
Gender	-4.28	-.02		.24	.03		-.12	-.01	
Morningness	-9.13	-.61***		.02	.05		-.10	-.06	
Good Sleep	1.70	.11		-.33	-.62***		-.25	-.13**	
Depressed Mood	-.33	-.02		.13	.21**		1.65	.73***	

Note. * $p<.05$, ** $p<.01$, *** $p<.001$, MSF = Mid-Sleep on Free Days, PSQI = Pittsburgh Sleep Quality Index, CES-D = Center for Epidemiologic Studies Depression Scale

The predictors were Age and Gender (Step 1), and Morningness, Good Sleep, and Depressed Mood for each of the regressions. As shown in Table **11**, Age was a significant predictor of MSF and remained significant after Morningness, Good

Sleep, and Depressed Mood were added into the regression at Step 2. Only Morningness and Age were significant predictors of MSF, with Morningness the strongest predictor of MSF (Part correlation = -.54, CI = [-11.08, -7.19]). Higher scores on Morningness and older Age predicted earlier MSF. For the PSQI, only Good Sleep (Part correlation = -.51, CI = [-.40, -.26]) and Depressed Mood (Part correlation = .18, CI = [.06, .21]) were significant predictors at Step 2. Good Sleep was the strongest predictor of PSQI with higher scores on Good Sleep predicting lower scores on PSQI. After removing the variance attributable to Age, the SCRAM scale predicting CES-D score most strongly was Depressed Mood (Part correlation = .64, CI = [1.44, 1.86]). Good Sleep was also a significant (negative) predictor of CES-D (Part correlation = -.11, CI = [-.44, -.07]). The examination of relationships between the SCRAM scales and well-validated measures of sleep quality, diurnal preference, and mood found stronger support for convergent compared with divergent validity of the SCRAM scales.

7.6   Study 3: Construct validity of the SCRAM scales to external correlates of sleep-wake behaviours

7.6.1   Method: Study 3.

7.6.1.1   Participants. Participants were 42 men who had been recruited for a previous study (Byrne & Murray, 2017a). For the present purposes, the key feature of the larger study design was that participants provided at least seven days of actigraphy data, were aged between 18-29 and screened to be physically and mentally healthy at the time of actigraphy data collection.

7.6.1.2   Equipment. A wrist-worn actigraph (Actiwatch-L or Actiwatch 2; Philips, Respironics Inc., Bend, Oregon) was worn consecutively for at least seven nights (worn on their non-dominant wrist). Recordings were sampled every 30 seconds or one minute: If data were sampled in 30 second epochs they were averaged across the minute in the data analyses.

7.6.1.3   Procedure. Participants who had previously provided actigraph data were contacted some 12-18 months later to complete the SCRAM Questionnaire. A total of 42 of the original 50 participants from the larger study consented to participate in this study, and were compensated with $10 AUD.

7.6.1.4   Data analytic approach: Study 3. Actigraphy data were screened for missing values prior to analyses. We considered 90 continuous minutes without

movement to be missing data. Of the 42 participants, nine were excluded (three with equipment malfunctions, six due to missing data). One participant had one night of missing data (watch removed 8:30pm and replaced 11am the following day). As this participant still had eight periods of available data, the night of missing data was removed from the data series prior to analysis.

Objective measures of sleep-wake behaviour included: sleep efficiency (SE), wake after sleep onset (WASO), total sleep time (TST), sleep onset latency (SOL), time of sleep onset (minutes relative to midnight), and time of sleep offset (minutes relative to midnight), averaged within-subjects across the 7 days of actigraphy recording. Inbuilt algorithms of the Respironics Actiware Software 6.0.9. (Philips, Respironics Inc., Bend, Oregon) were used to generate these variables.

For exploratory analyses, an average daily activity level across the middle six active periods was analysed. Measurement of the 24-hour activity rhythm was derived from three non-parametric variables taken across seven days for each participant: relative amplitude (RA); intradaily variability (IV); and, interdaily stability (IS; Van Someren et al., 1999). RA is derived from a ratio of the most consecutively active 10 hours (M10), and least consecutively active five hours (L5) in a 24-hour period. It is standardised relative to a predicted level of total activity to normalise individual differences in activity. A higher ratio is indicative of a more robust circadian rhythm (cf. Refinetti, 2004). IV measures the fragmentation of activity between rest and active periods. Higher fragmentation of daily activity patterns is indicative of a weaker circadian oscillator. IS examines the pairing of the 24-hour activity rhythm to the broader activity pattern across time. A lower IS score is indicative of a relatively unstable activity rhythm across the seven day sampling period (Van Someren et al., 1999).

7.6.2   Results: Study 3. Bivariate analyses tested the correlations between objective measures of sleep-wake behaviour variables and the SCRAM scales (displayed in Table 12).

Table 12

Correlations Between Actigraphy-Derived Variables and the SCRAM Scales for Study 3

	Morningness	Good Sleep	Depressed Mood
Total sleep time	-.30[+]	-.13	.04
Sleep efficiency	.11	.37*	.03
Wake after sleep onset	.07	-.20	-.18
Sleep onset latency	-.26	-.27	.04
Sleep onset time	-.46**	-.23	.05
Sleep offset time	-.60**	-.31[+]	.09
Relative amplitude	.24	.01	.08
Intradaily stability	.21	.02	-.08
Interdaily variability	-.08	-.19	-.09
Average 24-hour activity	.39*	.30[+]	-.31[+]

Note. [+]$p<.1$, * $p<.05$, ** $p<.01$,

As predicted, Morningness was negatively related to time of sleep onset and offset, indicating that higher Morningness was associated with earlier sleep onset and sleep offset times (see Table 12). Good Sleep scores were positively and significantly related to increased SE, but contrary to predictions Good Sleep was not related to TST, SOL, or WASO.

In exploratory analyses, average activity across the six full days was positively and significantly related to a greater score on Morningness, and trended towards a positive relationship with Good Sleep ($p = .094$), and a negative relationship with Depressed Mood ($p = .083$). Depressed Mood scores were not significantly related to any actigraphy measures. The SCRAM scales were not associated with RA, IV, or IS.

7.7   Discussion

The overarching aim of this project was to investigate the psychometric properties of the new three-scale SCRAM Questionnaire. As hypothesised, test-retest reliability and internal consistency was acceptable for each scale. Also, as predicted, in a regression-based competition for explanatory variance, Morningness, Good Sleep, and Depressed Mood were the strongest predictor of well-validated self-report measures of diurnal preference (MCTQ), sleep quality (PSQI), and depression (CES-D) respectively. Although the three convergent validity predictions for Study 2 were all supported, it is worth noting that divergent validity was not absolute: specifically, Good Sleep scores was negatively associated with CES-D scores, and Depressed

Mood was positively associated with PSQI scores. Finally, Morningness and Good Sleep were related to objective measures of sleep timing and SE, respectively, in expected directions. Contrary to predictions, Good Sleep was not related to other objective measures of sleep-wake behaviour (TST, SOL, WASO). In exploratory analyses average activity levels were positively associated with Morningness. The SCRAM scales were not related to other exploratory measures of RA, IV, and IS.

The SCRAM scales demonstrated acceptable internal consistency and high test-retest reliability across a two-week period in Study 1. Internal consistency was found to be similar to that found in the original study (Byrne, Bullock, et al., 2017). In the present study, test-retest reliability across two weeks was found to be appropriately stable. While Depressed Mood and Good Sleep were expected to display some variability across the two week period to mirror normal fluctuations in mood and sleep (Backhaus et al., 2002; Pemberton & Fuller Tyszkiewicz, 2016), a comparatively higher level of test-retest reliability in Morningness was demonstrated and aligns with the test-retest reliability of this trait construct (Roenneberg et al., 2004; Roenneberg, Wirz-Justice, et al., 2003).

To examine construct validity, in Study 2 we tested whether the respective SCRAM scale was the strongest predictor of well-validated measures of sleep quality, diurnal preference, and depression. As expected, when Morningness, Good Sleep, and Depressed Mood were entered into a regression (along with covariates Age and Gender), each SCRAM scale was the strongest predictor of the respective well-validated measures: Morningness was the strongest predictor of MSF scores on the MCTQ, Good Sleep the global PSQI score, and Depressed Mood the CES-D. Although a scientific aim of the SCRAM Questionnaire was to measure the constructs of Morningness, Good Sleep, and Depressed Mood in a relatively purified manner, it also has the pragmatic clinical aim of encouraging clinicians to consider all three processes as part of assessment. It was therefore important to demonstrate that SCRAM shows an appropriate pattern of convergent and divergent associations with commonly-used, well-validated measures of diurnal preference, sleep quality, and depression. While we have argued that these scales tend to be 'noisy' measures of these individual constructs (Byrne, Bullock, et al., 2017), they are nonetheless clinically significant external correlates for the SCRAM. The data of Study 2 found direction and magnitude of effects were as predicted, with bivariate analyses

showing significant moderate-strong relationships between Morningness and MSF, Good Sleep and PSQI, and Depressed Mood and CES-D. Moreover, regression analyses (controlling for Age and Gender) confirmed that the strongest SCRAM predictors of MSF, PSQI, and CES-D were Morningness, Good Sleep, and Depressed Mood, respectively. Consistent with our argument that each of these commonly-used, well-validated instruments combine variance that is more carefully parsed on the SCRAM, we note that each regression also had a small-moderate secondary SCRAM predictor: Good Sleep was a (non-significant) secondary predictor of MSF; Good Sleep was a significant secondary predictor of CES-D; Depressed Mood was a significant secondary predictor of PSQI. We think that the biobehavioural phenomena of sleep quality, diurnal preference, and mood are associated in nature, thus these correlations can be observed in the self-report questionnaires that aim to measure them. An important limitation of existing measures of sleep quality, diurnal preference, and mood is that no questionnaire before the development of SCRAM had actively designed scales to measure each of these processes separately; hence, for example, sleep quality as measured on the PSQI could also be measuring depressed mood as measured on the CES-D. This evidence supports that the SCRAM can optimally discriminate and account for important covariation between diurnal preference, sleep quality, and mood processes.

Finally, Study 3 provided some support for the validity of the SCRAM questionnaire by demonstrating that objective measures of sleep-wake behaviour relate to self-report scales of Morningness and Good Sleep. Sleep efficiency and sleep timing variables were related in expected ways to the Good Sleep and Morningness SCRAM scales, respectively. Other objective measures of sleep-wake behaviour – wake after sleep onset, total sleep time, sleep onset latency - were not related to the Good Sleep scale. Exploratory analyses found that average activity levels were positively related to greater Morningness, and non-significant trends were found between activity and Good Sleep, and Depressed Mood (negative). Earlier sleep times in individuals with a morning-preference have been found in previous diurnal preference questionnaires (Lehnkering & Siegmund, 2007; Roenneberg, Wirz-Justice, et al., 2003) and are strongly associated with biological markers of circadian phase (Baehr et al., 2000; Paine & Gander, 2016). The increased activity levels observed in those higher in Morningness may be explained

by greater time spent outdoors. Increased light exposure has previously been related to earlier sleep times and self-reports of morningness (Roenneberg, Wirz-Justice, et al., 2003). Among the objective sleep measures, only sleep efficiency was related to Good Sleep. The Good Sleep scale may load most heavily on factors associated with sleep efficiency. It is also possible that sleep efficiency may be a more stable trait measure of sleep-wake behaviour given the time delay between actigraphy measurement and completion of the SCRAM.

Despite providing some support for the psychometric properties of the SCRAM questionnaire, limitations should be noted. Three different data sets were used to investigate the psychometric properties of this questionnaire and there were sample limitations for all three data sets. Data were (mostly) drawn from a student population which may limit the generalisability of findings. As the university has an extensive online student population, mean age was somewhat higher than might be expected in a college sample; gender was also skewed, with a predominantly female sample for Study 1 and Study 2 (80%) and only men used in Study 3. In addition, 76% of the Study 2 sample were 'poor sleepers' according to established PSQI criterion cut-off scores (Buysse et al., 1989). A further limitation is that the actigraphy data used in Study 3 was collected up to 18 months prior to the completion of the SCRAM. PSQI and MCTQ data were not collected with SCRAM data so additional comparisons with existing measures cannot be made. This study is also largely limited to self-report correlates. Future work examining the psychometric properties of the SCRAM questionnaire should validate it against objective measures of sleep (such as polysomnography), and biological phase markers of the circadian system (dim-light melatonin onset).

Future SCRAM development needs to examine the discriminant and predictive validity of the SCRAM questionnaire in clinical populations. As part of this work, SCRAM profile norms can be established in clinical populations, and the utility of the questionnaire in clinical settings can be examined. The present investigation indicates that the SCRAM questionnaire may have the advantage of being related to well-validated measures in expected ways, while effectively discriminating between sleep quality, circadian function, and mood processes. Together, the continued SCRAM development project will may ultimately help clinicians to consider all three processes in clinical presentations.

7.7.1. Conclusions. The current project has generated preliminary supportive evidence of SCRAM's construct validity and reliability. The self-report instrument has potential to be used to explore the three processes of diurnal preference, sleep quality, and depressed mood in parallel, with high test-retest reliability demonstrated across a 2-week period and each SCRAM scale remaining the strongest predictors of their respective well-validated counterpart measures. Preliminary actigraphy data provide additional evidence that the Morningness scale is related to earlier sleep times and the Good Sleep scale is related to sleep efficiency. This brief, easily administered questionnaire has the benefit of concurrently measuring all three interacting processes, while optimally, discriminating between diurnal preference, sleep quality, and depressed mood. Next steps in the psychometric investigation of SCRAM should focus on generating norms in relevant clinical groups (e.g., major depression, insomnia, delayed sleep phase syndrome), and testing the instrument's discriminant and predictive validity in everyday clinical practice.

Chapter 8: Diurnal rhythms in psychological reward functioning in healthy young men: "wanting", liking and learning

8.1   Study 3: Linking Section

Byrne, J. E. M., & Murray, G. (2017). Diurnal rhythms in psychological reward functioning in healthy young men: 'wanting', liking and learning. *Chronobiology International, 34*(2), 287-295. doi:10.1080/07420528.2016.1272607

Study 3 investigated diurnal variation in psychological components of reward ("wanting", wanting, liking, and learning) at three time-points 10:00h, 14:00h and 19:00h in 50 healthy male participants. One gap in the literature has been whether diurnal and circadian variation observed in positive affect (e.g., Murray, Allen, & Trinder, 2002; Murray et al., 2009; Watson et al., 1999) can be identified in behavioural tasks and other psychological measures thought to measure reward motivation.

Study 3 is relevant to the overarching aim of the project to investigate critical aspects of the relationship between biological rhythms and reward motivation. Study 3, Study 4 (see Chapter 9), and Study 5 (see Chapter 10) all focused solely on the circadian predictor variable, investigating circadian modulation of reward motivation. Study 3 sought to advance the investigation of diurnal variation and reward motivation beyond self-reported positive affect. This is linked to Study 4 and Study 5 which aimed to identify circadian modulation in fMRI measures of reward motivation.

In the week prior to testing, participants in Study 3 wore an actiwatch for a week. The relationship between measures of sleep-wake behaviour obtained in this sample and their relationship to the SCRAM scales were reported on in the validation of the new SCRAM questionnaire presented in Study 2b (Chapter 7). A subsample of the 50 participants recruited in Study 3 were used in the fMRI study presented in 5 (see Chapter 10).

8.2   Abstract

A range of evidence suggests that human reward functioning is partly driven by the endogenous circadian system, generating 24-hour rhythms in behavioral measures of reward activation. Reward functioning is multi-faceted, but literature to date is largely limited to measures of self-reported positive mood states. The aim of this study was to advance the field by testing for hypothesized diurnal variation in previously unexplored components of psychological reward: "wanting", liking and learning using subjective and behavioral measures. Risky decision making (automatic Balloon Analogue Risk Task), affective responsivity to positive images (International Affective Pictures System), uncued self-reported discrete emotions, and learning-contingent reward (Iowa Gambling Task) were measured at 10.00 hours, 14.00 hours and 19.00 hours in a counter-balanced repeated measures design with 50 healthy male participants (aged 18-30). As hypothesized, risky decision making (unconscious "wanting") and ratings of arousal towards positive images (conscious wanting) exhibited a diurnal waveform with indices highest at 14.00 hours. No diurnal rhythm was observed for liking (pleasure ratings to positive images, discrete uncued positive emotions) or in a learning-contingent reward task. Findings reaffirm that diurnal variation in human reward functioning is most pronounced in the motivational "wanting" components of reward.

Keywords: circadian rhythms, diurnal rhythms, reward, wanting

8.3   Introduction

A range of evidence suggests that reward functioning is partly modulated by the endogenous circadian system (Murray et al., 2009). The study of circadian priming of reward motivation in humans has focused primarily on subjective measures, particularly self-reported positive affect (PA), understood as a manifestation of neural reward activation (Knutson et al., 2014). The present study sought to advance this literature by exploring different psychological facets of reward in a diurnal context.

8.3.1   Three psychological components of reward. Reward function is complex, with three interacting psychological components commonly recognised (Berridge & Robinson, 2003): (1) drive towards rewards ("wanting"/motivation); (2) hedonic association of the reward ("liking"), and (3) predictive cognitive understanding of reward reinforced by previous experience (learning; Berridge & Kringelbach, 2008; Berridge & Robinson, 2003; Yeates & Main, 2008). Berridge and colleagues use quote marks to distinguish unconscious processes ("wanting", "liking") from their conscious counterparts (wanting and liking; Berridge & Robinson, 2003). Despite often working together in the reward-behaviour cycle (Berridge & Kringelbach, 2015), parsing these components has been an area of growing interest.

In animals, the neural substrates of these three components of reward are reasonably well characterised. Dopaminergic projections from the ventral tegmental area (VTA) to the nucleus accumbens (NAc) are the neural underpinnings of the "wanting" pathway of reward (Berridge, 2007; Wyvell & Berridge, 2000). Peciña and colleagues (2003), for example, found that mice genetically modified to have a hyperdopaminergic response have an amplified "wanting" for sucrose while demonstrating no increased "liking" response. Cognitive predictions refer to the learned representation of the action-outcome relationship; that is, a learned expectation between an action and an outcome in a reward context (Berridge & Kringelbach, 2008). S. Robinson et al. (2005) found that in mice unable to synthesise dopamine, learning new reward-based associations was relatively unaffected. Similarly, Berridge (2007) note that hyperdopaminergic mice do not show increased speed of learning or increased perseveration to learned reward-based

associations. This suggests that dopamine is not necessary for reward learning, drawing a clear distinction with "wanting" processes (Berridge et al., 2009).

8.3.2   Existing evidence for diurnal rhythms in facets of reward. A number of naturalistic studies have found evidence for a diurnal rhythm in PA, the waveform of which is highest after midday with a decline around 9pm (Clark et al., 1989; Stone et al., 2006; Watson et al., 1999). In the first study to measure diurnal variation in reward at a neural level in humans, Hasler, Forbes, et al. (2014) found, using fMRI, greater striatal activity in monetary response to reward in the afternoon when compared to the morning scan, most likely indicative of the "wanting" component of reward activation.

Evidence that this diurnal rhythm has an endogenous circadian driver comes from more rigorous chronobiological protocols. In a constant routine study, Murray, Allen, and Trinder (2002) found that PA aligned with the core body temperature rhythm to peak in the afternoon. Building on this, Murray et al. (2009) demonstrated in a constant routine protocol 25% of the variance in PA was attributable to the circadian rhythm of core body temperature, with this rhythm also observed in a subsequent forced desynchrony protocol. The authors conclude that circadian rhythms prime human reward activation. Further, they emphasise that aligning with animal research, reward activation is a dopaminergic phenomenon but its measurement is currently limited to self-report in humans.

There is limited evidence for a circadian rhythm in learning or liking. Marmosets, golden hamsters and some rat strains demonstrate a reward-conditioned place preference only at the circadian time of prior training (Cain et al., 2004; Kurtuncu et al., 2004; Valentinuzzi et al., 2008). No animal research has identified a circadian component of "liking", but two human studies have found a circadian rhythm in subjective happiness (as measured by a single item visual analogue scale) (Boivin et al., 1997; Murray et al., 2009) providing preliminary evidence for a circadian component of conscious liking.

8.3.3   The present study. The aim of this study was to examine the diurnal modulation of human reward activation, recognising and exploring various facets of reward functioning. It was hypothesized that performance on reward tasks involving "wanting" and wanting would vary with time of day with a peak at mid-afternoon (consistent with existing studies of PA, above). We also explored the possibility that

a diurnal rhythm peaking at mid-afternoon could be observed in liking and learning aspects of human reward function.

8.4   Method

8.4.1   Participants. Due to age and gender effects on sleep and circadian function (Davis, Darrow, & Menaker, 1983; Duffy, Zeitzer, & Czeisler, 2007), participation was limited to males aged 18 to 30 years. Exclusion criteria included the presence of a current physical or psychiatric disorder, past history of severe mental illness, shift-work during the study, recent transmeridian travel and use of medication known to affect the circadian system. As this formed part of a larger neuro-imaging study (reported elsewhere), participants were required to be right-handed and were screened for contraindications of fMRI testing. The final sample consisted of 50 men (M=22.69 years, SD=3.20 years). One participant completed only two testing sessions but was included in analyses.

8.4.2   Measures.

8.4.2.1   "Wanting" component of reward. To measure the wanting component of reward, the automatic Balloon Analogue Risk Task (aBART; Lejuez et al., 2002; Pleskac et al., 2008) was used. Across 30 trials, participants select how many times they want to pump up the balloon, with each pump earning 5 cents; if the balloon pops all winnings are forfeited and the trial ends. In the aBART, participants are told the explosion point of each balloon ranges from the 1st to the 128th pump. If the balloon does not pop, participants are told how many pumps they could have achieved for that trial. "wanting" is operationalised in the number of selected pumps (more pumps = greater "wanting") averaged across all trials. This task has been shown to activate dopaminergic pathways (Rao et al., 2008) consistent with its measuring the "wanting" component of reward functioning.

8.4.2.2   Wanting component of reward. The International Affective Picture System (IAPS; P. J. Lang, Bradley, & Cuthbert, 2005) is a set of affective stimuli designed to separate pleasure and arousal responses. Sixty images (positive, neutral and negative) were presented in a random order. For this study, we focused on the 20 positive images presented. Positive images were either arousing (erotica) or unarousing (a flower scene)[1]. Participants viewed each image for six seconds and

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[1] IAPS image numbers: 1440, 1630, 1710, 1722, 2340, 2530, 4085, 4142, 4310, 4311, 4659, 4668, 4676, 4697, 5199, 5825, 5829, 8158, 8190, 8496

were asked to rate valence from 1 (most unpleasant) to 9 (most pleasant) (discussed below in "Liking component of reward"), and arousal from 1 (least arousing) to 9 (most arousing), immediately following each image. High arousal IAPS images are associated with increased pupillary and skin conductance levels, consistent with physiological preparedness to engage in goal-pursuit (M. M. Bradley, Miccoli, Escrig, & Lang, 2008; Carver, 2006; Chiew & Braver, 2011). In the present design, 'arousal' ratings to positive images were assumed to quantify the conscious wanting reward component for each image, indexing a physiological preparedness to engage in reward seeking behaviour.

8.4.2.3   Liking component of reward. Ratings of 'pleasantness' of the 20 positive IAPS images was used to operationalise the conscious liking component of reward function. Positive valence images have been linked to neural structures of limbic brain regions and ventromedial prefrontal cortex (Kringelbach, 2005; Tempesta et al., 2015).

The modified Differential Emotions Scale (mDES; Cohn, Fredrickson, Brown, Mikels, & Conway, 2009) was used to assess uncued discreet emotions. Participants rated their emotional state on 10 positive emotion adjectives (from 0 "not at all", to 4 "extremely"): amusement, awe, compassion, contentment, gratitude, hope, interest, joy, love and pride. As increases in self-reported positive emotions (pre- to post-scan) are related to greater ventral striatum and putamen activation (Speer, Bhanji, & Delgado, 2014), the mDES was assumed to also quantify the liking component of reward function.

8.4.2.4   Learning component of reward. To measure learning of cost versus risk choices, the Iowa Gambling Task (IGT; Bechara et al., 1994) simulates real-life decision making using uncertainty, rewards, and penalties. Participants select a card from one of four decks. Two decks contain greater gains but greater losses (net loss) and two decks contain smaller gains and smaller losses (net gain). Participants are explicitly told that the rewards and losses associated with each deck are not randomised, emphasising the learning component of the task. Poor reward learning is operationalised on the IGT as selecting from the net loss decks. Participants who have deficits in creating cognitive predictions perform poorly on the IGT (Fukui, Murai, Fukuyama, Hayashi, & Hanakawa, 2005; Lawrence, Jollant, O'Daly, Zelaya, & Phillips, 2009; X. Li et al., 2010) suggesting that the task measures the learning

component of reward function (Bechara et al., 1994). Here, participants completed 300 trials at each session.

8.4.3   Time Sampling. To balance the trade-off between adequate measurement of the predicted diurnal waveform against participant burden, participants were tested at three times of day. Specific times were selected on the basis of prior research into the naturalistic diurnal rhythm of PA (above). 10.00 hours and 19.00 hours were selected to minimise sleep restriction during the testing times while capturing the expected lowering of PA at the start and end of the day (Clark et al., 1989; Watson et al., 1999). The afternoon time of 14.00 hours was selected to capture the expected peak of the waveform of reward functioning as observed previously in naturalistic investigations of PA (e.g., Murray, Allen, & Trinder, 2002; Murray et al., 2009). Participants were counterbalanced to begin testing at 10.00 hours, 14.00 hours or 19.00 hours due to known habituation effects with repeated exposure to reward tasks (Hasler, Forbes, et al., 2014), emotional stimuli (C. I. Wright et al., 2001), and learning (X. Li et al., 2010; van den Bos, Houx, & Spruijt, 2006).

8.4.4   Procedure. Participants were recruited from a convenience sample of Swinburne University of Technology students and associates of the researchers. The university ethics board approved study procedures. The mDES was completed before each testing session. Measures were presented using Inquisit (Inquisit, 2014; aBART) and E-Prime 2.0 (Schneider, Eschman, & Zuccoloto, 2007; IGT and IAPS). Participants were reimbursed, and informed that compensation was not based on performance. Participants were tested in small groups; completing all three sessions within 24 hours.

8.4.5   Data analytic approach. As data from repeated measures are nested within the individual, multilevel modelling was chosen for data analysis and HLM 7.01 software employed (Raudenbush, Bryk, Cheong, & Congdon, 2013). Performance on behavioural tasks (aBART and IGT), and IAPS and mDES self-reports served as Level 1 predictors of time of day (10.00 hours, 14.00 hours, 19.00 hours) repeated measures, clustered within participant (Level 2).

8.4.6   Analyses. An intercept only model was conducted for each outcome measure displayed below:

Level 1 Model:

Measure of reward $_{ij}$ = β_{0j} + r$_{ij}$

Level 2 Model:

β_{0j} = γ_{00} + u$_{ij}$

The time of day hypothesis was tested in the Level 1 model:

Level 1 Model: Measure of reward $_{ij}$ = β_{0j} + β_{1j} (time of day) + r$_{ij}$

β_{0j} represents each participant's mean reward response on the task, and, r$_{ij}$ represents the within person variance. β_{1j} represents the time of day slope of the fitted quadratic waveform with a peak at 14.00 hours for each participant. This was dummy coded in analyses as -1 (10.00 hours), 2 (14.00 hours), and, -1 (19.00 hours), no differences were expected between 10.00 hours and 19.00 hours. Variables were group mean centred prior to inclusion in the model.

8.5 Results

8.5.1 Preliminary analyses. Scores on the IGT had heterogeneous variance; however as log transformations did not alter results untransformed analyses are presented. Outliers were detected by a z-score of ± 3.29 at each iteration for the dependent variables. One participant's scores were extreme outliers on multiple measures and all of his scores were excluded from final analyses (leaving N=49 included in the final analysis). Other univariate outliers were deleted from analyses. Intraclass correlations of .42-.89 for each reward outcome measure suggest a large proportion of changes in reward responsivity were attributable to the individual, supporting multilevel analysis that controls for spurious inflations of error that occur when observations are not independent (Hox, 2010).

8.5.2 Hypothesis testing. The null and Model 1 results are displayed for each dependent variable in Table 13 with robust standard errors reported. Figure 8a-e displays the scores on the dependent variable at each time-point with a quadratic waveform fitted to the data.

Table 13

Multilevel Models Predicting Reward Response at 10.00 hours, 14.00 hours and 19.00 hours in Healthy Young Men

Model	Fixed Effect		Unstandardized β Coefficient	*SE*	*t*(48)	*p*-value	CI (95%)
	Outcome Variable: Automatic Balloon Analogue Risk Task, wanted pumps						
	Mean level, intercept, β_0	γ_{00}	67.38	1.42	47.56	<.001	
Model 1	Time of Day slope, β_1	γ_{10}	0.81	0.36	2.24	.030*	[.09, 1.53]
	Outcome Variable: International Affective Picture System, rating of arousal for Positive images						
	Mean level, intercept, β_0	γ_{00}	5.34	.20	26.96	<.001	
Model 1	Time of Day slope, β_1	γ_{10}	.07	.03	2.46	.017*	[.01, .12]
	Outcome Variable: International Affective Picture System, rating of pleasure for Positive images						
	Mean level, intercept, β_0	γ_{00}	6.57	.16	40.83	<.001	
Model 1	Time of Day slope, β_1	γ_{10}	-.004	.02	-.16	.87	[-.05, .05]
	Outcome Variable: modified Differential Emotions Scale, rating of Positive Emotions before testing						
	Mean level, intercept, β_0	γ_{00}	15.34	.90	17.11	<.001	
Model 1	Time of Day slope, β_1	γ_{10}	.11	.22	.47	.64	[-.34, .56]
	Outcome Variable: Iowa Gambling Task, net loss deck choices						
	Mean level, intercept, β_0	γ_{00}	101.42	6.33	16.03	<.001	
Model 1	Time of Day slope, β_1	γ_{10}	3.45	2.71	1.28	.21	[-1.96, 8.87]

Note. N=49, **p*<.05 for Model 1, CI = Confidence Interval
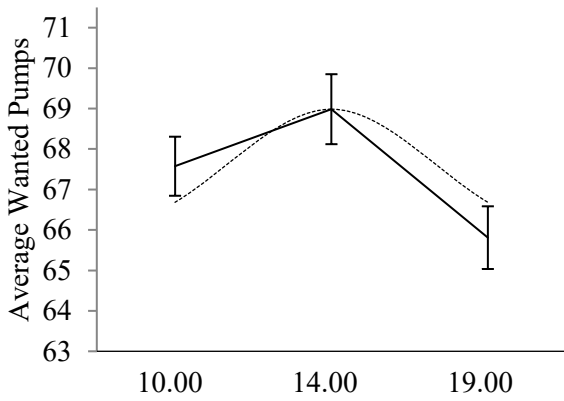
Figure 8a. Wanted pumps on the automatic Balloon Analogue Risk Task
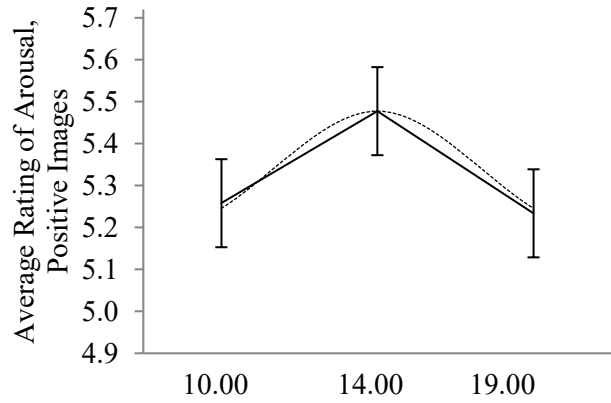
Figure 8b. Arousal rating for Positive images on the International Affective Picture Systems
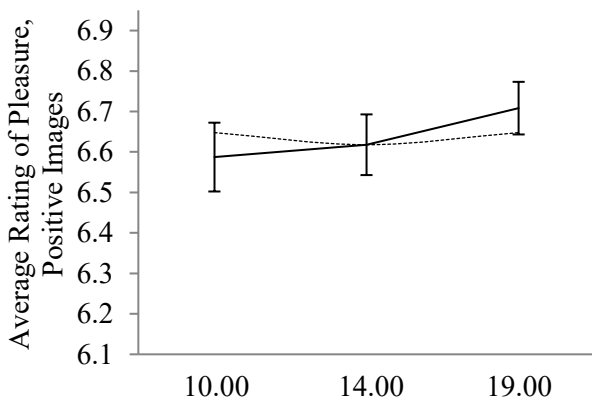
Figure 8c. Pleasure for Positive images on the International Affective Picture Systems
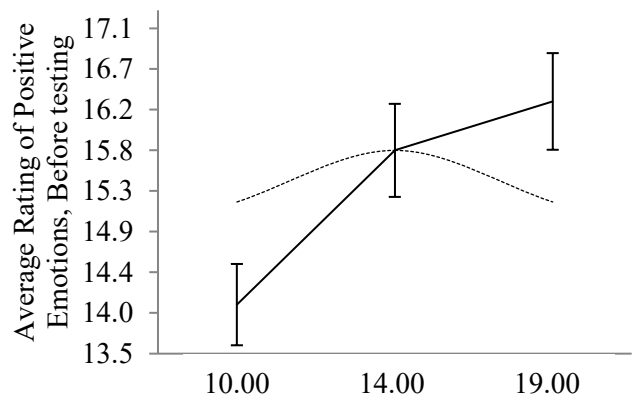
Figure 8d. Rating of Positive Emotions on the modified Differential Emotions Scale
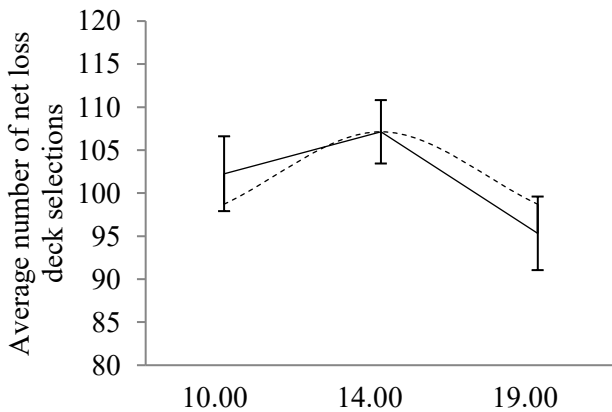
Figure 8e. Choices from net loss decks on the Iowa Gambling Task

Figure 8. (A) Wanted pumps on the automatic Balloon Analogue Risk Task (B) Arousal rating for positive images on the international affective picture systems (C) Pleasure for positive images on the international affective picture systems (D) Rating of positive emotions on the modified Differential Emotions Scale (E) Choices from net loss decks on the Iowa Gambling Task. Note. Closed lines represent the average scores at each time point for each reward function variable. Errors bars represent standard errors. Broken lines represent the quadratic waveform with a fitted peak at 14.00 hours.

8.5.2.1 "Wanting" – aBART. As expected, multilevel analyses found that a quadratic waveform with a 14.00 hours peak provided a significant fit to the data on number of wanted pumps, $t(48)=2.24$, $p=.030$. The model suggested that 2.43 additional pumps per trial would be expected at 14.00 hours relative to 10.00 hours and 19.00 hours (Figure 8a).

8.5.2.2 Wanting – IAPS Arousal. As expected, a quadratic waveform peaking at 14.00 hours provided a significant fit to the data on arousal ratings for positive images, $t(48)=2.46$, $p=.017$. The model suggested that each image was rated as .21 units more arousing at 14.00 hours than at 10.00 hours and 19.00 hours (Figure 8b).

8.5.2.3 Liking – IAPS Pleasure. A quadratic waveform peaking at 14.00 hours did not provide a significant fit to the data on ratings of pleasure for positive images, $t(48)=-0.16$, $p=.87$ (Figure 8c).

8.5.2.4 Liking – mDES. A quadratic waveform peaking at 14.00 hours did not provide a significant fit to the data on ratings of positive emotions, $t(48)=0.47$, $p=.64$ (Figure 8d). Inspection of Figure 8d suggests that uncued self-rating of positive emotions increased linearly between 10.00 hours and 19.00 hours.

8.5.2.5 Learning – IGT. A quadratic waveform peaking at 14.00 hours did not provide a significant fit to the data on choosing from net loss decks on the IGT, $t(48)=1.28$, $p=.21$ (see Figure 8e).

8.6 Discussion

Previous research has found that human reward functioning is partly driven by the endogenous circadian system. To date, diurnal variation in reward functioning has mainly been investigated in self-report PA, the aim of this study was to extend these findings by examining diurnal rhythms in three recognised facets of reward functioning: "wanting", liking and learning.

As hypothesized, a diurnal rhythm with a peak at 14.00 hours was exhibited in unconscious "wanting" components of reward seeking as measured behaviourally (aBART) and in conscious wanting through self-reported arousal to positive valence images (IAPS) compared to 10.00 hours or 19.00 hours. This diurnal rhythm is consistent with recent evidence for an afternoon (versus morning) peak in striatal activity (Hasler, Forbes, et al., 2014) and earlier research showing an early afternoon peak in self-reported PA (Murray, Allen, & Trinder, 2002; Murray et al., 2009;

Watson et al., 1999). Although the present design cannot illuminate mechanisms underlying this diurnal rhythm in wanting, it is possible that circadian-controlled mesolimbic dopaminergic activity may increase conscious and unconscious wanting in afternoon hours for young men (Berridge, 2007; Berridge & Kringelbach, 2008; Knutson et al., 2014; McClung, 2013; McClung et al., 2005; Wyvell & Berridge, 2000).

Hedonic liking measured by ratings of self-reported pleasure to positive IAPS images, and self-rated uncued positive emotions (mDES), did not exhibit a diurnal waveform, providing no evidence that liking is under circadian control. Self-rated uncued positive emotions linearly increased across the day to peak at 19.00 hours. Previous research finding a circadian rhythm in self-reported happiness (Boivin et al., 1997; Murray et al., 2009) was obtained in laboratory conditions where participants were in a time-free environment. This study used self-report measures of liking. One explanation for the current findings is that liking is more reactive to external stimuli with early evening being associated with hedonic activities namely: meal-times; socialising, and relaxation. More systematic inquiry into measures that assess unconscious "liking" as distinct from conscious liking is needed.

The learning facet of reward functioning as measured behaviourally by the IGT also did not fit a diurnal waveform. Successful performance on the IGT task requires learning of penalties and rewards associated with each deck. The present results do not offer evidence for a diurnal rhythm in learning cognitive predictions. As this is the first study to look at diurnal rhythms in learning in humans, extending these findings to specific learning components (e.g., speed of learning reward behaviours and changing or extinguishing learned reward behaviours) will be important to contextualise the present negative findings.

The present study has found further evidence for diurnal modulation of conscious and unconscious "wanting", but not for liking or learning. This pattern of results adds to previous studies' elevation of the "wanting"/wanting dopaminergic reward pathways in circadian rhythm investigations (Hampp et al., 2008; McClung et al., 2005; Sleipness et al., 2007b). The adaptation hypothesis for the circadian modulation of reward function is that humans are primed for environmental engagement in the daytime when the chance of reward is high and threat is low

(Watson, 2000b). The present works advances this idea by suggesting the "wanting" component of reward may be important for optimal reward functioning across the day.

The study had a number of limitations. Evidence for a diurnal rhythm in two measures of reward motivation is consistent with, but not evidence for a circadian genesis of this rhythm. Future research using rigorous chronobiological protocols (constant routine and forced desynchrony) could control for the influence of exogenous factors (social interaction, etc.) on reward measures. Future studies should expand to include females, a wider age range, and account for individual differences in sleep timing. While diurnal type was not controlled experimentally, this variable was measured for post hoc investigation (using the Munich Chronotype Questionnaire [Roenneberg et al., 2003], mid-sleep on free days and self-rating of chronotype variables as phase reference points for sleep). Controlling statistically for diurnal type had no effect on the dependent variables.   The diurnal rhythm of reward response was measured in a gross manner here (three time points), and more frequent time sampling would provide a more precise characterisation of the rhythm.

Finally, the challenges of parsing various components of reward seeking ("wanting", wanting, liking and learning) should also be noted. For example, while scores on the aBART predominantly index "wanting" of a reward, they also tap liking of reward (through the enjoyment of succeeding on an individual trial), and learning from past success or failure in preceding trials (via feedback after each trial).

Future research should systematically investigate the optimal measurement of all facets of human reward motivation, potentially using a matrix of behavioural and self-report variables (Berridge, 1996). Neurobiological work into diurnal rhythms of reward facets is a crucial next step to extend Hasler et al.'s (2014) novel finding of an afternoon peak in dopaminergic ventral striatal activity.

8.6.1 Conclusions. Within its limitations, the current findings provide some novel insights into our understanding of diurnal reward function in humans. By paying more attention to the way in which reward functioning is measured, the present study adds incrementally to a burgeoning literature that reward function may have a diurnal component with increased propensity to want rewards in the early afternoon. In the only human study to date, liking and learning were found not to

exhibit diurnal variation. More systematic work is now required in assessing the endogenous circadian variation in "wanting" and refining knowledge of the interaction between components of reward functioning. Dissociating components of diurnal rhythms in reward functioning through a range of measures is integral to advancing our understanding of healthy functioning of circadian-reward pathways.

Chapter 9: Systematic Review of Circadian Modulation of Neural Reward Motivation

9.1   Linking Section

Byrne, J. E. M. & Murray, G. (2017). The sleep and circadian modulation of neural reward pathways: A systematic review protocol. *Systematic Reviews, 6*(237). doi:10.1186/s13643-017-0631-3

Byrne, J. E. M., Tremain, H., Leitan, N. D., Keating, C., Johnson, S. L. & Murray, G. (Under Review). Circadian modulation of reward function: Is there an evidentiary signal in existing neuroimaging studies?. *Neuroscience and Biobehavioral Reviews*. Submitted 28th May, 2018.

Study 4 aimed to systematically review fMRI studies that generate data concerning circadian modulation of the reward system. Chapter 9 presents both the protocol paper for a pair of systematic reviews and one of the systematic reviews examining the circadian modulation of neural reward motivation. Study 4 has discussed a protocol for a circadian (presented within Chapter 9) and sleep (not presented in this thesis) modulation of neural reward functioning. As a large amount of methodological decision-making was carried out in the development of this review, a protocol paper was published independently of the reviews. The writing of the protocol included many methodological decisions for the procedures of the review; however, some additional notes to the development of the design as they relate to the overall project design are detailed below.

Initially, the plan was to publish a single literature review of circadian and sleep modulation of neural reward in one paper. After initial scoping of the literature, it became evident that this would generate significant heterogeneity and that the systematic analysis would be dramatically improved through independent, but related, reviews of (a) circadian modulation of neural reward pathways, and (b) sleep modulation of neural reward pathways. The strategy of a pair of reviews would permit a more meaningful synthesis in these two related, but separable, areas of study. Initial scoping of the literature confirmed sufficient empirical publications to conduct separate reviews.

A major consideration in designing the protocol for Study 4 was deciding how to operationalise reward. There were three major decision-making steps: (1)

What imaging methods would be included in the literature review? (2) Within fMRI, what protocols would be included? and, (3) What distinctions of reward would be made? Firstly, a broad approach was taken for which fMRI methods to include. While a small handful of studies examined the circadian and sleep modulation of neural reward through positron emission tomography (Červenka, Halldin, & Farde, 2008; Elmenhorst, Kroll, Matusch, & Bauer, 2012), single-photon emission computed tomography (Chiu et al., 2011; Lee, Chiu, Yang, & Chu, 2007; Martins et al., 2010), and magnetic resonance spectroscopy (Kubota et al., 2011; Soreni et al., 2006; Soreni, Noseworthy, Konyer, Pullenayegum, & Schachar, 2010), the different level of analysis of neurotransmitter compared to brain region findings made comparison of the already heterogeneous fMRI literature unmanageable. Due to the majority of studies using fMRI, article selection was limited to this imaging method. Secondly, task-based (both block- and event-related designs) was perhaps a clearer operationalisation of reward as this was an a priori target of the researchers (see General Discussion, Section 11.5.1 for further elaboration); however, resting-state data spoke to how brain regions and networks involved in reward motivation may be affected by circadian or sleep modulation. Lastly, it was intended to review evidence for sleep and circadian modulation of neural reward functioning for all three psychological components of reward; however, the final protocol focussed on reward anticipation ("wanting") and reward receipt ("liking", see Section 11.5 for how reward anticipation and reward receipt may relate to "wanting" and "liking"). This choice was made due to insufficient literature available for reward learning with no circadian literature focussing on the circadian modulation of neural reward, and only two sleep studies (Igloi, Gaggioni, Sterpenich, & Schwartz, 2015; E. B. Simon et al., 2015) offering evidence towards this reward component. Secondly, fMRI analysis does not lend itself to specifically teasing apart reward learning from other facets of reward, while event-related designs offers this distinction for reward anticipation ("wanting") compared to reward receipt ("liking", see Section 11.8.1).

Following the protocol paper, Chapter 9 presents the systematic literature review that aimed to examine circadian modulation of neural reward functioning. Adding to the overarching aim of this project to incrementally advance understanding of the relationship between biological rhythms and reward motivation,

Study 4 provided evidence for one way that the circadian system may modulate reward, through neural mechanisms.

Study 4 included the work presented in Study 5 (see Chapter 10) that used a repeated-measures time of day protocol to investigate diurnal variation in neural reward response in a task-based fMRI study. This review continued the work of Study 3 (see Chapter 8) as reward anticipation and reward receipt may index "wanting" and "liking" in the psychological components of reward.

9.2   The Sleep and Circadian Modulation of Neural Reward Pathways: A Protocol for a Pair of Systematic Reviews

9.2.1 Abstract.

Background: Animal research suggests that neural reward activation may be systematically modulated by sleep and circadian function. Whether humans also exhibit sleep and circadian modulation of neural reward pathways is unclear. This area is in need of further research, as it has implications for the involvement of sleep and circadian function in reward-related disorders. The aim of this paper is to describe the protocol for a study using a pair of systematic literature reviews to synthesise existing literature related to (1) sleep and (2) circadian modulation of neural reward pathways in healthy human populations.

Methods: A systematic review of relevant online databases (Scopus, PubMed, Web of Science, ProQuest, PsycINFO and EBSCOhost) will be conducted. Reference lists, relevant reviews, and supplementary data will be searched for additional articles. Articles will be included if, (a) they contain a sleep or circadian related predictor variable with a neural reward outcome variable, (b) using an functional magnetic resonance imaging protocol, (c) use human samples. Articles will be excluded if study participants had disorders known to affect the reward system. The articles will be screened by two independent authors. Two authors will complete the data extraction form, with two authors independently completing the quality assessment tool for the selected articles, with consensus reached with a third author if needed. Narrative synthesis methods will be used to analyse the data.

Discussion: The findings from this pair of systematic literature reviews will assist in the identification of the pathways involved in the sleep and circadian function modulation of neural reward in healthy individuals, with implications for disorders characterised by dysregulation in sleep, circadian rhythms, and reward function.

Systematic review registration: PROSPERO CRD42017064994

Keywords: sleep, circadian rhythm, diurnal rhythm, time of day, reward, systematic review

9.2.2 Background. There is growing interest in moderators of the human reward system, with biological rhythms (sleep and circadian function) being a particular focus because of their potential interplay in mental disorders. Sleep and circadian function have been shown to be important in numerous reward-related disorders (e.g., bipolar disorder, depression, drug and alcohol use; Alloy et al., 2016; Asarnow, Soehner, & Harvey, 2013; Boland & Alloy, 2013; Harvey, Mullin, & Hinshaw, 2006; Hasler, Casement, Sitnick, Shaw, & Forbes, 2017; Hasler, Soehner, et al., 2014; Hasler et al., 2015; Soehner et al., 2016) but is also relevant for optimal functioning in healthy individuals (Murray, Allen, & Trinder, 2002; Murray et al., 2009; Tang, Fiecas, Afolalu, & Wolke, 2017). Remarkably, no review to date has systematically examined existing brain imaging evidence for sleep or circadian modulation of the neural pathways of reward. Understanding the neural pathways in these two relationships may illuminate new clinical targets for stabilising interacting biological rhythm and reward dysregulation in these disorders. This protocol will begin with a brief summary of the evidence for sleep and circadian modulation of neural reward pathways, indicate how imaging may examine neural reward, and suggest some important issues in operationalising reward, before turning to the methods and data analytic plan for the proposed systematic review.

There is substantial evidence from animal research that circadian and sleep function modulates neural reward pathways. For example, Sleipness et al. (2007a, 2007b) demonstrated that time of day differences in dopamine transmission and reward-seeking behaviour was reliant on the central circadian pacemaker, the suprachiasmatic nucleus. Further, circadian clock gene expression in core reward regions (ventral tegmental area [VTA], nucleus accumbens [NAc] and the medial and dorsolateral prefrontal cortex [mPFC, DLPFC]) all exhibit circadian rhythmicity (Bellivier et al., 2015; Webb, Baltazar, Lehman, et al., 2009). In relation to sleep, Hanlon, Andrzejewski, Harder, Kelley, and Benca (2005) found that depriving rats of rapid eye movement sleep led to a decrease in motivation to seek rewards the following day. In humans, Volkow et al. (2012) found that sleep deprivation altered dopamine transmission in the ventral striatum, which may represent a pathway for the altered reward response seen in behavioural tasks (McKenna, Dickinson, Orff, & Drummond, 2007; Venkatraman et al., 2007; Venkatraman, Huettel, Chuah, Payne,

& Chee, 2011) and positive mood response (Haack & Mullington, 2005; van der Helm et al., 2010; Zohar et al., 2005) following sleep perturbations.

In humans, neuroimaging methods, particularly commonly used functional magnetic resonance imaging (fMRI) paradigms, have potential to illuminate the putative sleep and circadian modulation of neural reward pathways. In fMRI, neural activity is inferred from changes in the blood oxygen level dependent (BOLD) signal, premised on regional blood flow. A common approach to investigating neural reward functioning in fMRI is via presentation of reward stimuli within a task-based protocol (K. S. Wang, Smith, & Delgado, 2016). Reward studies have typically used food, money, happy faces, or attractive physical features to activate reward regions in fMRI (Pool et al., 2016). Task-based fMRI contrasts with resting state fMRI, a paradigm of growing interest which aims to detect patterns of fluctuating synchronous connectivity between structurally distinct brain regions in the absence of a stimulus (Cordes et al., 2000).

Any synthesis of fMRI studies of reward must attend to the multiple methodological dimensions on which studies may differ. One advantage of using task-based imaging is that it allows for event-related and block-based tasks to temporally distinguish between these reward components. Block designs employ blocks of similar trial types which gives higher power across many trials; event-related designs can distinguish between trials in a block, and separate out components within a trial (Petersen & Dubis, 2012). Reward in humans is probably not a unitary process. Event-related designs have the potential to distinguish between reward anticipation and reward consumption (Knutson, Fong, et al., 2001). Block designs are less sensitive temporally sensitive but more powerful in detecting effects (Knutson & Cooper, 2005; Knutson, Fong, et al., 2001; Petersen & Dubis, 2012). A second methodological consideration is that imaging tasks use different stimuli (e.g., food, money, social rewards) to measure neural reward (Pool et al., 2016). In the present context, sleep and circadian function may have different interactions with (for example) food and money, making it important to discriminate between studies using one or other of these reward stimuli. A final consideration is reward can be examined outside of stimuli in resting state fMRI. Resting state fMRI may capture a physiological preparedness to engage with rewarding stimuli in the environment (reward anticipation).

9.2.2.1   Objectives. The aim of this study is to synthesise existing research on the putative modulation of neural reward pathways by sleep and circadian function. An initial scoping of the literature strongly suggested that, (a) these two modulation propositions would be best investigated separately to minimise heterogeneity and facilitate synthesis, and (b) there were sufficient studies in each area to support two separate systematic reviews. Therefore, the objective of this study is to conduct a pair of systematic reviews, driven by the following questions.

9.2.2.2   Research Questions.

1) What evidence is there for modulation of neural reward pathways by sleep?

2) What evidence is there for modulation of neural reward pathways by circadian function?

9.2.3   Methods. This systematic review will be written using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) guidelines (Additional File 1). This systematic review has been registered with the International Prospective Register of Systematic Reviews (PROSPERO, registration number: CRD42017064994).

9.2.3.1   Criteria for study inclusion.

9.2.3.1.1   Study Methods. Studies will be included if they use naturalistic designs or experimental designs (including cross-sectional, longitudinal, case-control studies, and cross-over) to manipulate sleep or circadian function to examine neural reward functioning through fMRI. In addition, articles must be written in English and published in a peer-reviewed journal.

9.2.3.1.2   Study Participants. Studies will be eligible for inclusion if they include samples of human subjects of any age. In the sleep systematic review studies that include insomnia, symptoms or disorders will be included if this quasi-experimental groupings formed the predictor variable; compared to another sleep comparison group. So too, in the circadian systematic review delayed or advanced sleep-wake phase will be included if these symptoms or disorders are related to another circadian function comparison group. In both reviews, studies that use samples with psychological or physical illnesses that may affect reward will be excluded. Studies using samples with neurological or physiological disorders that have a pronounced effect on sleep (e.g., narcolepsy, Kleine-Levin syndrome,

obstructive sleep apnoea) or circadian function (e.g., blind individuals or traumatic brain injury) will be excluded from both reviews. Studies that use pharmacological, acupuncture, transmagnetic stimulation, or administered reward related substances (alcohol, drugs [including caffeine and nicotine]) will be excluded, as this intervention may affect both the sleep or circadian predictor variable and the neural reward activation outcome variable. Individuals who have diagnoses of disorders known to affect the reward system (e.g., bipolar disorder, major depressive disorder, gambling disorder, alcohol and drug use disorders) will be excluded. Studies investigating altered reward response specific to a population (e.g., displaying images of alcohol to heavy alcohol users) will also be excluded, on the grounds that they effectively add an additional interaction term to the two broad relationships of interest in this systematic review.

9.2.3.1.3   Search Strategy for Study Identification. Relevant health and neuroscience electronic databases (Scopus, PubMed, Web of Science, ProQuest, PsycINFO and EBSCOhost) will be searched for articles from the database inception until October, 2017. Reference lists of selected articles, relevant reviews and meta-analyses, and supplementary data files will be examined to identify any additional articles. The search strategy includes examining the article title, abstracts and keywords for relevant criteria (Figure 9).

1	TITLE-ABS-KEY(sleep OR *REM OR adenosine OR nap)
2	TITLE-ABS-KEY(striatum OR "anterior cingulate" OR "ventral tegment*" OR putamen OR VTA OR Nac OR accumben* OR "medial prefrontal cortex" OR MPFC OR "orbitofrontal cortex" OR OFC OR thalamus OR insula OR "dorsolateral prefrontal cortex" OR DLPFC OR amygdal* OR "locus coeruleus" OR LC OR dopamine* OR seroton* OR limbic OR caudate)
3	TITLE-ABS-KEY (reward OR arousal OR happ* OR food OR money OR 174ositive* OR affect OR emoti* OR reinforcement OR instrumental)
4	TITLE-ABS-KEY(imag* OR FMRI OR MRI)
5	NOT TITLE-ABS-KEY(rat OR rodent OR mouse OR mice OR hamster OR drosophila)
6	(LIMIT-TO(DOCTYPE,"ar ") OR LIMIT-TO(DOCTYPE,"ip"))
7	2 OR 3
8	1 AND 4 AND 5 AND 6 AND 7

Figure 9. Example search for sleep modulation of neural reward using keywords in Scopus

1	TITLE-ABS-KEY(SCN OR suprachiasmatic OR circadian OR diurnal OR "clock gene*" OR "time of day" OR cortisol OR melatonin OR owl OR lark)
2	TITLE-ABS-KEY(striatum OR "anterior cingulate" OR "ventral tegment*" OR putamen OR VTA OR Nac OR accumben* OR "medial prefrontal cortex" OR MPFC OR "orbitofrontal cortex" OR OFC OR thalamus OR insula OR "dorsolateral prefrontal cortex" OR DLPFC OR amygdal* OR "locus coeruleus" OR LC OR dopamine* OR seroton* OR limbic OR caudate)
3	TITLE-ABS-KEY (reward OR arousal OR happ* OR food OR money OR positive* OR affect OR emoti* OR reinforcement OR instrumental)
4	TITLE-ABS-KEY(imag* OR FMRI OR MRI)
5	NOT TITLE-ABS-KEY(rat OR rodent OR mouse OR mice OR hamster OR drosophila)
6	(LIMIT-TO(DOCTYPE,"ar ") OR LIMIT-TO(DOCTYPE,"ip"))
7	2 OR 3
8	1 AND 4 AND 5 AND 6 AND 7

Figure 10. Example search for circadian modulation of neural reward using keywords in Scopus

As seen in Figure 9 and 10, search term 1 aims to identify studies collecting data on sleep (Figure 9) or circadian function (Figure 10). All studies must have a predictor variable which is an experimental manipulation, or a naturalistic (quasi-experimental) quantification of sleep or circadian function.

    a. For the sleep review, studies that included different sleep stages or insomnia symptoms will be included as well as more traditional sleep deprivation or sleep extension studies.

    b. For the circadian function review, studies will be deemed to speak to the circadian function of reward if they use a repeated measures protocol at different times of day (measuring a diurnal [daily] rhythm), and measure circadian phase through preformed chronotype (morning, evening type individuals) groups, or, use more endogenous

markers of circadian function such as circadian genes, melatonin or
cortisol levels.

Search term 2 identifies studies collecting data on the neural basis of reward,
while search term 3 identifies reward stimuli that may be used in imaging studies.
Neural reward activation as measured by fMRI will be the outcome variable of both
the planned systematic literature reviews. Reward functioning can be examined as an
outcome of reward tasks, or through resting state scans that examine brain regions or
neuronal activity associated with rewards. Search terms will be broad, including
terms for reward stimuli, neural reward regions of interest and whole-brain analyses
in fMRI studies. Search term 4 identifies fMRI paradigms, with search term 5
excluding commonly used animals in sleep and circadian research, and limits to full
articles that are already in press (search term 6). Search term 7 aims to identify
studies that have searched for or identified neural reward regions or used an imaging
paradigm with reward-based stimuli.

9.2.3.2 *Study selection.* Articles will be screened in two stages. Stage 1
(titles and abstract) will screen for inclusion and exclusion criteria (see Additional
File 2). Stage 2 will collate the study selection results and two authors will review
the full-texts for any discrepancies with Cohen's Kappa for inter-rater agreement
assessed and reported. If agreement cannot reached a third reviewer from the authors
will make the final decision.

9.2.3.3 *Data extraction. A* data extraction form in Microsoft Excel will be
used to compile the method and results from each of the selected studies for the (1)
sleep systematic review, and (2) the circadian systematic review (see Additional File
3). Two independent reviewers will complete this form for the selected articles.
Given the diverse measurements of sleep, circadian function and reward this form
will detail the sleep or circadian variable and how this was used in the method,
whether a stimuli was or was not used in the neuroimaging protocol (with a
description of the reward stimuli), participant information and characteristics, the
imaging procedures used and regions of interest investigated and/ or identified,
results, interpretation, and limitations of the research, with two reviewers
independently completing this extraction. Two authors will then complete a quality
assessment of the articles using the Effective Public Health Practice Project
(http://www.ephpp.ca/PDF/Quality%20Assessment%20Tool_2010_2.pdf ; Project

EPHP) quality assessment tool measuring the robustness of articles through an examination of selection bias, study design, confounders, blinding, data collection methods, withdrawal and dropout, intervention integrity, and analyses. The strength of this measure is that it allows for component and global ratings to be made, thus components in this literature that may be less relevant (such as blinding) can be discussed without losing the important cross-study evaluation of the relevant quality assessment components. Where consensus is not reached on the quality assessment, a third reviewer will be relied on. In studies which investigate bi-directional influences between sleep/circadian and reward activation, only the primary direction of interest here (sleep and circadian modulation of reward) will be considered.

   9.2.3.4 Data analysis. As we expect the studies to be heterogeneous in both the sleep and circadian systematic reviews, and the operationalisation of reward variables, the main data analysis will follow a narrative synthesis of articles in both cases. Popay et al.'s (2006) four-step framework for developing an effective narrative synthesis will be used. The first step in the narrative synthesis will provide an explanation for how sleep or circadian function may causally impact different neural reward pathways. This step will map the potential neural pathways of reward in humans, and how these may relate to the different reward stages (reward anticipation and reward outcome). The second step entails a preliminary synthesis of the identified studies, describing the pattern of results by sleep and circadian function separately. The primary aim of this step will be to identify whether the neural reward outcome is modulated by sleep or circadian function, paying attention to the region affected, the direction of effect and the magnitude of observed effects in each individual study. A third step will involve analysis of these findings across studies, concentrating on cross-study design and methodological factors that may explain discrepancies between studies. For the present review, an important focus at this step will be cross-study differences in reward measurement (stimuli and imaging method used) and the reward stage (anticipation and outcome) examined. The final step will involve assessing the strength of evidence for the sleep and circadian modulation of reward as organised by reward stage and region. This will involve collating the results of the EPHP quality assessment (above) to see if some findings should be weighted more highly through both the quantity of evidence for an

approach and the design qualities which may best address the current research question for the final narrative synthesis.

9.2.4 Discussion. Currently no systematic literature reviews have considered the impact of either sleep or circadian function on neural reward pathways. This is an important gap in knowledge, because recent empirical and theoretical evidence (e.g., Alloy et al., 2017; Antúnez, Capella, Navarro, & Adan, 2016; Hasler, Smith, et al., 2012; Klumpp et al., 2017; Lall, Atkinson, Corlett, Broadbridge, & Bonsall, 2012) have suggested a disturbed interaction between sleep/circadian function and reward processes may be pivotal to serious reward-related psychopathologies including bipolar disorder, major depression, and alcohol and drug use disorders. Better evidence for the putative existence, direction and strength of such relationships at the neural level in a pair of systematic reviews has the potential to improve understanding and ultimately management of a range of psychopathologies.

9.2.4.1 Limitations. We expect that the primary limitation of these systematic literature reviews will be heterogeneity across identified studies. The measurement of neural reward activation has not been standardised across studies, with different designs using different types of reward stimuli, and varied focus between reward stages (anticipation, and outcome). In addition, some studies will investigate neural reward through stimuli-response paradigms while others use resting state data to speak to a neural preparedness to engage in reward behaviour. While all these studies may speak to a sleep and circadian modulation of neural reward activation, differences in study paradigms will be important qualifications on any synthesis. On the basis of the results of the narrative synthesis however, we expect to be able to identify which protocols may best illuminate the sleep and circadian modulation of neural reward activation in future research.

A final potential limitation of the literature is that few studies are expected to speak to both sleep and circadian function, which are known to be deeply interdependent. As such these pair of reviews will emphasise that while it is scientifically important to examine sleep and circadian functioning separately, practically these two studies will be confounded by the respective sleep or circadian process. As a result these two systematic reviews can help inform future research of

some ways that neuroimaging may better manage the interplay between sleep and circadian rhythms in their joint determination of neural reward functioning.

9.3   Circadian modulation of reward function: Is there an evidentiary signal in existing neuroimaging studies?

9.3.1   Abstract.

Although animal research strongly suggests that parameters of circadian function can modulate the reward system, little is known about such effects in humans. The aim of this study was to address this deficit via a systematic review. Fifteen articles met inclusion criteria of measuring a range of proxies for circadian function and a neural reward outcome using fMRI. In the context of significant heterogeneity of study designs, a narrative synthesis indicated a circadian signal (including measures of genes, diurnal variation, and circadian preference) in the reward system in humans. In terms of brain regions modulating this effect, the ventral striatum, medial prefrontal cortex, anterior cingulate cortex, putamen, and broader connectivity of the default mode network may be putatively involved. A circadian signal of brain regions was found for anticipation of reward, but stronger support was observed for the reward receipt phase. The results support the need for a program of research that systematically interrogates the circadian and reward systems using fMRI in the context of psychology and pathophysiological conditions where these systems are implicated.

9.3.2 Introduction.

A growing literature proposes that circadian function may modulate reward circuitry in humans. These mechanisms are fairly well characterised in animals, with substantial support towards circadian clock mechanisms regulating reward system mechanisms (cf. Logan et al., 2014; McClung, 2013; Parekh & McClung, 2016; Parekh et al., 2015; Schnell, Albrecht & Sandrelli, 2014 for recent reviews); however comparable data is sparse in humans. Recent reviews have emphasised the potential theoretical importance of circadian function in healthy reward processes (Alloy et al., 2017; Alloy et al., 2015; J. Scott et al., 2016a) however, a review of the neural mechanisms has yet to be conducted. The aim of the present study was to review findings from existing studies that have collected functional magnetic resonance imaging (fMRI) data speaking to an association between some measure of circadian function, and a measure of neural reward activation. We first begin with a review of evidence for circadian modulation of dopaminergic functioning in animals, and evidence for diurnal and circadian rhythms in self-reported affect and reward tasks in humans. A distinction is drawn between two stages of psychological reward processing – reward anticipation and reward receipt – which may be differentially modulated by circadian functioning. We then briefly characterise different fMRI protocols in terms of their relevance to the key question here before the design of the present study is introduced.

9.3.2.1. Interactions between the circadian and dopaminergic systems. The most robust evidence of circadian modulation of the reward system currently exists in the animal literature where circadian modulation of the mesolimbic dopaminergic has been replicably observed (see Webb, Lehman & Coolen, 2015 for a review). The neurotransmitter dopamine is crucial to reward processing, organising behaviour in the context of appetitive stimuli (Alcaro, Huber, & Panksepp, 2007; Berridge, 2007; Sharot, Shiner, Brown, Fan, & Dolan, 2009), with blunted phasic dopamine transmission implicated in low reward, anhedonic states, such as that seen in depression (Roiser et al., 2005; Tremblay et al., 2005; Wise, 1982; see Pizzagalli, 2014 for a review). There is evidence that the dopaminergic system is modulated by circadian genotype (Hampp & Albrecht, 2008; Hampp et al., 2008; Sleipness et al., 2007a, b; Webb, Baltazar, Lehman, et al., 2009; see Webb, 2017 for a review). For example, mutations in circadian clock genes *Period*, *Clock* and *Cycle* in drosophila

have been linked to decreased cocaine sensitisations, behaviourally thought to be associated with increased drug craving (Andretic et al., 1999). Mice with a mutation in the *Clock* gene (Roybal et al., 2007), were found to display extreme hyperactivity in response to novelty mimicking the pathological reward activation of human mania (see also McClung et al., 2005). Ozburn et al. (2012) found that *Clock* mutant mice did not exhibit the diurnal variation in drug acquisition and maintenance that wild type mice did, and drug intake was higher in mice with the *Clock* mutation. *Per2* mutant mice have been shown to exhibit reduced diurnal expression of monoamine oxidase A (an enzyme that catalyses dopamine) in the ventral tegmental area (VTA), and striatum (nucleus accumbens [NAc] and caudate putamen, Hampp et al., 2008). These circadian genes may regulate reward neurocircuitry in the brain relating to substance abuse disorders. In mutant mice, altered circadian period (*Clock*, *Per1*, and *Per2*), and arrhythmicity (*Clock* and *Per2*) is observed with circadian gene mutations, with altered drug behaviours such as hypersensitivity to cocaine, and increased preference towards alcohol (see Logan et al., 2014). Webb (2017) proposes that the weight of literature suggests a bi-directional relationship between abnormal reward behaviours and the circadian system. One pathway in this relationship is that circadian clock genes may alter mesocorticolimbic (VTA, NAc, mPFC) circuitry which may lead to abnormal drug taking and seeking. Together, animal studies reveal mounting evidence that the circadian system influences reward system function.

In humans, self-reported positive affect (a subjective manifestation of the brain reward activation, Knutson et al., 2014) exhibits a diurnal rhythm (Clark et al., 1989; Murray, Allen, & Trinder, 2002) that is partly of endogenous circadian origin (Boivin et al., 1997; Murray et al., 2009). For example, Murray et al. (2009) found that 25% of variance in the positive affect rhythm was explained by the unmasked endogenous core body temperature rhythm. Recent work has extended Murray et al. (2009) findings beyond self-reported positive affect: Diurnal rhythms have been demonstrated in behavioural tasks in reward anticipation (Byrne & Murray, 2017a) and also in ecological momentary assessments of reward anticipation and receipts (te Lindert et al., 2018). Each of these studies suggest that cognitive and behavioural reward propensity may be highest in the mid-afternoon, consistent with the

evolutionary hypothesis that organisms are primed to seek out rewards when vision is optimal – daytime for humans (Watson, 2000).

For the present project, it is important to recognise that reward functioning is not unitary. In particular, following Berridge's influential work on reward in animals, we will distinguish here between neural pathways activated by the anticipation of reward (a motivation phase, characterised as 'wanting'), and pathways activated during the phase of hedonic pleasure in receiving rewards (characterised as 'liking', Berridge, 2007; Berridge & Kringelbach, 2013; Berridge & Robinson, 2003; Castro & Berridge, 2014a). The former have been shown to involve mesolimbic dopaminergic circuits (Berridge, 2007; Wyvell & Berridge, 2000), while the opioid and endocannabinoid neurotransmitter systems are implicated in the latter (Peciña & Berridge, 2005; 2013; see Castro & Berridge, 2014b for a review).

In humans, fMRI paradigms hold promise to illuminate aspects of reward function (Knutson & Cooper, 2005; Knutson et al., 2014). In terms of understanding neural reward activation, our review of existing studies must distinguish between two major fMRI methodologies. Task-based fMRI measures absolute changes in regional oxygenation or blood oxygen level dependent (BOLD) response in the presence of stimuli, and resting state fMRI measures the spatiotemporal patterns of connectivity when the brain is at rest (Cordes et al., 2000; Lang et al., 2014; van den Heuvel & Hulshoff Pol, 2010).

Task-based fMRI maps participants' neural activity through task-dependent brain activation (Wang et al., 2016). Two major types of design are used in task-based fMRI: block and event-related designs. Block designs capture the haemodynamic response as a function of recurrent experimentally-similar stimuli over multiple trials through "on" periods where stimuli is presented, and "off" times where a target stimulus is not presented (this could be a rest, baseline, or a different target block; Mechelli, Henson, Price, & Friston, 2003; Price, Veltman, Ashburner, Josephs, & Friston, 1999). Event-related designs map the haemodynamic response to a single event type over one trial beginning at stimulus onset (Mechelli et al., 2003). One benefit of mapping a haemodynamic response over a single trial is that the stage of reward process can be distinguished within trials (Richards, Plate & Ernst, 2013, see Figure 11). For the present systematic review, event-related designs are unique in

permitting a distinction between Berridge's motivational ('wanting') and hedonic

('liking') aspects of reward processing (Kumar et al., 2014; J. J. Simon et al., 2010).
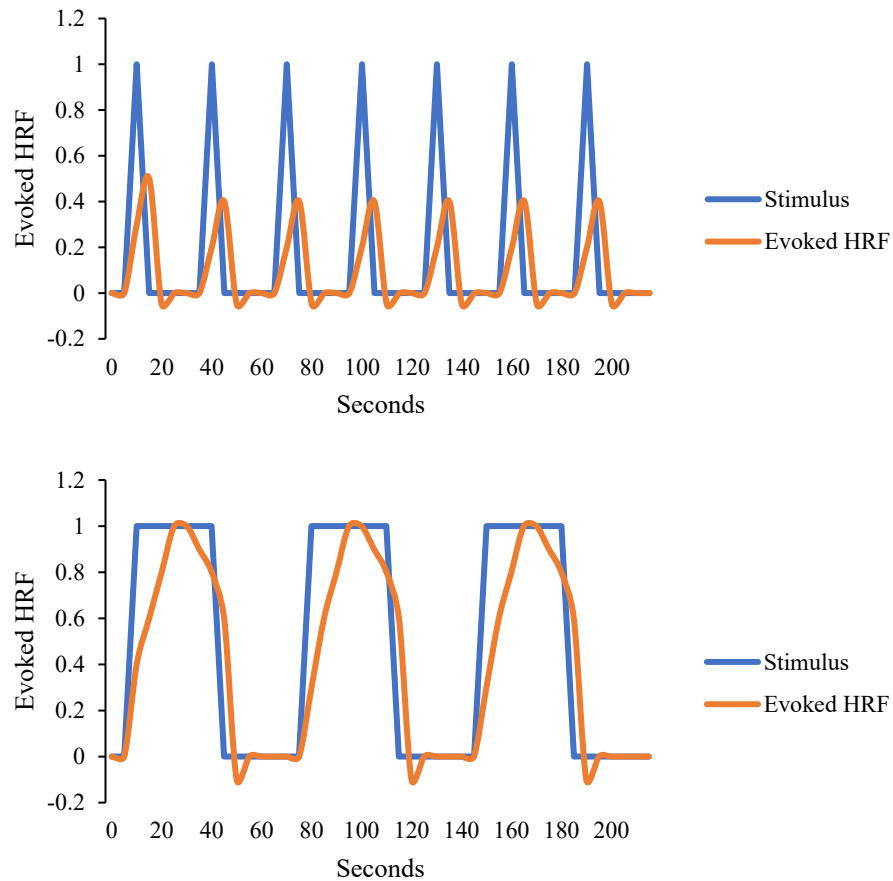
Figure 11. The relationship between time and the haemodynamic response function

in (a) event-related designs, and (b) block designs. The blue stimulus line shows

when a stimulus is being displayed to a participant.

An important source of heterogeneity across task-based reward processing

fMRI studies is the variety of reward stimuli (Knutson & Cooper, 2005). Commonly

used stimuli include primary (food, sexual, and social rewards) and secondary

(monetary) rewards; with exposure potentially through all senses (visual, ingestion,

touch, auditory, olfactory). The reward stimulus most commonly used in reward

research is money (presented visually, Pool et al., 2016). The nature of the reward

stimulus may have important implications for neural activation patterns. For

example, while the orbitofrontal cortex (OFC) is activated in response to erotic, food odours and monetary rewards (Jiang et al., 2015; Sescousse et al., 2010), the anterior OFC may have greater relative activation in response to monetary gains compared to the phylogenetically older posterior lateral OFC which is optimally sensitive to erotica and food (Sescousse et al., 2013; Sescousse et al., 2010). The striatum, amygdala, mediodorsal thalamus, anterior insula, OFC and the pregenual anterior cingulate cortex (ACC), crossing into the medial prefrontal cortex (mPFC) all commonly activate in response to food, money, and erotic rewards (Sescousse et al., 2013).

In contrast to task-based fMRI, resting state data may illuminate changes in connectivity with reward networks and across reward regions as a function of circadian parameters. Regional connectivity in resting state studies, has suggested a role for many brain regions in reward processing. Among healthy participants, increased self-reported willingness to approach rewards (high scores on the fun-seeking scale of the behavioral activation system, Carver & White, 1994) was associated with increased resting-state connectivity between the middle OFC and putamen (Angelides et al., 2017). In psychiatric illnesses associated with altered reward functioning (e.g., Parkinson's disease, mood disorders, and post-traumatic stress disorder [PTSD]) altered connectivity is observed in resting state data relative to healthy controls groups. Arnold Anteraper et al. (2018) focused on the connectivity of the subcortical region of the subthalamic nucleus and reward circuitry. The subthalamic nucleus is difficult to scan given the signal-noise ratio in these deep midline structures (Arnold Anteraper et al., 2018); however, Wagenbreth et al. (2015) found that deep-brain stimulation of this region regulated action in reward contexts in dopamine-deficient Parkinson's patients. Using resting state, Arnold Anteraper et al. (2018) found strong connectivity between the subthalamic nucleus and the VTA, insula, ACC, putamen, anterior prefrontal cortex, and precuneus. Among patients with PTSD and comorbid major depressive disorder, reduced connectivity was observed between the basolateral amygdala-OFC, NAc-thalamus, and the NAc-hippocampus relative to PTSD without depression and healthy controls (Zhu et al., 2017b). Investigation of the connectivity of these structures at-rest may be important in understanding reward functioning in the context of circadian modulation.

Many resting state studies focus on the default mode network (DMN). The DMN is a network of brain regions including the mPFC, posterior cingulate cortex (PCC), precuneus cortex, and the lateral parietal cortex, that is thought to reflect the brain's intrinsic activity at rest (Fox et al., 2005; Raichle, 2015). The DMN has stronger activity when participants are told to rest quietly in the absence of stimulation or other goal-directed thought or actions and is deactivated in tasks requiring attention (Raichle et al., 2001; Raichle & Snyder, 2007). It is possible that DMN connectivity may be involved more broadly in reward processing. For example, in one study, decreased connectivity between the precuneus, cingulate cortex, and frontal regions were observed in those with a higher ratio of self-reported trait reward sensitivity relative to inhibition (as measured by the behavioural activation scales, Olivo et al., 2016). When the reward system has been investigated in individuals with psychiatric illnesses, altered responses of the DMN and other reward-related regions have been reported, in comparison to control groups (cf. Broyd et al., 2009 for a review). Relative to healthy controls, those with alcohol use disorders have increased connectivity within the posterior DMN, a network consisting of the OFC, mPFC, ACC, amygdala, and insula; and a putamen, caudate, and amygdala network (Zhu et al., 2017a). In sum, altered DMN connectivity may reflect broader abnormalities in reward circuitry.

9.3.2.3.   The present study. The aim of this study was to advance understanding of possible circadian modulation of reward in humans, by systematically reviewing existing fMRI studies which have reported data speaking to this putative relationship in healthy human populations. There are three research questions:

• Question 1: Is there evidence in fMRI studies of a circadian signal in reward circuitry in healthy humans?

• Question 2: Which specific reward-related brain regions subserve the relationship between circadian and reward systems in healthy populations?

• Question 3: What evidence is there of a circadian signal for two reward phases: reward anticipation and reward receipt?

9.3.3 Method.

9.3.3.1 Search strategy. The systematic review was developed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

guidelines (Moher, Liberati, Tetzlaff, & Altman, 2009). It is registered with the International Prospective Register of Systematic Reviews (PROSPERO, registration number: CRD42017064994) as fully described in the protocol paper outlining a pair of reviews by Byrne and Murray (2017b; the second paper will review fMRI evidence for a sleep signal in reward processes). In brief, articles were screened from Scopus, PubMed, Web of Science, ProQuest, PsycINFO, and EBSCOhost from inception until October, 2017; reference lists of selected articles, dissertations, and supplementary data files were screened to identify additional articles. A search algorithm included terms for circadian function (SCN, suprachiasmatic, circadian, diurnal, "clock gene*", or "time of day" OR cortisol OR melatonin OR owl OR lark); reward (striatum OR "anterior cingulate" OR "ventral tegment* OR putamen OR VTA OR NAc OR accumben* OR "medial prefrontal cortex" OR MPFC OR "orbitofrontal cortex" OR OFC OR thalamus OR insula OR "dorsolateral prefrontal cortex" OR DLPFC OR amygdal* OR "locus coeruleus" OR LC OR dopamine* OR seroton* OR limbic OR caudate) or reward-related stimuli (reward OR arousal OR happ* OR food OR money OR positiv* OR affect OR emoti* OR reinforcement OR instrumental), and imaging (imag*, fMRI, "functional MRI"). Articles were limited to human studies, in English language, peer-reviewed journals.

 9.3.3.2 Study selection. Articles were included if they used a naturalistic or experimental design and generated data of a circadian signal in reward circuitry. To minimise a positive publication bias (Stern & Simes, 1997) we included studies regardless of whether the study shared the present aim to find a circadian signal in reward function. The circadian system is a multi-level biobehavioural system which is difficult to measure directly; included studies used different proxies of circadian function:

- the use of a repeated measures protocol at different times of day (measuring a diurnal [daily] rhythm),
- proxies of circadian phase measured through chronotype (morning, evening type) groups,
- biological markers of circadian function including circadian genotype, time of melatonin onset or daily patterns in cortisol levels (both circadian controlled hormones),
- timing of the sleep phase,

- changes between weekday and weekend sleep times (larger shifts in sleep times are seen as a reliable proxy for evening preference, Roenneberg, Wirz-Justice, et al., 2003; Wittmann et al., 2006).

Samples that included participants with circadian rhythm sleep-wake disorders of delayed / advanced sleep-wake phase, shift work, or jet-lag were included if these quasi-experimental groupings formed the predictor variable. We permitted studies where the putative circadian variable was a diurnal rhythm, while recognising that evidence of a diurnal rhythm is not evidence for an endogenous circadian rhythm. Studies reporting on samples with neurological or physiological disorders that have a pronounced effect on circadian function (e.g., blind or traumatic brain injury samples) were excluded. No age restriction of studies was used.

Studies were excluded if they included participants with psychological or physical illnesses (such as mood or addictive disorders) that may affect the reward system. While a growing literature suggests circadian involvement in pathologies of reward motivation (see Alloy et al., 2017; Hasler et al., 2015 for a review of circadian contributions to bipolar disorder and alcohol use disorder, respectively), this paper takes the preliminary step of examining the circadian modulation of neural reward activation in the general population. General population samples, however, that included proportional levels of individuals with a history or current mental illness were included to increase the generalizability of these findings. Studies that investigated altered reward response specific to a population (e.g., displaying images of alcohol to heavy alcohol users) were excluded, on the grounds that they effectively add an additional interaction term to the circadian-reward relationship of interest in this systematic review. Studies administering pharmaceuticals, acupuncture, transcranial magnetic stimulation, or reward-related substances (alcohol, drugs [including caffeine and nicotine]) were excluded, as this intervention may have affected the circadian predictor variable and the reward outcome variable. In studies that contrasted a clinical sample with a control group, data for the control group were used when provided separately.

BOLD response to reward was the outcome variable. This could be examined using a reward task (block- or event-related designs), or through resting state connectivity analyses of reward-related regions. The response to reward stimuli was

defined as the BOLD signal change in reward-related brain regions (task-based fMRI) and changes in connectivity between reward-related structures and networks (e.g., the DMN).

After removal of duplicate articles, two stages of screening were used: Stage 1 (title and abstract) screened for inclusion and exclusion criteria independently by authors JB and HT. At Stage 2, articles were collated and the two reviewers reviewed the full-text for any discrepancies with Cohen's Kappa for inter-rater agreement assessed and reported. A third rater (GM) resolved discrepancies in ratings for two articles.

9.3.3.3   Data extraction and quality evaluation. A data extraction form was completed for each included study. This form detailed the aim of the study, the circadian variable, neuroimaging procedure, regions of interest, a description of the reward stimuli (if used), sample size, sampling strategy, participant characteristics, results, interpretation, and limitations of the research. Following other recent work in this area (e.g., Ong, Kim, Young, & Steptoe, 2017) we adapted the Effective Public Health Practice Project (Project EPHP) quality assessment tool for our purposes. The EPHP tool assesses six study domains: selection bias; study design; confounders; blinding; data collection methods; withdrawal, and dropout component scores, with overall global ratings. Each section is rated as Strong, Moderate or Weak. As this tool was originally designed for health interventions we made adaptations as necessary. This tool examines study quality based on different intervention groups. We replaced the term 'interventions' with 'circadian function'. For example, in the confounder's domain the question became: "Were there important differences between groups aside from circadian functioning?" JB and HT rated the included studies independently with any discrepancies discussed with a third author (GM). Given the expected heterogeneity in study designs and variables, a narrative synthesis following Popay et al. (2006) methodology was conducted.

9.3.3.4   Analytics and reporting approach. Following a narrative synthesis approach, articles were collated into three sections based on the fMRI methodology employed: resting state designs, block designs, and event-related designs. In the results below, at the end of each fMRI design section, the direction and consistency of findings across studies is synthesised to address the first two research questions. In this synthesis paragraph, methodological quality of each study in robustness and

the heterogeneity across studies is also considered. To address the third research question, event-related designs were further divided into reward anticipation and reward receipt. As part of the preliminary synthesis suggested by Popay et al. (2006), for each included study the method and the circadian variable of interest were detailed with the results of any relationship between the circadian variable and BOLD response to reward that was investigated. We also focused on the study's contrasts that compared the rewarding stimuli to a baseline (i.e., Win > Control contrasts), rather than a loss condition (i.e., Win > Loss contrasts).

9.3.4 Results.

9.3.4.1 Included studies. Scopus returned 1411 articles, EBSCOhost 625 articles, PsycINFO 395 articles (including 31 dissertation abstracts), ProQuest Central 353 articles (including 11 dissertations), PubMed 226 articles, and Web of Science 1087 articles, totalling 4097 articles. When duplicates were removed 2521 articles remained. An independent Stage 1 excluded 2501 articles leaving 19 articles. After consensus discussions, the Stage 2 review of full-texts excluded a further six articles. Four articles were excluded as they used a cognitive task and no resting state data to examine the circadian modulation of reward (Gorfine & Zisapel, 2009; Marek et al., 2010; Reske, Rosenberg, Plapp, Kellermann, & Shah, 2015; Vandewalle et al., 2011), one article was a conference abstract with no full-text available (Calvert, Owen, & Tavassoli, 2011), and a final article was excluded as there were two independent control groups (one study provided a circadian variable, and the other study provided the reward variable, McKenna, Drummond, & Eyler, 2014). A third reviewer (GM) was used for one article (Klumpers et al., 2015) with a final decision to exclude the article as reported data were insufficient to analyse the circadian signal in reward functioning. From the reference lists of the selected articles and endnote libraries of the researchers, three additional references were identified (Blautzik et al., 2013; Blautzik et al., 2014; Yoncheva, Castellanos, Pizinger, Kovtun, & St-Onge, 2016) and agreed on by both reviewers. Cohen's Kappa for inter-rater agreement was "substantial" (Cohen's κ = 0.71) at Stage 1, and "almost perfect" (Cohen's κ = 0.97) following full-text revision (Landis & Koch, 1977). The final review included 15 articles reached by consensus (see Figure 12).
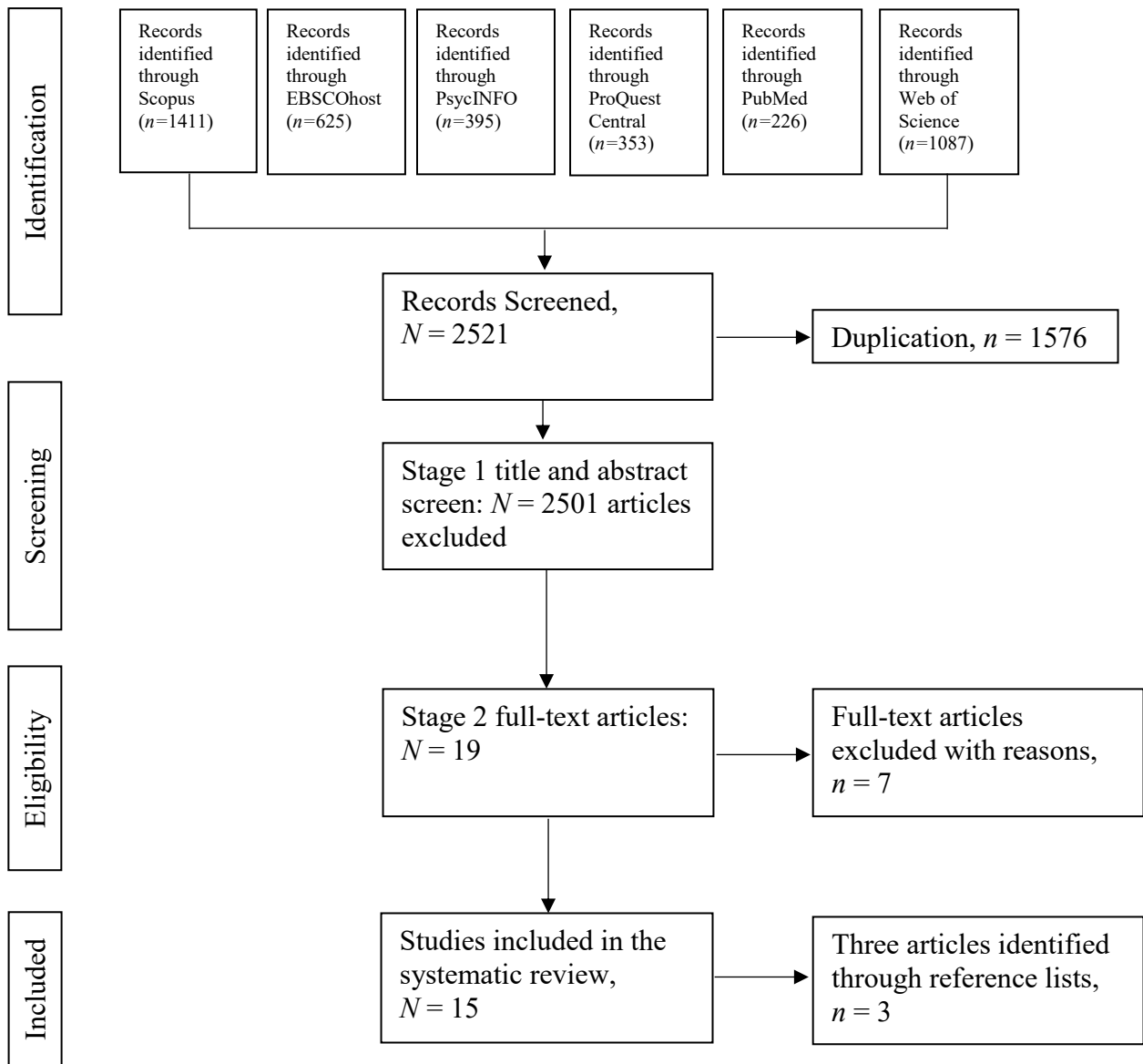
Figure 12. Flowchart of article selection

Table 14

Study design for the 15 reviewed studies

Study	Overarching aim of the study	Design	Participants relevant to the review	Key measures relevant to review	Circadian IV of interest for review	Reward stimuli ('fMRI paradigm') relevant to the review	Design strengths for the review question	Design limitations for the review	Authors' conclusions relevant to the present review
BLOCK DESIGNS									
Baranger et al. (2016)	To examine whether environmental stress moderates the association between *PER1* rs3027172 allele types, environment, later problematic alcohol use and VS reactivity to reward	Participants were scanned once	665 participants aged 18-22 (19.64 +/- 1.24, 294 men, 123 with a DSM-IV Axis 1 disorder)	*PER1* rs3027172 genotypes to predict neural response in the VS through early life stress and alcohol use	*PER1* rs3027172 genotypes	Decision-making task; card-guessing game for monetary rewards, 30 trials	Controlled for sleep quality	Some of the sample had a psychiatric diagnosis (but psychiatric diagnosis was not related to geneotypes)	There was no relationship between rs3027172 allele type and the VS activation in response to rewards
Byrne et al. (2017)	To investigate the neural response to reward stimuli at three times of day (10am, 2pm, and 7pm)	Within subjects, participants were scanned in the fMRI as 10am, 2pm and 7pm with counterbalanced start times. Used block design imaging	N = 16, 100% Male, M = 22.65 (2.87), no psychiatric or physical conditions thought to affect circadian rhythms	BOLD Contrast	Time of day	Decision-making task; card-guessing game for monetary rewards	Three time points, counterbalancing participants	Did not a priori control for sleep-wake times, only tested men	Neural response to rewards is modulated by time of day. Decreased activation of the left putamen was thought to represent a 'prediction error of the brain' where rewards at unexpected times evoked greater neural activation in the left putamen

Study	Overarching aim of the study	Design	Participants relevant to the review	Key measures relevant to review	Circadian IV of interest for review	Reward stimuli ('fMRI paradigm') relevant to the review	Design strengths for the review question	Design limitations for the review	Authors' conclusions relevant to the present review
Hasler et al. (2014)	To examine the diurnal rhythm in neural reward response	Two fMRI scans one AM (on average 1.56 h after wakening) one PM (8.23 h after waking), scan times counterbalanced, before each scan participants completed PANAS	11, 7 Female, 21.51 (1.72), healthy individuals with normal sleep-wake cycle and sleep quantity	BOLD contrasts, block related designs	Time of day	Decision-making task; card-guessing game for monetary rewards, 45 trials	Counterbalanced scans	PANAS did not show significant difference in affect (perhaps due to small sample size), block design – cannot distinguish anticipation from receipt	Neural correlates of reward function exhibited a pattern of daily changes, with increased VS activity in the afternoon, consistent with a circadian modulation of neural reward processes
Masterson et al. (2016)	To investigate the impact of time of day on neural responses to food stimuli	Two scans counterbalanced one 6:30-8:30am (under fasted state), one 5:30-7:30pm (prior to evening meal) scans separated by one week, assessments were only conducted during normal week. Ate identical diets on both scan days that best represented typical dietary intake. Prior to scan completed VAS with six hunger/food related self-report variables. 10 images of same type of stimuli per block, each block of images followed by 10 blurred. Participants said whether food was breakfast or dinner, or warm or cool colour for distractor images	N = 15, 100% Female, Mean age 23.33 (1.02), Pre-menopausal, required to have slept at least 7 hours night before scan and not eaten after 8pm and refrained from vigorous exercise, alcohol and caffeine in prior 24 hours. Weight stable, normal sleep and regular consumers of breakfast, lunch and dinner in past six months. Excluded if highly active (>4 times p/week x 20 mins) or dieting	BOLD Contrast, self-report ratings of hunger, satiety	Time of day, and high energy versus low energy food	Food, high energy (120 images, baked goods, ice-cream, candy, high fat restaurant foods) and low energy (120 images, vegetables, fruits, fish, wholegrains). Complex visually appealing distractor pictures (120), blurred pictures (360) corresponding to each of the pictures	Self-report ratings of food were included	Findings may be specific to food reward, only tested women	A significant main effect of time of day was observed with increased activation of many neural reward regions in the morning relative to afternoon. Decreased sensitivity to food stimuli in the evening may prompt greater motivation to seek out food (to attain the morning levels of activation)

EVENT-RELATED DESIGNS

Study	Overarching aim of the study	Design	Participants relevant to the review	Key measures relevant to review	Circadian IV of interest for review	Reward stimuli ('fMRI paradigm') relevant to the review	Design strengths for the review question	Design limitations for the review	Authors' conclusions relevant to the present review
Forbes et al. (2012)	To examine the effect of circadian genotypes and sleep times on neural reward activation	fMRI scan and genotyipng. Actigraphy was collected for two weekday and two weekend nights after the scan in participant home environment	90, 51.5% female, 11.9 years (.7), Healthy adolescents, Girls 11-12 years old, boys 12-13	BOLD contrasts, event related design: Looked at reward anticipation> baseline, reward receipt> baseline.	Genotype (rs2304672, rs2304674) and weekend sleep mid-point	Decision-making task; card-guessing game for monetary rewards, 24 trials	Used actigraphy to measure weekend sleep mid-point	Only looked at the first run of the fMRI task, due to concerns about reward attenuation over time	First study to report a gene-brain-behaviour relationship between circadian and reward function in humans, mPFC activity is moderated by allele type of rs2304672
Hasler et al. (2013)	To examine the neural mechanisms of reward response in morning, and evening chronotypes	Single fMRI scan between 9am and 4pm (30 of 34 completed scan between 12-4)	34, 100% Male, 20 years old, Recruited from Pitt Mother and Child Study examining resilience and vulnerability in low SES boys and their families, utilised data from lab visit at 20 years old. 21 evening types, 13 morning types. Of the 13 morning types one had current MDD, one past alcohol abuse, and one current SUD. In evening types it says three of the 21 had a past MDD, one current and one past alcohol abuse, three current one past substance abuse and one current two past substance dependence (it is unclear whether these are comorbid).	BOLD contrasts, event related design: Looked at win>control and reward anticipation > control	Chronotype	Decision-making task; card-guessing game for monetary rewards, 24 trials	Used alcohol and drug consumption questionnaire, and alcohol dependence scale as a validated measure of risk-taking in adolescents, did a whole brain analysis first to test for the effect of time of day outside of chronotype	Self-report measures of chronotype, only men, psychiatric diagnosis in some participants	The reward response observed with stronger activation in the left mPFC in morning types for reward anticipation, but greater activation in the striatum in evening types in win receipts, is indicative of the circadian system driving reward-related problems seen in adolescent evening types

Study	Overarching aim of the study	Design	Participants relevant to the review	Key measures relevant to review	Circadian IV of interest for review	Reward stimuli ('fMRI paradigm') relevant to the review	Design strengths for the review question	Design limitations for the review	Authors' conclusions relevant to the present review
Hasler et al. (2017)	To investigate whether chronotype longitudinally predicts activation in the VS and mPFC, stability of circadian preference and reward-related brain function, and whether circadian preference at age 20, and alcohol and substance use at age 22 is mediated by VS or mPFC response	Two fMRI scans, one at age 20 and one at age 22 (scanned between 9am and 4pm)	Part of an ongoing longitudinal study for low-income boys. Valid reward task fMRI data was present for 93 participants at both ages	BOLD ROI analyses	Chronotype at age 20	Decision-making task; card-guessing game for monetary rewards, 24 trials	Tested correlation between ROI data and time of scan with no significant differences and was therefore not included as a covariate	Self-report measures of chronoype, only men, unable to account for sleep loss, unclear the test-retest reliability of the task	Circadian preference relates directly to activation in reward-related brain regions in response to reward receipts but not anticipation, and greater evening preference may lead to alcohol use and dependence through the indirect path of the mPFC activation to win receipts
Hasler et al. (2012)	To investigate the association between weekend-weekday shifts in sleep timing and neural reward functioning	Scans occurred mid-week prior to actigraphy assessment. Actigraphy to measure sleep-wake behaviour collected data from Friday to Tuesday to get two weekend and two weeknight data, measured PANAS-C in participants home environment (mobile), 20 items administered 1x per day subset of 8 items (4 positive) administered at other calls	N = 56 12.34 (0.88), 55.4%F, girls were 11-12, boys were 12-13, approximately 2/3 of the sample was in the mid-to-late puberty stage, and participants were not depressed.	BOLD contrast, event related design	Weekend-weekday shift in sleep times (actigraphy), pubertal stage, PANAS-C	Decision-making task; card-guessing game for monetary rewards, 48 trials	Using actigraphy to measure sleep changes, controlled for sex, pubertal status, and affectivity	Cross-sectional, no precise quantification of circadian misalignment, also scans occurred before actigraphy	Bigger shifts in sleep timing were related to a diminished mPFC and VS neural response to rewards. In later pubertal stages greater shifts in sleep across week were related to less reward regulation (less mPFC activation in response to rewards) while less developed were associated with lower reactivity to basic reward reactivity (less striatal response to reward)

Study	Overarching aim of the study	Design	Participants relevant to the review	Key measures relevant to review	Circadian IV of interest for review	Reward stimuli ('fMRI paradigm') relevant to the review	Design strengths for the review question	Design limitations for the review	Authors' conclusions relevant to the present review
LeMoult et al. (2015)	To examine the effect of pubertal development stage on diurnal cortisol production and VS activity during reward anticipation	Diurnal cortisol measured within two weeks of scan. Measured over two days, eight-sample collection (immediately upon waking, 30 mins after waking, 3:00pm, 30 mins before bedtime). fMRI task was one run, 100 trials (shape presentation determined response circle (gain), square (loss), triangle (neutral), also trials with 0 was presented for participants to press button as quickly as possible	N = 38, 100% Female, age range 9-14, 21 pre-menarcheal and 17 post-menarcheal, 20 girls had a mother with a diagnosis of depression during daughter's lifetime, 18 girls had mothers with no Axis 1 disorder	BOLD contrasts, behavioural reaction times to task	Pubertal stage, cortisol	Money - KIDMID, child version of the monetary incentive delay tasks	Objective measure of circadian parameters	Using menarche as indicator of puberty (hormone levels may be similar pre/post menarche), wide age range, only girls	No significant RT / VS activity correlation for either gain or loss trials. Cortisol levels increased significantly within 30 mins of awakening and then decreased throughout the day, menarcheal group not a significant factor.

RESTING STATE DESIGNS

Blautzik et al. (2013)	To examine the rhythmicity of resting state connectivity over the course of the day, controlling for sleep timing preferences	Participants were scanned four times every 2.5 hours. Start times were staggered according to individual chronotype with intermediate types beginning first finishing with moderately late chronotypes	15 healthy intermediate-moderately late chronotypes, 9 females, 23 +/- 3.0 years	Used the MCTQ to determine chronotype using BOLD sequence accounting for baseline levels of connectivity	Time of day (controlled for mid-sleep on free days)	No stimuli	Controlled for individual chronotype for scan times and individual strengths in connectivity, used four different scanning sessions	Daily oscillations in respiratory and cardiac functions may impact the connectivity	While some patterns of connectivity in the brain are stable, others appear to show a neural rhythmicity in particular the DMN previously described including regions important for motor and somatosensory processes

Study	Overarching aim of the study	Design	Participants relevant to the review	Key measures relevant to review	Circadian IV of interest for review	Reward stimuli ('fMRI paradigm') relevant to the review	Design strengths for the review question	Design limitations for the review	Authors' conclusions relevant to the present review
Blautzik et al. (2014)	To examine time of day effects on neuronal resting states between healthy elderly adults and elderly adults with amnestic mild cognitive impairment	Participants were scanned four times in one day at 2.5 hours intervals, with staggered start times dependent on the corrected MSF. Scanning covered approximately 10 hours of the day beginning at 9am with earlier chronotypes	Twelve healthy elderly participants (5 females, 65.1 +/- 5.7 years), with no subjective memory complaints	rs-fMRI	Time of day (controlled for mid-sleep on free days)	No stimuli	Controlled for individual chronotype for scan times and individual strengths in connectivity, used four different scanning sessions	Daily oscillations in respiratory and cardiac functions may impact the connectivity, didn't explain differences among controls	A sensorimotor, cerebellar, and visual network were associated with high rhythmicity peaking later in the day, peaking ~12 hours after the mid-sleep
Coutinho et al. (2015)	To examine the relationship between jet-lag and pattern of activation in the DMN	5 min resting state fMRI	In the final sample 10 control participants, 10 with jetlag, 3F in each group with a mean age of 25.6 (5.8), 22-42 years of age (four participants excluded due to MRI contraindications) transmeridian flight from America to Europe 12 hours before the study. Healthy participants	BOLD fMRI	Jet-lag versus control condition	No stimuli	Control group, matched for age, sex, and gender	Did not control for sleep deprivation, and travel discomfort that may occur as a result of travel, or stresses related to travelling, small sample size, non-random allocation to groups	Decreased activation in the jetlag relative to control populations: bilateral medial frontal gyrus (mPFC), right anterior cingulate gyrus (ACC), left parahippocampal gyrus, and left angular gyrus.

Study	Overarching aim of the study	Design	Participants relevant to the review	Key measures relevant to review	Circadian IV of interest for review	Reward stimuli ('fMRI paradigm') relevant to the review	Design strengths for the review question	Design limitations for the review	Authors' conclusions relevant to the present review
Hodkinson et al. (2014)	To investigate circadian and sleep homeostatic effects on connectivity in the DMN and the regional cerebral bloodflow	Participants scanned on two separate days morning scan (0800-1000) and afternoon (1500-1900) randomised across participants, on scan days saliva was collected at 1200, 1600 and 2000 and CAR (at awakening, 30 mins after, 60 mins after awakening)	13 participants, 100% men, 27 (4), range 23-38	BOLD: whole-brain rs-fMRI	Cortisol awakening response and area under the curve (as a measure of circadian amplitude of cortisol production)	no stimuli	Within subjects, measured cortisol as an indicator of circadian activity, controlled for scan order	No way to control for the homeostatic sleep drive component of this diurnal variation, restricted age and sex sample	Decreased synchrony was present in the DMN AM>PM, predominantly localised to midline association and important connector nodes such as the PCC, mPFC, and temporal cortex.
Kyeong et al. (2017)	To examine circadian disruption in delirium using resting-state fMRI	5 min resting state fMRI	38 non-delirious controls (77.6 +/- 9.1 years, 74-100 years) from a databank. Databank included people who were scanned due to a medical condition with findings within normal limits	fMRI connectivity	SCN ROI	no stimuli	Looking at direct connectivity from the SCN	Have not controlled for time of day of the scan. No data presented on the scan time	SCN activity was positively correlated with the OFC, ventral ACC, insula, hippocampus, basal ganglia, and brain stem and negatively correlated with activity in DLPFC, pre- and postcentral gyrus, and precuneus

Study	Overarching aim of the study	Design	Participants relevant to the review	Key measures relevant to review	Circadian IV of interest for review	Reward stimuli ('fMRI paradigm') relevant to the review	Design strengths for the review question	Design limitations for the review	Authors' conclusions relevant to the present review
Yoncheva et al. (2016)	To examine the effects of normal and delayed sleep and meal times on neural reward functioning in resting state fMRI	Randomised in-patient cross-over design. Four phases: normal sleep, normal meal; normal sleep, delayed meal; delayed sleep, normal meal; delayed sleep, delayed meal. Normal sleep times were midnight-8am, delayed 3:30-11:30am; normal mealtimes 1, 5, 11, 12.5 hours after waking; delayed mealtimes were 4.5, 8.5, 14.5 and 16 hours after awakening. Each phase participants were inpatients for 5 days with a scan on day 4 of the protocol (62min +/- 11min before dinner time)	Six participants (five completed all four study phases (one participants' scan was unavailable), one completed three phases); of the four reported participants (three were men, 25.3 +/- 4.6 years BMI = 29.2 ± 2.7 kg m−2, normal sleep quantity (7-9 hours), no extreme chronotypes, ate breakfast, and were inactive	rs-fmri	Normal versus delayed mealtimes	No stimuli	In-patient cross-over design, preserved sleep length	No information about what participants were allowed to do in the in-patient phases; small sample size	Misalignment of sleep and meal-times affects connectivity in reward-related areas outside of changes to sleep quantity; the largest effects were observed in the bilateral amygdala, with increased connectivity between the amygdala and hippocampal region with shifted sleep times, and increased insula connectivity following delayed sleep times; circadian desynchrony of sleep and meal times altered activation in the frontal pole and visual areas

The reviewed studies were largely independent, though four of the included studies (Forbes et al., 2012; Hasler et al., 2017; Hasler et al., 2012; Hasler et al., 2013) were conducted by the same group, with overlapping samples. The methodologies of the included studies (See Table 15) varied in terms of: the use of single assessments of reward function versus repeated measures, in age groups, and in the types of analyses conducted, and so are considered singly. Of the 15 studies, eight (Byrne, Hughes, Rossell, Johnson, & Murray, 2017; Forbes et al., 2012; Hasler, Casement, et al., 2017; Hasler, Dahl, et al., 2012; Hasler, Forbes, et al., 2014; Hasler, Sitnick, Shaw, & Forbes 2013; Masterson, Kirwan, Davidson, & LeCheminant, 2016; Yoncheva et al., 2016) shared the present aim of examining a circadian signal in reward processing, five (Blautzik et al., 2013; Blautzik et al., 2014; Coutinho et al., 2015; Hodkinson et al., 2014; Kyeong et al., 2017) had an interest in examining the circadian signal on non-reward specific brain activity, LeMoult et al. (2015) had an interest in the developmental stage moderators of the reward response, which included a circadian variable (cortisol), and Baranger et al. (2016) aimed to examine whether environmental stressors moderate the relationships between a circadian genotype, problematic alcohol use, and VS activation. Both LeMoult et al. (2015) and Hasler, Dahl, et al. (2012) considered how the circadian signal of reward activation may differ with pubertal stage. Kyeong et al. (2017) and Blautzik et al. (2014) compared healthy controls to individuals with delirium and mild cognitive impairment respectively, only data pertaining to healthy controls was examined. The various operationalisations of circadian functioning, fMRI paradigm and reward tasks for the selected studies are summarised in Figure 13.

Circadian predictor variable

Circadian genotypes
• Baranger et al. 2016
• *Forbes et al. 2012

SCN connectivity
• Kyeong et al. 2017

Repeated-measures at different times of day
• Blautzik et al. 2013
• Blautzik et al. 2013
• Byrne et al. 2017
• Hasler et al. 2014
• Masterson et al. 2016
• Hodkinson et al. 2014

Jet-lag
• Coutinho et al. 2015

Awakening cortisol, and amplitude of cortisol
• *LeMoult et al. 2015

Chronotype
• Hasler et al. 2013
• Hasler et al. 2017

Weekend-weekday sleep times
• Hasler et al. 2012

Sleep mid-point on weekend
• *Forbes et al. 2012

Sleep and mealtime delays
• Yoncheva et al. 2016

Reward stimuli

No stimuli
• Blautzik et al. 2013
• Blautzik et al. 2013
• Coutinho et al. 2015
• Hodkinson et al. 2014
• Kyeong et al. 2017
• Yoncheva et al. 2016

Monetary rewards
• Baranger et al. 2016
• Byrne et al. 2017
• Hasler et al. 2014
• Forbes et al. 2012
• Hasler et al. 2013
• Hasler et al. 2017
• Hasler et al. 2012
• LeMoult et al. 2015

Food rewards
• Masterson et al. 2016

fMRI paradigm

Resting state
• Blautzik et al. 2013
• Blautzik et al. 2014
• Coutinho et al. 2015
• Hodkinson et al. 2014
• Kyeong et al. 2017
• Yoncheva et al. 2016

Block design
• Baranger et al. 2016
• Byrne et al. 2017
• Hasler et al. 2014
• Masterson et al. 2016

Event-related design
• Forbes et al. 2012
• Hasler et al. 2013
• Hasler et al. 2017
• Hasler et al. 2012
• LeMoult et al. 2015

Figure 13. Operationalisation of circadian predictor variables and reward tasks with fMRI protocol used for selected studies. *Note.* Forbes et al. (2012) and LeMoult et al. (2015) used two circadian variables of interest

9.3.4.2 *Quality assessment.* As shown in Figure 14, on the modified EPHP global score for the quality of study methodology, most studies were classified as of Moderate quality (*n* = 8), followed by Strong (*n* = 5), with two rated as Weak.
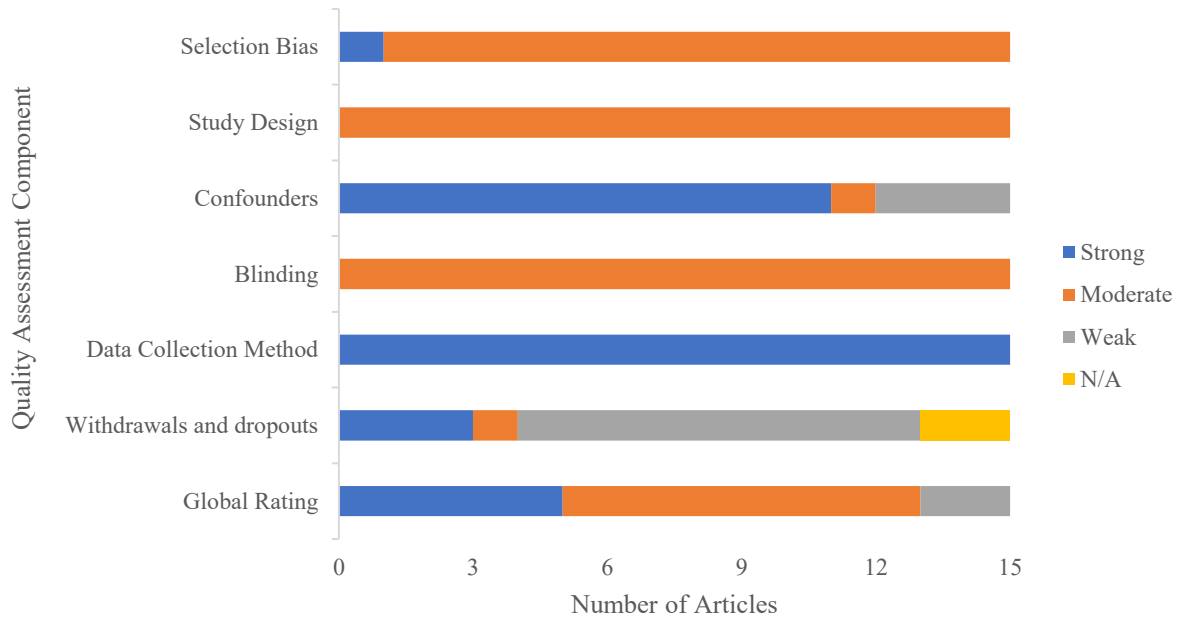
Figure 14. Quality assessment of the selected articles reached by two independent reviewers and broken into component and global scores

Table 15

Imaging findings for block design studies

	Data analysis of imaging	Covariates, variability correction	Amygdala	mPFC	Striatum (VS, NAc)	Anterior cingulate	Insula	Putamen	Implications for systematic review
Baranger et al. (2016)	ROI (bliateral VS)	Covariates included sex, age, ethnicity, psychiatric diagnosis, sleep quality, early life stress	Not examined	Not examined	rs3027172 genotypes was not related to bilateral VS reactivity to reward stimuli (*p*=.113)	Not examined	Not examined	Not examined	There was no evidence that circadian genotypes modulate neural reward circuitry
Byrne et al. (2017)	ROI (mPFC, VTA, ACC, caudate, Nac, putament) and post-hoc whole-brain analyses	Slice-time corrected, motion realigned	Not examined	Non-significant	Non-significant	Non-significant	Not an ROI, posterior region of the left insula there was a small cluster (18 voxels, MNI coordinates: -32 -30 20) was found for reward > baseline however this was non-significant	Left putamen significantly decreased activation at 2pm relative to 10am or 7pm	Lowered activation in the left putamen at 2pm relative to 10am or 7pm was thought to represent a prediction error of the brain. As rewards may be expected in the afternoon relative to earlier or later, reward receipt at earlier and later times of day evokes greater neural activation

	Data analysis of imaging	Covariates, variability correction	Amygdala	mPFC	Striatum (VS, NAc)	Anterior cingulate	Insula	Putamen	Implications for systematic review
Hasler et al. (2014)	ROI: striatal region (defined as caudate, putamen and VS) looked at win>control, but also looked at whole brain analyses	Motion realignment to first scan,	Not examined	Greater activation in response to first compared to second session but no significant time of day (so scan iteration was included as covariate)	Win > neutral was associated with stronger activation in PM than AM in the ventral striatum,	Not examined	In exploratory whole brain analyses, bilateral insula was associated with greater activation in PM>AM	In exploratory whole brain analyses, right caudate and putamen was associated with greater activation in PM>AM (however did not survive thresholding)	Time of day may affect the neural activation in response to rewards, with greater activation shown in PM hours relative to AM
Masterson et al. (2016)	Modelled high-energy, low-energy food blocks, and distractor non-food blocks, performed whole brain analyses	Non-food control blocks modelled, motion realignment, including aligning between scans, used voxel-wise p-value of <.001 and 40 contiguous voxels for spatial extent threshold	Bilaterally amygdala was not significant for time of day	Not examined	Bilaterally not significant for time of day in the 'accumbens area'. In the right ventral striatum/amygdala region it was significant for time of day	Not examined	Not examined	Left putamen significant for time of day	fMRI neural activation was greater in multiple reward regions in the morning relative to afternoon. This is in contrast to higher self-reported levels of desire to eat, food amount able to be consumed, urge to eat, and preoccupation with thoughts of food in the evening relative to morning.

9.3.4.3   Task-based fMRI: Block designs. Of the four studies using block designs, three used repeated measures protocols at different times of day as the circadian predictor variable (Byrne, Hughes, et al., 2017; Hasler, Forbes, et al., 2014; Masterson et al., 2016). As part of a larger study, Baranger et al. (2016) collected data on clock gene *PER1* genotypes, with allele variants of rs3027172 (the common T-homozygotes and the risk C-carriers), used as the circadian predictor variable for this review.

Using a repeated measures fMRI reward paradigm, Hasler, Forbes, et al. (2014) scanned 11 young adults (19-24 years old) in the morning and afternoon using a monetary reward task. Most participants completed both scans within 24 hours (one participant's scans were 13 days apart; scan interval did not alter findings). The scans took place on average at 10.11h (range: 07.32-11.47h) and 16.51h (range: 15.06-18.38h), adjusted for participants' sleep-wake times with sessions counterbalanced. A number of time-of-day differences were identified. ROI analysis found that right ventral striatal response was greater for *wins* (Win > Control blocks) in the afternoon compared to morning. In response to rewards, auxiliary whole brain analyses revealed greater bilateral middle and superior temporal gyri and insula activity in the afternoon relative to morning, a pattern which was also observed in a caudate and putamen region in the right hemisphere. Activation in the thalamus, cerebellum and caudate was increased in the morning relative to afternoon in response to monetary rewards.

Using the same monetary reward task as Hasler, Forbes et al. (2014), and a counter-balanced design, this time with three scanning sessions (10.00h, 14.00h, and 19.00h) Byrne, Hughes et al. (2017) tested for a diurnal rhythm in reward responses among 16 young men (22.65 ± 2.87 years). Of the 12 ROIs (bilateral mPFC, VTA, ACC, caudate, NAc, and putamen), only the left putamen exhibited time of day variation, viz. significantly lowered activation at 14.00h relative to 10.00h and 19.00h for the Win > Baseline blocks. The authors interpret this pattern of results (which contrasts with the inverted U pattern seen in behavioural measures of reward response in humans, Murray et al., 2009) as being consistent with a form of 'prediction error' (Schultz, Apicella, Scarnati, & Ljungberg, 1992; Takahashi, Langdon, Niv, & Schoenbaum, 2016): They argue that, if humans are chronobiologically primed to expect rewards in the early afternoon (p. 9 above), we

may expect to see a relatively decreased neural response to presentation of rewards at this time. Indeed, there is consensus that putamen activation is most sensitive to unexpected rewards (e.g., McClure, Berns, & Montague, 2003; O'Doherty, Dayan, Friston, Critchley, & Dolan, 2003).

Masterson et al. (2016) used a counter-balanced cross-over design to examine response to high- and low-energy food rewards in the morning (06.30-08.30h) versus the early evening (17.30-19.30h) in 15 weight stable females (23.33 ± 1.22 years). Given energy intake tends to be highest in the evening, the authors anticipated a stronger response to visual food stimuli in the evening, relative to morning. Contrary to expectations, whole brain analyses revealed that the BOLD response was lower in the left putamen, right lingual gyrus, right middle temporal gyrus, right parahippocampus/ hippocampus, right middle occipital gyrus, and right VS/ amygdala, in the early evening relative to the morning scan. No interaction between time of day and energy of food (high-energy compared to low-energy) was found. The authors propose that a decreased neural response to food stimuli in the evening may in turn trigger greater behavioural action to seek out food rewards at this time. This argument is consistent with self-report data showing participants could eat more and were more preoccupied with food, in the evening relative to the morning.

As part of a broader study which examined early life stress, alcohol use, circadian genotypes, and reward-related VS activity, Baranger et al. (2016) collected data testing the relationship between circadian *PER1* rs3207172 genotypes and VS activation in response to monetary rewards. In a large sample of 18-22 year olds, carriers of the C risk allele ($n = 182$) did not exhibit altered bilateral VS reactivity in response to monetary reward stimuli relative to TT homozygotes ($n = 483$, $p = .113$, presented in Supplemental Table 5).

In sum, these four articles present divergent results in the examination of a circadian signal in the reward system. The three studies using a repeated-measures protocol found a diurnal rhythm, broadly consistent with circadian modulation; however, the waveform of this rhythm was inconsistent across studies. Two studies (Byrne, Hughes, et al., 2017; Masterson et al., 2016) suggest the response to reward stimuli is lower in the afternoon (Byrne, Hughes, et al., 2017) and early evening (Masterson et al., 2016) relative to earlier times of day (and also later times of day, in Byrne, Hughes, et al., 2017); while Hasler, Forbes et al.'s (2014) work suggests

the reward response is elevated in reward-linked regions in the afternoon relative to morning. In addressing what specific reward-related brain regions may subserve this relationship two common brain regions were found to have different levels of activation across the day: Both Masterson et al. (2016) and Hasler, Forbes, et al. demonstrated right ventral striatal engagement to food and monetary rewards, with greater VS BOLD response observed in the morning in Masterson et al. (2016) and evening in Hasler, Forbes, et al. (2014). In Baranger et al. (2016), bilateral VS BOLD response did not differ with circadian genotype. Left putamen response was lower in the afternoon/early evening in response to monetary (Byrne, Hughes, et al., 2017) and food rewards (Masterson et al., 2016) but the differences in session times and stimuli cautions against considering this a replicated finding.

Table 16

Imaging findings for event-related design studies

	Data analysis of imaging	Covariates, variability correction	Amygdala	mPFC	Striatum (VS, NAc)	Anterior cingulate	Insula	Putamen	Implications for systematic review
Forbes et al. (2012)	ROI (ventral and dorsal striatum, mPFC, orbitomedial PFC and amygdala), and whole brain analysis	Small motion correction	**Reward anticipation:** Was activated in response to reward anticipation but was not associated with sleep mid-point **Reward receipt:** Was activated in response to reward receipts but was not associated with sleep mid-point	**Reward anticipation:** Was activated in response to reward anticipation but was not associated with sleep mid-point **Reward receipt:** Sleep mid-point was negatively correlated with mPFC during reward receipt (later sleep times were related to reduced mPFC activity). The mPFC was less active for the rare G allele in response to reward receipts, compared to CC homozygotes for the rs2304672 allele	**Reward anticipation:** Was activated in response to reward anticipation but was not associated with sleep mid-point **Reward receipt:** Was activated in response to reward receipts but was not associated with sleep mid-point. A strong negative association between mPFC and VS was seen in G carriers of rs2304672 in response to reward receipt, for CC types this was a weak nonsignificant association	**Reward anticipation:** Not examined **Reward receipt:** A region extending from the mPFC into the ACC activated during reward receipt was negatively correlated with later sleep-times, this activation was greater for G carriers of rs2304672 relative to CC carriers	**Reward anticipation:** Not examined **Reward receipt:** Not examined	**Reward anticipation:** Not examined **Reward receipt:** Not examined	Key role for clock-pathway genes in reward functioning in humans. Risk G allele associated with less activity in the mPFC region postulated to regulate striatal response to emotionally salient information in individuals with behavioural tendencies towards later sleep times, potentially indicating weaker inhibition of striatal response

	Data analysis of imaging	Covariates, variability correction	Amygdala	mPFC	Striatum (VS, NAc)	Anterior cingulate	Insula	Putamen	Implications for systematic review
Hasler et al. (2013)	ROI (VS, mPFC)	PSQI, motion corrected, time of scan	**Reward anticipation:** Not examined **Reward receipt:** Not examined	**Reward anticipation:** Morning types displayed greater mPFC reactivity to reward anticipation relative to evening types **Reward receipt:** Chronotype was not significantly related to response to neural reward receipts in the mPFC	**Reward anticipation:** Chronotype was not significantly related to response to neural reward anticipation in the striatum **Reward receipt:** In win receipts evening types were associated with greater VS activation to reward compared to morning types	**Reward anticipation:** In supplementary materials ACC was correlated with reward anticipation in individuals with higher morningness as a continuous measure (in-text the mPFC ROI extended into BA32 [the ACC]) **Reward receipt:** In supplementary materials ACC was correlated with reward receipt in individuals with higher morningness as a continuous measure	**Reward anticipation:** In supplementary materials when time of scan was examined later time of scan was associated with reward anticipation and left insula activation **Reward receipt:** In supplementary materials when time of scan was examined later time of scan was associated with reward receipt and left insula activation	**Reward anticipation:** In supplementary materials the putamen activation was related to eveningness for both reward anticipation (in-text the striatal region was anatomically defined as the Nac, caudate and putamen) **Reward receipt:** In supplementary materials the putamen activation was related to eveningness for both reward receipt	Initial whole brain analyses showed increased activation for reward anticipation and reward receipt with greater reward-related activation later in the day compared to earlier.

	Data analysis of imaging	Covariates, variability correction	Amygdala	mPFC	Striatum (VS, NAc)	Anterior cingulate	Insula	Putamen	Implications for systematic review
Hasler et al. (2017)	BOLD ROI focusing on the mPFC and VS	Corrected for head motions, spatially smoothed	**Reward anticipation:** Not examined **Reward receipt:** Not examined	**Reward anticipation:** Chronotype at age 20 did not predict activation of the mPFC in response to reward anticipation **Reward receipt:** Greater evening preference was associated with greater mPFC activation in response to reward receipt	**Reward anticipation:** Chronotype at age 20 did not predict activation of the VS in response to reward anticipation **Reward receipt:** Greater evening preference at age 20 was associated with greater VS activation in response to reward receipt at age 22	**Reward anticipation:** Not examined **Reward receipt:** Not examined	**Reward anticipation:** Not examined **Reward receipt:** Not examined	**Reward anticipation:** Not examined **Reward receipt:** Not examined	Chronotype may be a longitudinal predictor of neural activation of reward regions for reward receipt but not reward anticipation
Hasler et al. (2012)	ROI: striatal region and mPFC, looked at reward anticipation and receipt, also included whole brain analyses	Motion realignment, small motion correction, controlled for sex, pubertal stage, and mean total sleep time	**Reward anticipation:** Not significant (whole brain) **Reward receipt:** Not significant (whole brain)	**Reward anticipation:** Participants with larger mid-sleep advances from Saturday to Sunday were associated with lower activation of the mPFC (receipt and anticipation) in the context of reward anticipation	**Reward anticipation:** Not significant **Reward receipt:** Lowered activation in the VS in response to reward receipts was observed in participants with larger mid-sleep advances from	**Reward anticipation:** Lowered activation in the bilateral ACC in response to reward anticipation was observed in participants with larger mid-sleep advances from Saturday to Sunday	**Reward anticipation:** Not significant (whole brain) **Reward receipt:** Not significant (whole brain)	**Reward anticipation:** In the mid/late developmental group larger mid-sleep advances were associated with diminished reactivity in the bilateral putamen during reward anticipation **Reward receipt:**	Circadian misalignment appears to play an important role in reward functioning with larger advances leading to lowered neural response in reward regions in response to reward anticipation and receipt, this appears to be moderated by developmental stage.

	Data analysis of imaging	Covariates, variability correction	Amygdala	mPFC	Striatum (VS, NAc)	Anterior cingulate	Insula	Putamen	Implications for systematic review
				Reward receipt: Lower activation of the mPFC in the context of reward receipts was observed for participants with larger mid-sleep advances from Saturday to Sunday	Saturday to Sunday	**Reward receipt:** Not significant		Larger mid-sleep advances were associated with diminished bilateral putamen activation in response to reward receipts	
LeMoult et al. (2015)	ROI (VS)	Pubertal stage, maternal history of depression, motion corrected	**Reward anticipation:** Not examined	**Reward anticipation:** Not examined	**Reward anticipation:** Post-menarchal girls were associated with a positive correlation between VS and cortisol awakening response during reward anticipation. Greater cortisol amplitude was associated with increased VS activation reward anticipation for all girls.	**Reward anticipation:** Not examined	**Reward anticipation:** Not examined	**Reward anticipation:** Not examined	Circadian predictors of cortisol awakening response and cortisol amplitude predicted response to reward anticipation. This may be dependent on the biological changes that occur during puberty.

9.3.4.4   Task-based fMRI: Event-related designs. Five task-based studies used event related designs, four (Forbes et al., 2012; Hasler, Casement, et al., 2017; Hasler, Dahl, et al., 2012; Hasler et al., 2013) have the potential to distinguish reward anticipation and reward receipt at the neural level, while LeMoult et al. (2015) only report on reward anticipation. For the present purposes, the circadian predictor variables in these five studies were, respectively, group comparison of individual differences in chronotype (Hasler, Casement, et al., 2017; Hasler et al., 2013), daily cortisol patterns (LeMoult et al., 2015), circadian genotype (Forbes et al., 2012), and individual differences in weekend-weekday shifts in sleep timing (Hasler, Dahl, et al., 2012).

9.3.4.4.1   Reward anticipation. As part of an investigation of the impact of weekend-weekday shifts in sleep timing on emotional functioning in adolescents (11-13 years), Hasler et al. (2012) examined the association between individual differences in actigraphy-derived sleep timing, and reward functioning (striatal and mPFC ROIs) in the context of a monetary reward task. Larger advances of mid-sleep from Saturday to Sunday night were found to be associated with decreased BOLD response during reward anticipation in the mPFC and the caudate. The authors also examined the effects of pubertal stage. Larger mid-sleep advances were associated with reduced BOLD response in the mPFC and the right putamen for the mid/late pubertal group ($n = 37$) in response to reward anticipation (compared to smaller mid-sleep advances). Larger mid-sleep advances were related to reduced striatal activity in the pre/early pubertal group ($n = 19$) relative to smaller mid-sleep advances. The authors suggest that the circadian misalignment observed in greater mid-sleep changes across the week may have specifically altered reward functioning that depends on pubertal stage.

Forbes and colleagues (2012) examined the association between sleep mid-point on weekend nights (self-selected schedules) and the anticipation of monetary gains in adolescents (11-13 years, $N = 90$). Later sleep mid-point was not related to the ROIs of VS, dorsal striatum, amygdala, or mPFC BOLD response in anticipation of rewards.

LeMoult et al. (2015) used a female youth sample (9-14 years old, $N = 38$) to examine how diurnal cortisol production and pubertal development may affect anticipation of rewards, with the VS as the ROI. The circadian variables of interest,

for the present purposes, were the cortisol awakening response, and the amplitude of the daily cortisol rhythm. Participants completed a monetary incentive delay task involving reward for quick response to cues. Cortisol was collected over two days with four samples per day: awakening cortisol response (immediately upon awakening and 30 minutes later), 3pm and 30 minutes prior to bedtime. Steeper cortisol awakening response was associated with greater VS response in anticipation of rewards, but only in post-menarcheal girls ($n = 17$). Stronger daily amplitude of diurnal cortisol (greater area under the curve) was associated with increased VS activation to anticipation of rewards.

Hasler et al. (2013) examined the relationship between self-reported chronotype and neural responses (in VS and mPFC ROIs) to a reward task among 20-year old males. During reward anticipation, morning-types ($n = 13$) were found to exhibit greater left mPFC BOLD response compared with evening-types ($n = 21$); no chronotype differences were observed in the striatum. The authors concluded that decreased BOLD response in the mPFC may account for increased reward-seeking propensity commonly observed in evening-types through relatively reduced regulatory control during reward anticipation.

Hasler et al. (2017) re-assessed the sample described in their 2013 report (above) two years later, to investigate whether circadian preference (by making this a continuous measure of morningness-eveningness it increased their sample size to 93 participants) at age 20 predicted changes in neural reward anticipation at age 22. In the two ROIs (mPFC and VS), chronotype at age 20 did not predict neural reward anticipation two years later.

In sum, evidence for circadian signal in reward anticipation was mixed: two reviewed studies presented findings consistent with the prediction (Hasler, Dahl, et al., 2012; LeMoult et al., 2015), while two did not (Forbes et al., 2012; Hasler, Casement, et al., 2017). Hasler et al. (2013) found evidence of a circadian signal in one region (the left mPFC) but not the striatal ROI. The ROIs used across all five event-related designs, the mPFC and striatum, showed mixed relationships of a circadian signal in reward anticipation. Reduced neural activation in the mPFC in the context of reward anticipation was observed in evening types (Hasler et al., 2013) and was associated with increased weekday-weekend shifts in sleep times (Hasler et al., 2012). In contrast, no circadian signal of reward anticipation in the mPFC was

found by Forbes et al. (2012) in a similar cohort, and circadian preference did not predict mPFC activation two years later (Hasler, Casement, et al., 2017). Greater neural activation of VS was observed in girls who exhibited a larger cortisol awakening response and a larger cortisol amplitude across the day (LeMoult et al., 2015). This finding should be considered in the context that this cortisol response may be confounded by stress-related variables. Hasler et al. (2012) found reduced striatal activity amongst participants with greater advances in sleep times between weekday and weekends. Thus, increased cortisol amplitude, and regularity of sleep-wake times is associated with increased VS BOLD response to reward anticipation. Circadian modulation did not predict striatal activation in Forbes et al., Hasler et al. (2013), or Hasler, Casement, et al. (2017).

9.3.4.4.2 *Reward receipt.* Hasler et al. (2012) examined the relationship between weekday-weekend shifts in sleep timing and BOLD response in the mPFC and VS to monetary rewards (rewards receipt received) in adolescents. Greater weekday-weekend shift was associated with reduced mPFC and VS BOLD response during the reward receipt phase. The relationship between shifts in sleep timing and mPFC and VS BOLD response differed by pubertal stage. Larger sleep advances between weekday-weekend in mid/late pubertal groups were associated with reduced mPFC response in the reward receipt condition. Compared to smaller sleep advances, participants with larger sleep advances in the pre/early pubertal stages had an attenuated striatal (in the caudate) response to monetary reward (reward receipt). As the mPFC is thought to modulate the striatal response to reward (Forbes et al., 2010; Spear, 2000), Hasler et al. (2012) suggest the mPFC is more developed in mid/late pubertal stages. The mPFC may be more affected by shifts in sleep times compared to the less developed pre/early pubertal stages, who may recruit more from the striatum to interpret reward receipts.

Forbes and colleagues (2012) examined the effect of sleep mid-point on the response to monetary gains in the ROIs of the VS, dorsal striatum, mPFC, and amygdala in adolescents. Significant results were examined in the context of circadian genotype groups. Later sleep mid-point was associated with decreased response in the mPFC to reward receipt. No differences were found in other reward-related ROIs of the dorsal striatum (caudate and putamen), orbitomedial PFC, and amygdala. The authors suggest that individuals with later sleep times may have a

behavioural tendency towards inhibited cognitive processing (with less mPFC reward regulation) in response to rewards. Participants who carried the rare G allele of *PER2* gene rs2304672 exhibited significantly reduced mPFC response to reward receipt relative to carriers of the common CC allele. Connectivity between the mPFC and VS was also significantly decreased in G carriers in response to reward receipts, with no significant relationship in CC allele carriers. The authors conclude that enjoyment of reward outcomes (receipt) is modulated by circadian genes.

Hasler et al. (2013) investigated the association between chronotype and BOLD response in VS and mPFC ROIs, during reward receipt. In the reward receipt condition, evening chronotype was associated with greater BOLD response in the VS, while no chronotype differences were observed in the mPFC.

In the two year follow-up study, Hasler, Casement, et al. (2017) found that circadian preference at age 20 was significantly related to mPFC and VS response to reward receipt: specifically, greater evening preference at age 20 predicted greater BOLD response in the mPFC and VS to rewards at age 22.

These four studies provide evidence consistent with a circadian signal in the reward system in the context of reward receipt. Support for a circadian signal in the mPFC and striatum was observed for both ROIs although this was not unanimous. Later sleep times, carrying risk alleles of circadian genes (Forbes et al., 2012), and greater shifts in sleep times between weekdays and weekends (Hasler, Dahl, et al., 2012), were associated with decreased response of the mPFC to reward receipt. Greater evening preference at age 20 also predicted greater mPFC response to reward receipt at age 22 (Hasler, Casement, et al., 2017). Chronotype did not differ in mPFC response in a cross-sectional design (Hasler et al., 2013). Smaller shifts between weekday-weekend sleep times (Hasler, Dahl, et al., 2012), evening preference at baseline (Hasler et al., 2013), and at two-year follow-up (Hasler, Casement, et al., 2017) were associated with greater response of the VS to reward receipt compared to greater shifts in sleep times and morning preference respectively. The increased VS response was not observed with later sleep times (Forbes et al., 2012). This data provides some evidence for a circadian signal of the mPFC and VS in the context of reward receipt.

Table 17

Imaging findings for resting state studies

	Data analysis of imaging	Covariates, variability correction	Amygdala	mPFC	Striatum (VS, NAc)	Anterior cingulate	Insula	Putamen	Implications for systematic review
Blautzik et al. (2013).	Connectivity as determined by independent component analysis to create 20 temporally coherent networks	Individual connectivity at baseline	Not examined	Part of the independent components that showed daily fluctuations particularly in the ventromedial portion	Not examined	Part of the independent components that showed daily fluctuations; however was also part of IC6 (which was the least rhythmic region)	Connectivity in this region (IC6) was quite stable (lacking rhythmicity)	Not examined	DMN demonstrated neural rhythmicity at rest
Blautzik et al. (2014)	20 resting state networks	Motion correction, spatial smoothing	Not examined	A widespread network including this region was considered amongst the least rhythmic	Not examined	A widespread network including this region was considered amongst the least rhythmic	Not examined	A widespread network including this region was considered amongst the least rhythmic	Rhythmicity was low in the DMN subsystem and an OFC network in elderly individuals. Increased circadian rhythmicity was seen in sensorimotor, visual and cerebellar networks
Coutinho et al. (2015)	Resting state fMRI: DMN was identified in resting state in ROIs of the pCC, Pcu, mPFC, bilateral IPC and left ITC	Head motion realignment, used slice time correction	Not examined	Decreased activation in the bilateral medial frontal gyrus for jetlag group relative to controls	Not examined	Decreased activation in the right anterior cingulate gyrus for jetlag group relative to controls	Not examined	Not examined	In individuals with jetlag lower activation was observed in the mPFC and ACC relative to controls, this may explain reward-related deficits observed during jetlag

	Data analysis of imaging	Covariates, variability correction	Amygdala	mPFC	Striatum (VS, NAc)	Anterior cingulate	Insula	Putamen	Implications for systematic review
Hodkinson et al. (2014)	Resting state fMRI	fMRI was co-registered independently of ASL analyses to the same structural scan for each session, before spatial normalising	Not examined	Less synchrony was observed between the mPFC and other regions of the DMN during afternoon hours	Not examined	Not examined in resting state fMRI (but looked at in ASL data)	Not examined	Not examined	A loss of synchrony in the DMN in the afternoon might reflect a natural decline in our ability to support exploratory monitoring of the external environment, and thus our readiness to respond to sensory stimuli.
Kyeong et al. (2017)	Resting state fMRI with the SCN used as an ROI (± 4, 5, -10)	Slice timing and motion correction	Not examined	Not examined	Not examined	Positive correlation with the SCN	Positive correlation with the SCN	Not examined	Multiple regions of reward circuitry are functionally related to the master circadian oscillator at rest in elderly non-delirious controls
Yoncheva et al. (2016)	Resting state connectivity, 9 ROIs (including the amygdala, insula, and VS)	24 head motions parameters, image registration	With delayed meal times left amygdala exhibited increased activation with hippocampal region, left putamen, right insula; right amygdala stronger connectivity with hippocampal regions	Not examined	Delayed meal times were associated with increased connectivity between the left VS and left occipital fusiform gyrus, and right lateral occipital cortex	Late meals correlated with increased connectivity between left amygdala and right paracingulate gyrus	Late sleep was related to increased left insula and right somatosensory, pre-/post-central gyrus connectivity	Late meals was correlated with increased connectivity between left amygdala and left putamen	Circadian misalignment of sleep and mealtimes alters connectivity of many reward-relevant regions; internal desynchrony (when sleep OR mealtimes were altered in connectivity in brain areas related to food reward and introception

9.3.4.5   Resting state fMRI. Six resting state studies (Blautzik et al., 2013; Blautzik et al., 2014; Coutinho et al., 2015; Hodkinson et al., 2014; Kyeong et al., 2017; Yoncheva et al., 2016) met inclusion criteria. For the present purposes the circadian variables in theses six studies were: repeated measures protocols at different times of day (Blautzik et al., 2013; Blautzik et al., 2014; Hodkinson et al., 2014), jet-lagged participants (Coutinho et al., 2015), the suprachiasmatic nucleus (the primary coordinator of the circadian system, Mohawk et al., 2012) as the ROI (Kyeong et al., 2017), and circadian misalignment of sleep and mealtimes (Yoncheva et al., 2016).

Coutinho et al. (2015) employed a cross-sectional design to examine the effects of circadian disruption (jet-lag) on the DMN. The BOLD signal using regions of interest (ROI) of the DMN structures was measured after transmeridian travel in 10 jet-lagged adults (22-42 years old) who had flown in the 12 hours before testing from America to Europe as compared to 10 control participants. Relative to controls, jet-lagged participants exhibited decreased activation in the left mPFC, right ACC, right medial superior frontal gyrus, left middle frontal gyrus, left parahippocampal gyrus, and left angular gyrus. The authors tentatively conclude (noting possible confounds of time of day of assessment, and sleep deprivation) that circadian disruption of reward centres, particularly the mPFC and ACC, may explain the emotion regulation difficulties associated with transmeridian travel.

Kyeong et al. (2017) examined connectivity between the suprachiasmatic nucleus (SCN) and other brain regions at rest among elderly participants. Participants were drawn from a register of non-delirious elderly individuals (aged 74-100, $n = 38$) with medical conditions (information was unavailable) but brain scans within normal limits. SCN activity was positively associated with activity in numerous regions including the OFC, ventral ACC, and the insula. Negative correlations between the SCN and activation in the dlPFC, pre- and postcentral gyrus, and precuneus were found. The results suggest that (at rest) activity in the SCN is correlated with multiple regions associated with reward processing (although time of day of scanning was uncontrolled).

To examine the daily time course of resting-state connectivity patterns, Blautzik et al. (2013) scanned healthy young adults ($N = 15$) four times at fixed intervals of 2.5 hours (beginning at 09.00h). To account for individual sleep

preferences, mid-sleep on free days was used to stagger assessment times. Additionally, individual differences in strength of connectivity were controlled by calculating an individual mean z-value for each session. Rhythmicity was measured as deviation from the mean level of connectivity across the day. Using independent component analyses (ICA, Biswal et al., 2010), 20 connectivity patterns were considered. Blautzik et al. (2013) found rhythmic oscillations in three connectivity patterns. Two of these were dorsal subregions of the DMN with stronger connectivity in the morning relative to the afternoon, while the third (extending over sensorimotor regions) peaked in the middle of the day, and was lower at earlier and later times. One of the connectivity patterns that showed the least rhythmic connectivity was an area encompassing the anterior cingulate gyrus and the insula. The authors propose that these results suggest an inherent neural rhythmicity varying systematically over the course of the day in at least some aspects of connectivity. For the purposes of this review, two areas implicated in reward processing were highly rhythmic, but one other area involved in reward-related processing was one of the least rhythmic ICAs.

Developing the work done in a young adult population, Blautzik et al. (2014) examined the neural rhythmicity of resting state networks in 12 healthy elderly adults. As above, individual differences in sleep times and strength of connectivity were controlled. The three networks (sensorimotor, cerebellar, and a visual network) that exhibited a high degree of rhythmic oscillation, with peak connectivity occurring ~12 hours after mid-sleep on free days were not reward regions. Blautzik et al. (2014) suggest that discrepancies in the rhythmicity networks relative to their earlier study (Blautzik et al., 2013) may be associated with age-related degeneration of the SCN or basal forebrain. Resting state networks encompassing reward regions of the mPFC, ACC and putamen, and in the OFC network were the least rhythmic. No circadian signal, measured as time of day fluctuations, were observed in reward-related regions in healthy elderly adults.

In a repeated measures resting state fMRI protocol, Hodkinson et al. (2014), examined connectivity in the DMN at two times of day (08.00-10.00 h and 15.00-19.00 h) in 13 men (23-38 years old). In the afternoon relative to the morning, 'synchrony' (strength of connectivity) was reduced in the DMN (in the PCC, mPFC,

and temporal cortex). No significant time of day changes were observed in the 'task positive network' (which includes the reward-related dlPFC and insula regions).

Yoncheva et al. (2016) used a novel method to examine misalignment of sleep and mealtimes in a young healthy sample. Holding sleep duration constant, a small sample (*N*=4) completed a randomised cross-over control design with four protocols where sleep and mealtimes were manipulated over a five day in-lab period, with a scan completed on the evening of day 4 in each protocol. Sleep times were either normal (00.00h – 08.00h) or delayed (03.30h – 11.30h); and mealtimes were either normal (1, 5, 11, and 12.5 hours after awakening) or delayed (4.5, 8.5, 14.5, and 16 hours after awakening), resulting in four combinations of protocols that all participants undertook (e.g., normal sleep, delayed mealtimes). Delayed sleep times were associated with increased connectivity between the left insula and right somatosensory, and pre-/ and post- central gyrus. Following delayed mealtime protocols, the amygdala showed the most varied connectivity with stronger connectivity between the left amygdala and hippocampal region, left putamen, right insula; and stronger connectivity between the left VS and left occipital fusiform regions and right lateral occipital cortex. Internal desynchronization of timing cues (normal sleep, delayed mealtimes condition, or, delayed sleep, normal mealtime condition) led to an increase in connectivity between the frontal pole and visual areas relative to aligned sleep and mealtimes. Relative to participants experiencing normal sleep and mealtimes, delayed and internal desynchronization of timing cues increased connectivity in many reward-related brain regions, which the authors suggest may underlie changes in food-reward motivation following circadian disturbance.

Evidence for a circadian signal in neural reward was found in four of the five resting state studies, with the exception (Blautzik et al., 2014) finding reward-related regions to be the least rhythmic across the day. The circadian predictor variables were related to a range of reward-related brain regions. Circadian dysregulation in individuals with jet-lag was associated with decreased activation in the left mPFC (Coutinho et al., 2015). Activity in the SCN was positively related to activity in the OFC, ventral ACC, insula, and negatively related to activity in the dlPFC (Kyeong et al., 2017). Diurnal rhythmicity was observed in DMN connectivity with Blautzik et al. (2013) and Hodkinson et al. (2014) both finding afternoon connectivity within the

DMN weaker relative to morning. Circadian misalignment also affected reward-related areas. Increased connectivity between the amygdala and putamen was seen with delayed, relative to normal, meal times, and between the insula and somatosensory cortex, with delayed, relative to normal, sleep times (Yoncheva et al., 2016). Blautzik et al. (2014) found the lowest daily fluctuation in reward areas covering the OFC, ACC, mPFC and putamen. In sum, reviewed studies provide evidence that activation in reward-related brain regions and connectivity within reward-relevant networks and between brain regions may be related to circadian oscillation (Kyeong et al., 2017), affected by circadian disturbances (Coutinho et al., 2015; Yoncheva et al., 2016), or show systematic rhythmic variation across the day (Blautzik et al., 2013; Hodkinson et al., 2014); one study (Blautzik et al., 2014) has not found a circadian signal in reward-related areas. In relation to our secondary research question, the review found evidence for the potential involvement of many reward regions; no particular regions of interest arose as more critical to this relationship across all studies.

9.3.5 Discussion. The aim of this study was to systematically review fMRI studies reporting data on a complex, clinically-important, and under-studied question, viz., does the circadian system modulate the reward system in humans? Three specific research questions were used to focus the investigation across 15 identified studies, which were heterogeneous in their aims, proxy measures of circadian function, and reward paradigms: (1) what evidence exists for a circadian signal in the reward system?, (2) is there evidence that the relationship is subserved by some specific reward-related neural structures/networks more than others?, and (3) is modulation observed equally for anticipation and receipt phases of reward processing? Broadly, analyses of these questions suggested that (1) at least some evidence consistent with circadian modulation of reward was found in 13 of 15 studies, (2) evidence consistent with circadian modulation of the reward system was particularly prominent in the brain regions of the mPFC and VS (task-based fMRI) and for DMN connectivity (in resting state studies), and, (3) evidence consistent with circadian modulation of reward was adduced from studies of both reward anticipation and reward receipt conditions, with evidence being somewhat more consistent for the latter. The discussion will interrogate these findings in the context

of the study's limitations, prior to outlining next steps in the investigation of the neural basis of circadian X reward modulation in humans.

9.3.5.1   *Evidence for a circadian signal of reward function.* Preliminary conclusions about whether the circadian system may modulate the reward system can be drawn from the 15 studies. Of the included studies, all bar two (Baranger et al., 2016; Blautzik et al., 2014) found some evidence towards a circadian modulation of reward. Indeed, nine different circadian variables (see Figure 13, including: time of day, sleep times, circadian genes, chronotype) modulated aspects of reward processing. Circadian effects on reward processing were observed across various paradigms, including both task-based (event-related and block design) and resting state fMRI.

While this set of studies is broadly supportive of the prediction that the circadian system modulates the reward system as demonstrated via the results of fMRI paradigms, the present findings need to be considered within the context of the heterogeneity of measures. Cross-study comparisons were difficult, given the rich array of circadian variables and approaches to measuring reward processing. Even the most common paradigms or tasks (such as the human connectome project gambling task) differed in key ways (number of trials included, inclusion of control blocks). Researchers differed in the use of single versus repeated measures time-of-day of testing and have examined varying ROIs. Although the vast majority of reviewed studies indicate some form of circadian effect, the heterogeneity of studies warrants caution in making any clear statement of how circadian function may affect neural reward substrates.

9.3.5.2   *Evidence for brain regions and networks involved in the circadian modulation of the reward system.* As reviewed above, at the current time, the weight of evidence has observed a circadian signal in multiple regions with strongest support for the mPFC, VS, putamen, ACC and the DMN. In task-based fMRI, there was strong evidence for the mPFC and VS (frequently used as ROIs) with emerging but inconsistent support for the striatum more broadly in the putamen. Circadian parameters (greater circadian disturbance) were related to decreased VS activation in one study (Hasler, Dahl, et al., 2012) but not in other studies (Forbes et al., 2012; Hasler, Casement, et al., 2017; Hasler et al., 2013). Other studies suggest that VS activation is likely to be conditional on other factors, with the degree of activation

associated with larger cortisol amplitude (LeMoult et al., 2015) and time of day (Hasler, Forbes, et al., 2014; Masterson et al., 2016), and greater VS activation when mealtimes were delayed (Yoncheva et al., 2016). The direction of this effect has been ambiguous, circadian disruption in mealtimes has greater VS activation while circadian disruption in sleep times was related to decreased VS activation (Hasler, Dahl, et al., 2012) in reward-contexts. The discrepancy of findings must be noted in the context of different age groups and the times that the repeated measures studies were conducted. In adolescents, there has been some debate over whether increased or decreased neural activation to rewards is associated with risky behaviour. Like Hasler and colleagues (2012), Holm et al. (2009) found in adolescents shorter sleep times were associated with increased striatal reactivity in response to rewards. Thus sleep-deprived adolescents may seek out more exciting rewards to achieve equivalent levels of neural reactivity to well-rested adolescents. Masterson et al. (2016) found right VS activation was reduced in the afternoon hours, while VS activation was greater in the afternoon in Hasler, Forbes et al. (2014), relative to the morning scans; however, the Masterson morning scan occurred on average >2 hours earlier, and the evening scan >2 hours later than the study by Hasler, Forbes et al. Participant age and times of sampling may both contribute to the lack of consistency in the present findings and future research will need to determine the conditions under which the VS is modulated by the circadian system and how this relates to the specific role of the VS in reward circuitry.

Generally the 'at risk' circadian groups (eveningness, larger shifts in sleep times, jet-lag) were associated with reduced mPFC response in task-based fMRI (Forbes et al., 2012; Hasler, Dahl, et al., 2012; Hasler et al., 2013) and in resting state ; while one longitudinal study (Hasler, Casement, et al., 2017) found that circadian preference of eveningness was related to greater mPFC response two years later during a monetary reward task. None of the repeated measures studies at different times of day found evidence for a diurnal variation in three task-based mPFC response (Byrne, Hughes, et al., 2017; Hasler, Forbes, et al., 2014; Masterson et al., 2016) or in the rhythmicity of resting state connectivity patterns (Blautzik et al., 2014); one study (Blautzik et al., 2013) did find greater daily rhythmic connectivity patterns in resting state data in a region including the ventral mPFC. In sum, these findings suggest that time of day does not diminish mPFC responsivity,

but circadian disruption is associated with mPFC attenuation. This could reflect that the diurnal changes in reward circuitry may not be observed in frontal circuitry. Alternatively, diurnal changes are likely to be more subtle to the larger-scale circadian disruptions of acute jet-lag and chronic changes in sleep times or evening chronotypes.

Four studies provide support for the putamen being modulated by circadian function, with the putamen exhibiting time of day differences in response to rewards, with higher levels at 10am and 7pm relative to 2pm (Byrne, Hughes, et al., 2017) and 6:30-8:30am relative to 5:00-7:00pm (Masterson et al., 2016). Evening type individuals also had greater putamen activation during task-based fMRI (as part of the striatal ROI, Hasler et al., 2013), and when mealtimes were delayed, connectivity increased between the amygdala and left putamen relative to normal mealtimes (Yoncheva et al., 2016); however in an elderly population connectivity of regions including the putamen were amongst the least rhythmic (Blautzik et al., 2014). The putamen is selectively thought to be involved in integrating reward history in selecting reward actions (Muranishi et al., 2011), discerning how circadian modulation may impact this functioning may speak to the more mechanistic interplay between the circadian and reward processes. Thus, increased putamen activation may be partly attributable to circadian disturbance but may also reflect a reward prediction error in a circadian context with higher levels of putamen activation at times of day evolutionarily associated with low reward potential (when there is low light availability; Byrne, Hughes, et al., 2017).

In resting state designs, circadian modulation of the DMN, and ACC and connectivity between these regions were typically examined. In resting state data jet-lag was related to decreased ACC response relative to non-jet-lagged controls (Coutinho et al., 2015) and greater connectivity between the amygdala and paracingulate gyrus in delayed mealtimes relative to normal mealtimes (Yoncheva et al., 2016). These two studies align with the positive correlation found between the SCN and ACC connectivity (Kyeong et al., 2017) and the rhythmic oscillations observed in temporal connectivity in the ACC and PCC by Blautzik et al. (2013); however the ACC did not display rhythmicity in all studies (Blautzik et al., 2014). The DMN more generally may be modulated by the circadian system with high rhythmicity across the day observed by Blautzik et al. (2013) and jet-lagged

individuals exhibiting disturbed connectivity in the DMN (Coutinho et al., 2015); however one study found the DMN did not show large diurnal rhythmicity (Blautzik et al., 2014). The disruption to reward-relevant regions at a resting state level may be relevant neural mechanisms to the higher levels of obesity risk observed in individuals with jet-lag or social jet-lag. For example, a recent study found that circadian misalignment increased levels of ghrelin, an appetite stimulating hormone which was associated with an increased desire for energy dense foods (Qian, Morris, Caputo, Garaulet & Scheer, 2018). Only limited conclusions can be drawn from the resting state data looking at diurnal variation in neural networks. It is unclear whether the diurnal variation observed in these networks relate directly to reward processes, or other processes which also display circadian variation, such as cognition (C. Schmidt, Collette, Cajochen & Peigneux, 2007). Future work mapping neural networks to behavioural tasks either inside or outside the scanner may answer what behavioural correlates resting state changes to these networks may reflect.

9.3.5.3 Evidence for the circadian modulation of reward anticipation and reward receipt. There was some evidence for circadian modulation of reward anticipation and reward receipt. Both anticipation and receipt were associated with altered mPFC and VS reward response with individual or group differences in various markers of circadian function. Circadian modulation was more consistently found in reward receipt studies relative to reward anticipation. The receipt response to rewards appeared stronger in the VS than reward anticipation. VS activity in response to reward receipts was positively associated to evening preference (Hasler, Casement, et al., 2017; Hasler et al., 2013) and negatively associated with larger shifts in weekday-weekend sleep times (Hasler, Dahl, et al., 2012); however was not seen in those with a circadian risk allele (Forbes et al., 2012). Evidence for circadian involvement of the mPFC was observed in both reward anticipation and reward receipt. Reduced mPFC was seen in response to reward anticipation (Hasler, Dahl, et al., 2012; Hasler et al., 2013), and reward receipt (Forbes et al., 2012; Hasler, Dahl, et al., 2012). Greater mPFC response during reward receipt was found two years later in those with greater evening preference (Hasler, Casement, et al., 2017). In a meta-analysis Knutson and Greer (2008) found reward anticipation (compared to reward receipt) had increased activation in areas including: the bilateral NAc (a structure within the VS), right ACC, right insula, and left caudate; increased

activation in the left mPFC, left putamen, left amygdala, and right caudate was observed in reward receipt relative to reward anticipation. Thus, the present findings of a greater VS activation to reward receipt are in contrast with previous work which suggested a specialised role in reward anticipation for the NAc. In addition, a stronger signal in reward receipt is somewhat surprising given that most animal literature that has investigated the role of circadian modulation of reward processes has observed differences in mesolimbic dopamine (Hampp et al., 2008; McClung et al., 2005; Ozburn et al., 2016; Roybal et al., 2007; Sleipness, Sorg, & Jansen, 2005; Sleipness et al., 2007a, 2007b), a pathway more strongly (although not in its entirety) related to the anticipation of rewards, relative to reward receipts (Berridge, 1996; Berridge & Kringelbach, 2015; Berridge & Robinson, 1998). In addition, the measurement of the circadian predictor variable should be considered. Each circadian variable measure was a chronic variable. Thus, future work should examine whether there is an acute effect of circadian modulation on neural reward anticipation in the VS. This could be examined using a repeated measures diurnal variation protocol to observe how reward anticipation and reward receipt vary as a function of time of day. The reviewed data suggests that using event-related designs, there is more evidence for the circadian modulation of reward receipt relative to reward anticipation; however, the mechanisms underlying this relationship are not understood.

　　　9.3.5.4   Limitations of the review. This review has several limitations. We included studies that used variables thought to be related to circadian function (including time of day, sleep times, diurnal preference), but conclusions cannot be made as to whether these proxies of circadian function were of an endogenous origin (Czeisler & Wright, 1999; Moore-Ede, 1986b). Methodologically, evidence for an endogenous circadian function modulation of reward neurocircuitry would necessitate changes to neuroimaging paradigms, because of the temporal isolation needed to separate the circadian system from exogenous influences. On this point, each circadian predictor variable has limitations as a proxy of circadian function. For example, repeated measures using time of day as a circadian variable is limited (in the reviewed studies) to only capturing a 12-hour window of the day, with the sampled times unlikely to measure the nadirs of diurnal variation in neural reward measures. Similarly, the circadian rhythm is unlikely to fit a perfect quadratic

waveform, with selected testing times in the afternoon or early evening overlapping in part with a mid-afternoon dip or the wake maintenance zone, which have not been controlled for. Assessing chronotype is limited by chronotype being a self-report variable which may not reflect actual phase of entrainment, reflecting more the sleep-wake behaviours rather than the 24-hour activity cycle (Roenneberg, Wirz-Justice et al., 2013). While weekend sleep midpoint, and weekday-weekend shifts in sleep times offers a stronger indicator of sleep-wake behaviours it is limited by both the chronic and acute effects of sleep loss that are related to larger changes in sleep times. Alternatively, using mid-sleep as a variable does not capture the reasons for larger sleep timing shifts: it is possible that individuals with larger shifts have more social commitments which may drive the changes in sleep times. Degree of sociability and social connectedness may have effects on neural reward independent of circadian factors.

A second limitation is that although we tried to minimise a positive publication bias by including articles that did not themselves set out to directly test the primary question of this systematic review, a broader publication bias towards significant results may skew the data found here towards positive findings (Stern & Simes, 1997). Thirdly, measuring reward anticipation and receipt using event-related designs may not fully dissociate these psychological components of reward as assumed here (Havermans, 2011, 2012). Finally, most of the studies presented in this systematic literature review have recruited a homogenous sample commonly restricting age or recruiting one gender which may limit generalisability of results. For example, we included studies with participants of any age, but this should be interpreted in the context of greater sensitivity of the reward system in adolescents (see Doremus-Fitzwater, Varlinskaya, & Spear, 2010; Somerville, Jones, & Casey, 2010 for reviews) and the sleep and circadian changes that occur across the lifespan (see Ohayon, Carskadon, Guilleminault, & Vitiello, 2004 for a review).

Finally, there are statistical limitations in the reviewed studies. Included studies were, in general, quite limited in size, and we have not accounted for the different sample sizes across studies. Additionally, many of the included studies used statistical thresholds that are considered liberal by current standards (Poldrack et al., 2017). As noted by Poldrack et al. (2017) low statistical power and flexibility in data

analysis may contribute to difficulty in replicating findings. This, in part, may account for the inconsistent findings across studies in the present review.

  9.3.5.5 Future directions. This review provides evidence broadly consistent with the hypothesis that neural substrates of reward may be modulated by circadian function in humans. A program of research is needed that systematically and rigorously investigates the circadian modulation of reward functioning now that this preliminary step has identified a circadian signal in reward neurocircuitry in healthy individuals. This research should include: paradigms that investigate the endogenous circadian functioning in an fMRI reward context, set ROIs (based in part on the findings of this review), and measuring behavioural variables of reward activation (e.g., positive affect) to ensure that neural findings are aligned with behavioural findings. Similarly, future research should investigate the modulation of neural reward circuitry by biological markers of circadian processes (such as DLMO or core body temperature), as opposed to the downstream proxies of circadian functioning utilised in reviewed studies to date. It is also important that this future work controls for variables (endogenous circadian markers, sleep timing, sleep quantity, sleep quality, age, gender, trait reward sensitivity) that may affect either the circadian predictor variable or the receipt reward variable. Basic science research should continue to pursue work aimed at distinguishing between the neural responses to reward anticipation and reward receipt in a circadian context. In addition, future work should include circadian investigation of the third reward process identified by Berridge, reward learning (Berridge & Robinson, 1998; Berridge & Robinson, 2003; Berridge et al., 2009).

  While beyond the scope of the present review, understanding how these systems may relate to reward-related disorders motivates the need for future work. A burgeoning literature has begun to investigate the relationship between circadian function and reward; emphasising this relationship may be critical in identifying risk factors for emerging disorders and in the remittance of clinical symptoms (Alloy et al., 2016; Asarnow et al., 2013; Harvey et al., 2006; Hasler, Casement, et al., 2017; Hasler, Soehner, et al., 2014; Hasler et al., 2015; McKenna et al., 2014). Studies from Hasler and colleagues (Hasler, Casement, et al., 2017; Hasler, Dahl, et al., 2012; Hasler et al., 2013) have found evidence for alcohol involvement in the relationship between the circadian predictor and the neural reward receipt. The

clinical importance of this work is perhaps most evident in the diathesis between the circadian system and reward system in bipolar disorder (Alloy et al., 2017). Bipolar disorder has well-replicated circadian abnormalities such as altered daily activity rhythms (Gershon et al., 2015; J. Scott et al., 2016; J. Scott et al., 2016; J. Scott, Vaaler, Fasmer, Morken, & Krane-Gartiser, 2017), reduced heart rate variability (Faurholt-Jepsen, Kessing, & Munkholm, 2017), variable sleep-wake patterns (Robillard et al., 2015), delayed biological rhythms (Robillard, Naismith, Rogers, Scott, et al., 2013), and evening preferences (Robillard, Naismith, Rogers, Ip, et al., 2013) that are hypothesised to be related to the pathogenesis of the disorder, and offer potential treatment targets (E. Frank, 2007, 2013; E. Frank, Swartz, & Boland, 2007; E. Frank et al., 2000; Hickie, Naismith, Robillard, Scott, & Hermens, 2013). Greater sensitivity towards rewarding events may disrupt the underlying circadian system in those with already altered or disturbed circadian rhythms, such as that seen in bipolar disorder (Alloy et al., 2017; Boland et al., 2015).

9.3.5.6   *Conclusions.* This is the first study to review the putative circadian modulation of neural reward mechanisms in healthy humans. This is consistent with the circadian modulation of reward functioning observed in animal research and behavioural research in humans. Through a variety of experimental and naturalistic protocols there is evidence for a circadian modulation of reward. The weight of evidence indicates that the circadian system modulates regions including most consistently, the VS, mPFC, putamen, ACC and the DMN. Within the limitations of a small number of heterogeneous studies, there is more evidence for a circadian modulation of reward receipt compared to reward anticipation. We highlight the need for a future program of research to systematically and rigorously replicate findings in an endogenous circadian context, operationalizing clear ROIs, distinguishing reward anticipation from receipt, and begin to investigate how this reward dissociation may manifest in clinical disorders related to circadian function and reward.

Chapter 10: Time of Day Differences in Neural Reward Functioning in Healthy Young Men

10.1   Linking Section

Given the limited, but growing, literature examining circadian modulation of reward motivation, Study 5 advanced the project's aim of increasing understanding into how diurnal variation may present in neural reward functioning. Study 5 extended the work of Study 3 (see Chapter 8): Study 3 observed a peak at 14:00h in psychological and behavioural measures of wanting and "wanting", Study 5 sought to explore the neural mechanisms that may underpin this reward motivation in healthy humans. The participants used in Study 5 were a subsample of participants in Study 3.

Study 5 was in part based on the reviewed work of Study 4 (which included Study 5 as one the reviewed articles, see Chapter 9). Study 4 found only three studies (Byrne, Hughes, et al., 2017; Hasler, Forbes, et al., 2014; Masterson et al., 2016) investigated diurnal variation in task-based reward functioning (including Study 5), and two resting state studies examined resting state functional connectivity at four times of day (Blautzik et al., 2013; Blautzik et al., 2014).

10.2   Abstract

Reward function appears to be modulated by the circadian system, but little is known about the neural basis of this interaction. Previous research suggests that the neural reward response may be different in the afternoon; however the direction of this effect is contentious. Reward response may follow the diurnal rhythm in self-reported positive affect, peaking in the early afternoon. An alternative is that daily reward response represents a type of prediction error, with neural reward activation relatively high at times of day when rewards are unexpected (i.e., early and late in the day). The present study measured neural reward activation in the context of a validated reward task at 10.00h, 14.00h, and 19.00h in healthy human males. A region of interest blood oxygen level dependent (BOLD) functional magnetic resonance imaging (fMRI) protocol was used to investigate the diurnal waveform of activation in reward-related brain regions. Multi-level modelling found, as expected, a highly significant quadratic time-of-day effect focusing on the left putamen (p <.001). Consistent with the 'prediction error' hypothesis, activation was significantly higher at 10.00h and 19.00h compared to 14.00h. It is provisionally concluded that the putamen may be particularly important in endogenous priming of reward motivation at different times of day, with the pattern of activation consistent with circadian-modulated reward expectancies in neural pathways; viz., greater activation to reward stimuli at unexpected times of day. This study encourages further research into circadian modulation of reward, and underscores the methodological importance of accounting for time of day in fMRI protocols.

10.3   Significance statement

This is one of the first studies to employ a repeated measures imaging procedure to explore the diurnal rhythm of reward activation. While self-reported reward (most often operationalised as positive affect) peaks in the afternoon, the present findings indicate that neural activation is lowest at this time. We conclude that the diurnal neural activation pattern may reflect a prediction error of the brain, where rewards at unexpected times (10.00h and 19.00h) elicit higher activation in reward brain regions than at expected (14.00h) times. These data also has methodological significance, suggesting that there may be a time of day influence which should be accounted for in neural reward procedures.

10.4   Introduction

Reward function in animals and humans appears to be adaptively modulated by the circadian system (Murray, Allen, & Trinder, 2002; Murray et al., 2009). Theoretically, the human reward system is primed to be more active during daytime hours when reward potential is high and risk relatively low, and less active overnight when this balance is reversed due to poor night vision (Watson, 2000b). Existing research has found a circadian rhythm in self-reported positive affect (the subjective manifestation of reward activation), peaking in the early afternoon and paralleling the circadian rhythm of core body temperature under naturalistic conditions (e.g., Boivin et al., 1997; Murray et al., 2009). It has been hypothesised that this circadian reward rhythm should also be measurable in reward neurocircuitry (e.g., Murray et al., 2009), but research to date is limited.

A small number of studies have taken the preliminary step of testing for a diurnal rhythm (a waveform across the waking day that may or may not be of endogenous circadian origin) in various measures of neural activation in humans. Hasler and colleagues (2014) used a within-subjects fMRI procedure to observe greater striatal activity to monetary rewards in the afternoon compared to morning. A recent study (Masterson et al., 2016) found a significant time of day effect on neural activation in the right ventral striatum and left putamen in response to visual food stimuli. Activation was higher in these reward regions during the morning (06.30-08.30h) compared to the evening scan (17.30-19.30h; Masterson et al., 2016). Together, these studies indicate the presence of a neural diurnal rhythm in response to rewards; however, the timing of this rhythm is ambiguous and has been limited to two measurement points thus far.

The reliable finding of a mid-afternoon peak in positive affect (above) does not necessarily suggest that a circadian rhythm in neural reward activation would have the same waveform. It has been argued (Schultz, 2002, 2016; Schultz et al., 1992) that dopaminergic neurons innervate the terminal striatal regions with greater intensity *when an environmental reward deviates from previous reward expectancies*. Additional work (McClure et al., 2003) has demonstrated higher levels of striatal activation (with strongest lateralized activation in the left putamen) in response to unexpected reward stimuli. Other human fMRI studies have found this same 'prediction error' in response to reward with a positive correlation between

unexpected reward and ventral striatum activity (Hare, O'Doherty, Camerer, Schultz, & Rangel, 2008; O'Doherty et al., 2003; Valentin & O'Doherty, 2009) and more dorsal striatal regions (Valentin & O'Doherty, 2009). In sum, a circadian rhythm in neural reward activation may be measurable as an elevated response to rewards at unexpected times of day: earlier and later in the day in humans (Murray et al., 2009; Watson, 2000b), and inverted relative to the waveform observed in positive affect under naturalistic conditions.

The present study used an fMRI procedure to examine the diurnal rhythm of activation in reward neurocircuitry in response to a reward stimulus. Activity in the mPFC, VTA, anterior cingulate cortex, caudate, NAc, and putamen were examined. To model the diurnal rhythm, we advanced existing research by scanning participants at three times of day (10.00h, 14.00h, 19.00h). Reward activation was hypothesised to vary with a quadratic waveform, consistent with an underlying circadian driver; that is, with 14.00h having an altered neural reward level relative to 10.00h and 19.00h. Based on the 'prediction error' assumption higher levels of neural activation were predicted earlier in the day (10.00h) and later in the day (19.00h); however, the fitted sine curve was also modelled with a peak in the quadratic waveform at 14.00h to align with Hasler, Forbes, et al., (2014) whose data indicates neural reward activation may mirror the demonstrated rhythm in self-reported positive affect, peaking later in the day relative to earlier.

10.5   Method

10.5.1   Participants. Participants were 16 right-handed males (M = 22.65, SD = 2.87 years) screened to exclude previous and current mental illness, shift-work, and transmeridian travel within three months of participation.

10.5.2   fMRI task. The gambling reward procedure (Delgado et al., 2000) from the Human Connectome Project is a pseudo-reward task which involves guessing the value of a card (1-9). The trial begins with a question mark displayed on the screen for 1500ms with responses recorded on a response box. A white fixation cross is presented if response is made before 1500ms with feedback for 1000ms. Cards are pre-determined so that 40% of trials are rewarding (+$1, green up arrow), 40% loss (-50c, red down arrow), and 20% neutral trials (-, double-headed grey arrow). Non-responses are presented with a screen stating that response was too slow.

In the present study, eight trials were presented in four blocks, of which two were mostly reward (Reward Block = six reward trials, and two neutral or loss trials) and two mostly loss trials (Loss Block = six loss trials, and two neutral or reward trials). Following each block of eight trials there was a 15 second fixation cross, which was used as the Baseline comparison. The data were acquired during four scanning runs (each consisting of four blocks taking 3 minutes: 12 seconds per run) at each time point with a short break between runs. Prior to the first run at each time point a practice run acclimatised participants to the task. To increase task motivation across sessions, participants were informed that they would receive additional reimbursement for their best task performance across the three sessions. Due to the pre-determined values, participants received $27 AUD.

10.5.3   MRI data acquisition. Structural and functional images were acquired with a 3T Siemens TIM Trio MRI scanner at Swinburne University of Technology (Hawthorn, Australia). During fMRI scanning, visual stimuli were presented on a rear projection screen viewed by participants through a mirror attached to the 32-channel head coil. All aspects of stimulus delivery and response logging was performed using E-Prime 2.0 (Psychology Software Tools Inc, 2002) for Windows.

Each scanning session began with the acquisition of a high-resolution T1-weighted scan using a magnetization prepared gradient echo (MPRAGE) sequence (192 sagital slices; 1 mm isotropic voxels; flip-angle 9°; field-of-view = 256 x 192 mm; TR = 2200 ms; TE = 3.29 ms; matrix = 256 x 192). During each of the four fMRI task scanning runs in each session, 73 T2*-weighted images were acquired using a gradient echo EPI sequence (39 interleaved axial slices; 3 mm isotropic voxels; flip-angle 90°; field-of-view = 205mm, TR = 2000 ms TE = 25 ms; matrix = 64 x 64).

10.5.4   MRI data preprocessing. All aspects of MRI image preprocessing and statistical analysis were conducted using SPM12 (Ashburner et al., 2014; Frith) and associated toolboxes. Initially, the high-resolution structural image and functional time-series were manually realigned to closely match the MNI template in SPM12. Subsequently, highly variant EPI slices were corrected using an interpolation algorithm in ArtRepair tools (version 5b: Mazaika, Hoeft, Glover, & Reiss, 2009). These artifact-corrected images were slice time corrected using the

middle slice acquired in time as a reference, then realigned to the first EPI acquired. The realigned images were then co-registered to the T1 image, which was then transformed (normalised) into MNI space. The parameters of this transformation were applied to co-registered EPIs, which were then smoothed with a 6mm FWHM Gaussian filter and high-pass filtered (<128 s). Finally, Artifact Detection Tools (ART: Whitfield-Gabrieli, Nieto-Castanon, & Ghosh, 2011) were used to determine outlying images, defined as any image +/- 3 standard deviations from mean signal intensity of the time-series, or images exhibiting >1.5mm of movement from the preceding image.

10.5.5   Statistical analysis of fMRI data. Participant level modelling was performed using an epoch-based general linear model in SPM12. The blood oxygen level dependent (BOLD) signal for Reward and Loss blocks was modelled using a boxcar function defined by the onset and duration of each block convolved with the canonical hemodynamic response function supplied with SPM12. The periods of fixation cross presentation constituted the Baseline, but as is common practice in fMRI analyses, these blocks were not explicitly modelled as this leads to the model being overdetermined. Additionally, regressors of no interest were modelled, including one regressor for each motion realignment parameter (3 translational, 3 rotational) and one regressor for each outlying image determined using Artifact Detection Tools (ART: https://www.nitrc.org/projects/artifact_detect/); <10% of images for each participant. After model estimation, the contrasts of Reward > Baseline, Reward > Loss, Loss > Baseline were computed then entered into a second-level random effects repeated-measures ANOVA model with factor 'Time of Day' (10.00h, 14.00h, 19.00h). We then examined the data for a main effect of Time of Day by employing an uncorrected voxel level threshold of $p <.001$. Given the a priori reward regions of interest, we used a small volume correction at the cluster level (see, Worsley et al., 1996).

10.5.6   Procedure. Participants maintained sleep and daily activity diaries and wore an actigraph in the week prior to the study to test for sleep-related variables on the testing day. To account for repeated measures confounds participants start times were counterbalanced, with all testing completed within 24 hours. Scan time was one hour for the first session (with structural scans completed) and 30 minutes for the second and third sessions. The task was run in E-Prime 2.0, with a BOLD

signal fMRI times series used to acquire images for the voxels within each region of interest (ROI).

10.6   Results

A main effect was observed in the ventral portion of the left putamen (MNI co-ordinates of peak voxel: -28 4 -2, peak F-value: 13.97, cluster size: 23 voxels; see Figure 15), for the Reward > Baseline contrasts. This effect was observed in a similar location in the Reward > Loss contrast (MNI co-ordinates of peak voxel: -28 10 -8, peak F-value: 11.51, cluster size: 4 voxels). In the bilateral caudate a small cluster was observed; however did not survive cluster level correction (left caudate 1 voxel, $F = 6.11$, $p = .61$, MNI coordinates: -12 14 14; right caudate 4 voxels, $F = 6.34$, $p = .49$, MNI coordinates: 14 16 10). Even at a more liberal voxel-wise threshold ($p < .05$, uncorrected) bilaterally the mPFC, VTA, anterior cingulate cortex, NAc, and the right putamen were all non-significant to different activation at time of day. No clusters in the a priori reward regions showed a time of day effect for the Loss > Baseline contrasts.
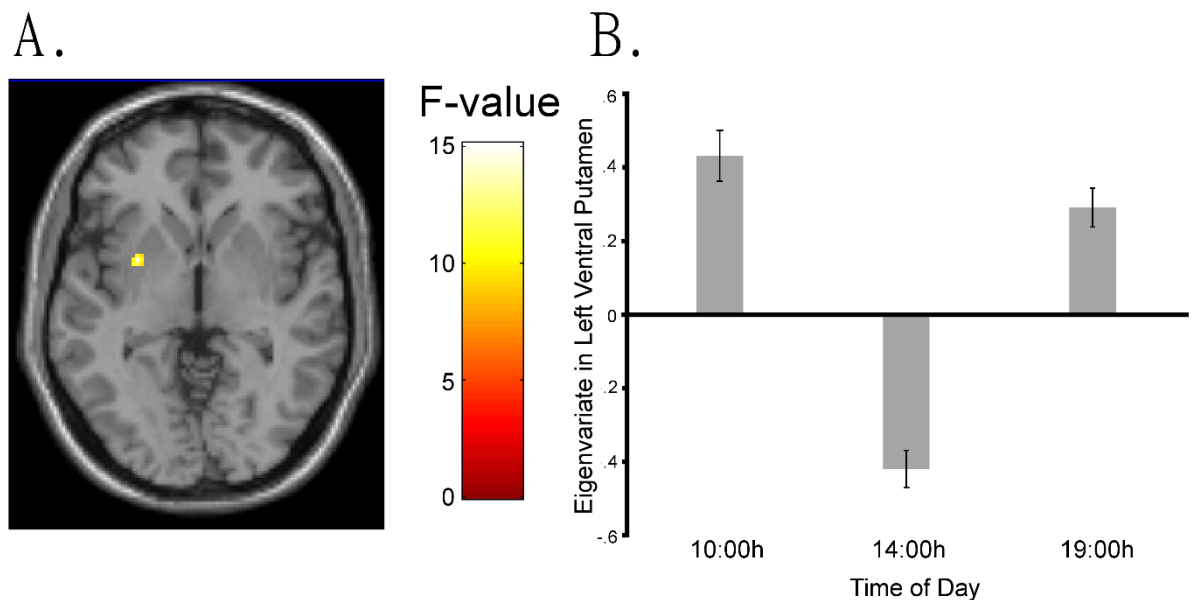

Figure 15. BOLD contrast of Reward > Baseline with a repeated-measures 'Time of Day' factor entered into the model. (a) Activation of left putamen significant ($p < .001$) for a Time of Day effect. (b) Activation of left putamen significantly decreased at 14.00h, compared to 10.00h or 19.00h

A volume of interest (sphere, 2mm radius) centred on the peak voxel of this cluster was constructed, and the first eigenvariate extracted from the modelled contrast images. These data were entered into multi-level modelling that tested the quadratic waveform fit of the repeated measures Level 1 variable (Time of Day) with a nadir at 14.00h. An intercept only model was conducted for the left putamen voxel cluster. The Level 1 Model (Left Putamen activation$_{ij}$ = β_{0j} + β_{1j} (time of day) + r_{ij}) tested the time of day effect, with group mean centering performed prior to model inclusion. $\beta 0j$ represents each participant's neural activation in the significant voxel, and r_{ij} represents the within person variance. $\beta 1j$ represents the time of day slope of the fitted quadratic waveform with a nadir at 14.00 h for each participant, and no difference modelled between 10.00 or 19.00 h. The analyses dummy coded this as 1 (10.00 h), - 2 (14.00 h), and, 1 (19.00 h). The quadratic waveform provided a highly significant fit to the data (p <.001), with activation in the left putamen being significantly lower at 14.00h than 10.00h or 19.00h.

For completeness, a whole-brain analysis was performed. Using an arbitrary clusterwise threshold of 10 contiguous voxels, a cluster in the left insula (in the posterior region; 18 voxels, MNI coordinates: -32 -30 20) and the middle frontal gyrus (in the anterior region; 26 voxels, MNI coordinates: -32 52 6) was found for the reward> baseline analyses, these effect were all non-significant (ps>.5). No other significant time of day threshold voxel clusters were observed, even when a liberal (p<.05, uncorrected) threshold was applied. There was no iteration effect of repeated measures testing of the neural reward rhythm on putamen activation.

10.7   Discussion

This study investigated the rhythm of neural activation to rewards across the course of the waking day. The hypothesis that activation of reward circuitry would be lowest at 14.00h compared to 10.00h and 19.00h gained preliminary support, with a significant waveform fit found in left putamen activation in the context of a validated reward task. Other reward regions of interest did not show a significant time of day effect.

10.7.1 Left putamen exhibits diurnal changes. Left putamen activation exhibited a diurnal waveform with relatively decreased activation in the early afternoon. Existing literature suggests that the putamen is a core component of reward-related function in humans (O'Doherty et al., 2003), rodents (Gallardo et al.,

2014), and monkeys (Muranishi et al., 2011). Muranishi and colleagues (2011) demonstrated that pharmacological inhibition of the left putamen in monkeys impaired reward-based decision making. Furthermore, Szczypka et al. (2001) found that sucrose preference in dopamine-deficient mice was restored with supplanted dopamine in the caudate putamen or nucleus accumbens; however, dopamine replacement only in the caudate putamen restored feeding behaviour, suggesting the putamen is core to the neural reward circuitry and has specified reward functions.

This study provides preliminary evidence of the importance of the putamen in understanding the putative interaction between circadian and reward function. In animal studies, the putamen has been innervated by the endogenous circadian system in reward functions, including: food anticipation (Gallardo et al., 2014), the circadian locomotor rhythm (Masubuchi et al., 2000), and in circadian gene expression following methamphetamine injection in rodents (Nikaido, Akiyama, Moriya, & Shibata, 2001). Similarly, two earlier human diurnal imaging studies have found time-of-day variation in left putamen activation (Hasler, Germain, et al., 2012; Masterson et al., 2016). Given the interconnectedness of neural reward pathways and broader striatum region (Haber & Knutson, 2010), more work is now needed to investigate diurnal variation in other reward-related regions including the mPFC, VS, caudate, and anterior cingulate cortex. The present results suggest these reward regions do not exhibit time of day effects, but larger samples and alternative imaging methods (discussed below) may detect additional signals of circadian modulation.

10.7.2 Putamen activation to reward is lowest in the early afternoon. Prior studies have found that positive affect, a subjective manifestation of reward activation, is highest in the mid-afternoon (Clark et al., 1989; Murray et al., 2009; Watson et al., 1999). This finding has been interpreted as indexing an adaptive preparedness to pursue rewards when environmental conditions are optimal (Wehr, 1990). In the present neuroimaging study, by contrast, neural reward circuitry was relatively low in the mid-afternoon: The diurnal waveform in the left putamen reward region had its nadir at 14.00h.

As noted above, we propose that this pattern of findings can be understood as a type of prediction error. Specifically, we propose that rewards presented at 14.00 are expected (by circadian priming), and thus lack the novelty of rewards appearing at 10.00h or 19.00h. Consistent with this explanation, we note that a bigger

haemodynamic response to unexpected reward has previously been observed in the left putamen in comparison to expected rewards (McClure et al., 2003; O'Doherty et al., 2003). When the brain expects rewards to be in abundance then reward accrual elicits less neural excitation (Schultz, 2016; Schultz et al., 1992). Schultz, Dayan and Montague (1997) propose that optimal reward functioning is contingent upon an organism's prior conditioning that predicts the timing and magnitude of rewarding events. Here, we extend this contention to the 24-hour time frame by suggesting that the circadian system is the primary endogenous mechanism that conditions individuals to anticipate reward at different times of day.

An intriguing extension to these findings is that the neural reward response to reward stimuli may have an inverted diurnal waveform to self-reported ratings of positive affect. Multiple ambulatory (Clark et al., 1989; M. A. Miller et al., 2015; Stone et al., 2006; Watson et al., 1999) and circadian (Boivin et al., 1997; Murray, Allen, & Trinder, 2002; Murray et al., 2009) studies have found a peak in self-reported positive affect in the afternoon hours. Two explanations for the finding of lowered neural intensity in reward regions at times typically associated with higher self-reported positive affect warrant consideration. Firstly, Masterson and colleagues (2016) found decreased activation in reward regions in response to food stimuli from 1730-1930 in the evening (as opposed to 0630-0830 in the morning) while self-reported interest in food and hunger was greater in the evening. The authors conclude that the dampened neural sensitivity to food stimuli in the evening may instigate a greater behavioural drive for food to obtain the same reward levels as observed in the morning. The type of reward stimuli is an important consideration, with Masterson et al. using food and our study and previous work in diurnal rhythms (e.g., Hasler, Forbes, et al., 2014) using monetary rewards. Neural reward activity may exhibit different daily activation patterns depending on stimuli used and future work should attempt to investigate the role of diurnal rhythms across various reward stimuli.

Secondly, the observed decrease in neural activation of the putamen may be explained by a methodological limitation of BOLD fMRI imaging. The associated energy demands that the BOLD response is capturing are not sensitive to differences between excitation and inhibition of neuronal activity (Nair, 2005). Higher activation at unexpected times may in fact be capturing greater inhibition of reward

regions to monetary incentives in the putamen. Future studies should monitor self-reported positive affect while collecting repeated-measures neural data to test this important proposition that self-report positive affect and neural activation in response to rewards may be inverted. Complex relationships between neural, subjective and behavioural measures of reward function have been reliably documented (Berridge et al., 2009), and more research is required to understand this interplay in the diurnal/circadian context.

Although there are strong reasons to expect neural reward activation to be lowest in the afternoon hours, it is important to note that the present results conflict with Hasler, Forbes, et al.'s (2014) findings. Several methodological differences should be noted between the two studies. Firstly, while we found an effect in the dorsal striatum (left putamen), Hasler, Forbes, et al. found a time of day effect in the ventral portion of the striatum. While both regions are associated with reward neurocircuitry we do not have enough literature to assert whether reward regions exhibit similar diurnal neural rhythms. Secondly, Hasler, Forbes, et al.'s study had a single PM time-point (15.06-18.38h) sitting between our afternoon (14.00h) and evening (19.00h) scans. Thirdly, unlike the present design, Hasler, Forbes, et al. experimentally controlled for individual sleep and wake times; a post hoc investigation revealed no significant effect of sleep variables on the diurnal neural waveform found here. Lastly, while the fMRI task was similar in both studies, the present design used more trials and runs, and used a non-motor Baseline while Hasler, Forbes, et al. used a button-pressing control condition. More broadly, neuroimaging data analysis has been notoriously difficult to replicate particularly for less established or weaker findings (Poldrack et al., 2017; Poldrack & Poline, 2015). In sum, multiple methodological differences may partially explain the difference in findings here versus the sole related study, and we propose that this discrepancy should motivate more systematic and intensive research. Additionally, we agree with Hasler, Forbes, et al. that event-related designs – which allow for distinguishing between anticipation and consumption of rewards – may help to extend our understanding of the neural reward rhythm.

10.7.3 Limitations, clinical application, and future research. Although this study provides an important advance to our understanding of the diurnal rhythm of neural reward circuitry, several limitations should be noted. The primary

limitation of this study was that while the ultimate framework for this project is circadian, the data collected only speaks to a diurnal rhythm, the endogeneity of which is unknown. To confirm the endogeneity of this rhythm future research should examine whether the timing of this reward rhythm is generated from internal cues rather than external learned associations of the rewarding potential of a certain time of day. While this would traditionally be done through constant routine or forced desynchrony circadian rhythm protocols, practical constraints around mobility of sleep laboratories and imaging equipment do not allow for this. Novel approaches are now required to consider how time-free environments could be created to test for a circadian relationship. Future work should consider using more testing sessions to examine more precise waveform characteristics over the waking day, similarly extending these findings to a larger sample, women and a wider age range will help generalise the present results.

Understanding the role of the circadian system in modulating the neural reward response has potential clinical implications. Abnormalities of circadian reward functioning have been noted in individuals experiencing mood disturbance. For example, in studies of diurnal mood variation, individuals with depressive symptoms (Gordijn, Beersma, Bouhuys, Reinink, & Van den Hoofdakker, 1994; Murray, 2007) exhibit lower variability in daily positive mood, and altered waveform patterns. Von Zerssen et al (1987) found, for example, lower mood for clinically depressed individuals in the morning whereas for healthy matched controls it was lowest in the subjective night when sleep was interrupted to take measurements. Beyond circadian phase, recent work suggests individuals with depression and bipolar disorder may have a decreased circadian amplitude in positive mood variation (Grierson et al., 2016; Murray, 2007). Disruptions to both the phase and amplitude of circadian rhythms have long been hypothesised to contribute to the pathogenesis and maintenance of mood disorders (Czeisler, Kronauer, Mooney, Anderson, & Allan, 1987).

These preliminary findings raise different avenues for future research. In the present study task-based fMRI was used to examine neural reward activity in the context of rewarding stimuli. Alternative imaging methods such as arterial spin labelling may better capture hourly temporal changes as a more sensitive measure of the diurnal changes in regional brain function intensity (Goel, Basner, Rao, &

Dinges, 2013; Hermes et al., 2007; Mikita, Mehta, Zelaya, & Stringaris, 2015). Future research should endeavour to investigate whether the known mid-afternoon circadian dip in alertness may be relevant to interpreting the neural signal in reward activation. Methodologically, the present findings speak to the necessity of controlling for time of day when performing neuroimaging studies. The diurnal rhythm in reward functioning observed here raises questions about findings from neuroimaging protocols that have neither controlled for nor reported time of day.

Within its limitations, this study is among the first to examine variation in human neural reward functioning in relation to time of day. This preliminary evidence suggests that there is a diurnal rhythm in left putamen activation, part of the neural circuitry involved in reward. It extends the small collection of studies that have looked at this relationship by using three time-points to better capture the shape of the diurnal neural reward rhythm in the context of reward stimuli. This work is a first step in testing the chronobiological hypothesis of a Circadian Reward Rhythm, adding to a burgeoning imaging literature interested in how the circadian system regulates reward circuitry (Byrne & Murray, 2017a; Forbes et al., 2012; Hasler, Dahl, et al., 2012; Hasler, Forbes, et al., 2014). This novel finding also underscores the importance of future research between how vulnerability to, or experience of mental illnesses known to affect reward and circadian pathways may differ from healthy individuals which can facilitate targeted clinical intervention. These insights provide a foundation for understanding that diurnal neural reward rhythms exist in healthy individuals.

Chapter 11:   General Discussion

11.1   Structure of General Discussion

The overarching aim of this project was to incrementally advance understanding of the relationship between biological rhythm function and a number of variables related to the functioning of reward motivation in humans. To address this general aim, five investigations were conducted to characterise the relationship between biological rhythms and reward motivation, largely defined as positive affect (Study 1 and Study 2), and to investigate critical aspects of the circadian modulation of reward motivation (Study 3, Study 4, and Study 5). This final chapter has four aims. Firstly, the chapter begins by reviewing the hypotheses and key findings from each of the five studies (see Sections 11.2 through 11.6). For each study, implications and future research directions will be considered in the context of the study's limitations. Thirdly, while each investigation has specific methodologies that warrant separate sections for findings, limitations, implications, and future research sections, three larger assumptions of the project are then critiqued (11.7), and finally, three integrative points are made about the findings across studies (11.8), before concluding remarks are presented (11.9).

11.2   Study 1: Characterising the Relationship Between Biological Rhythms and Reward Motivation

As part of characterising the relationship between biological rhythms and reward motivation, Study 1 (see Chapter 5) was a critical literature review of cross-sectional, experimental, and prospective studies of the relationship between biological rhythms and reward motivation. In this review (to be published as a book chapter), reward motivation was largely operationalised as self-reported positive affect.

11.2.1   Circadian modulation of positive affect. The review of Study 1 found that mechanisms linking circadian function to reward motivation have been observed in different disciplines from molecular biology (e.g., Chung et al., 2014; Logan, Parekh, et al., 2018) to behavioural psychology (e.g., Bullock & Murray, 2014; see Section 5.3). Study 1 focused on one specific pathway linking circadian function and positive affect: the circadian modulation of positive affect. Study 1 found evidence supporting diurnal and circadian variation in levels of positive affect. The reviewed studies were largely conducted as repeated measures designs where positive affect was rated multiple times and modelled against clock time (in

naturalistic, diurnal studies) or other biological markers (CBT and heart rate in laboratory, studies designed to test hypotheses about circadian modulation). While a diurnal rhythm in positive affect has been tested in a number of studies (e.g., Clark et al., 1989; Murray, Allen, & Trinder, 2002; Stone et al., 2006; Watson et al., 1999), only one series of linked investigations have tested whether this daily rhythm in positive affect may have an endogenous circadian component (see Section 2.3 for measuring circadian rhythms; Murray, Allen, & Trinder, 2002; Murray et al., 2009).

11.2.2   Sleep and positive affect. The review of Study 1 drew preliminary conclusions about the relationship between sleep parameters and positive affect in cross-sectional, experimental, and naturalistic prospective studies. Firstly, evidence for associations between poorer sleep quality and shortened sleep length, and lowered next day positive affect was considered. The modulation of positive affect by sleep was observed in ecological momentary assessment studies, cross-sectional studies, and experimental sleep deprivation and nap studies (see Section 5.4.1, Table 2). Secondly, there is some data consistent with an association between sleep quality and sleep quantity parameters and positive affect in the preceding wake period (see Section 5.4.2, Table 3). In Section 5.4.3 it was proposed that the arousal level of positive affect may be important in predicting the effect on sleep parameters. Specifically, work by Tavernier et al. (2016), suggests that higher levels of high arousal positive affect (e.g., *excited*) may increase sleep latency with a trend towards worsened sleep efficiency. In turn, higher levels of low arousal positive affect (e.g., calm) may improve sleep quality, with a non-significant trend towards longer sleep duration.

Amongst the small set of longitudinal studies examining a putative bidirectional relationship between sleep parameters and positive affect (e.g., de Wild-Hartmann et al., 2013; Galambos et al., 2009; Simor et al., 2015; van Zundert et al., 2015), there was some evidence for bidirectionality, with poorer sleep quality, linked to lower positive affect and vice versa (with weaker evidence for the latter pathway). The majority of these studies found that shorter total sleep time was associated with lower next day positive affect; however, Kalmbach et al. (2014) found scores on *serenity* predicted longer total sleep time but sleep length did not predict *serenity*, *joviality*, or *self-assurance*. Doane and Thurston (2014) found no significant relationship between sleep length and positive affect, and one study

(Takano et al., 2014) found shorter sleep times to be associated with an *increase* in positive affect (see Section 5.4.3, Table 4). In sum, relationships between sleep parameters and positive affect were found, with strongest evidence for sleep modulation of next day positive affect.

11.2.3   Limitations and future research directions from Study 1. One pathway that Study 1 (and Study 3 and Study 5) emphasised by design was diurnal and circadian variation in positive affect. There are many other pathways by which circadian function may be linked to reward motivation. For example, as discussed in Chapter 4 (see Section 4.1) evidence from animal literature indicates that circadian gene (e.g., *clock*) and protein (e.g., PER1 or PER2) expression are rhythmically expressed in genetic information in the NAc, dorsal striatum, VTA, PFC, and amygdala (see Webb, Lehman, & Coolen, 2015 for a review). While many studies using animals have found evidence of molecular clock mechanism involvement in reward motivation (see McClung, 2007, 2013; Parekh et al., 2015 for reviews), research in humans has been scarce. A small set of studies has found that a variety of clock gene SNPs have been associated with increased alcohol consumption (Comasco et al., 2010; Kovanen et al., 2010; Sjöholm et al., 2010) and cocaine addiction (Shumay et al., 2012) in humans. One study has also found that in response to monetary reward receipt a *Per2* SNP was related to decreased activation in the mPFC (Forbes et al., 2012). This small set of studies would benefit from examining how circadian genes may be associated with other components of reward motivation, such as levels of positive affect. Aside from a circadian rhythm in positive affect (discussed above in Section 11.2.1) circadian modulation of positive affect could also be investigated by looking at other parameters of circadian function. For example, circadian misalignment can be characterised as differences in phase angle (e.g., between DLMO and sleep onset; Emens, Yuhas, et al., 2009). Differences in phase angles may be related to depressive symptomology (Hasler, Buysse, Kupfer, & Germain, 2010; Swanson et al., 2017). In samples with major depressive disorder, there is preliminary evidence of misaligned phase angles, relative to healthy controls (Buckley & Schatzberg, 2010; Hasler, Buysse, et al., 2010), and also evidence that greater phase angles are associated with depressive severity (Emens, Lewy, Kinzie, Arntz, & Rough, 2009; Hasler, Buysse, et al., 2010; Swanson et al., 2017). Importantly, the findings by Swanson et al. (2017) were dependent on gender. For

males a greater phase angle was associated with depressive symptomology, in females depression severity was linked to a shorter phase angle. While current efforts in investigating the relationship between circadian functioning and motivation are largely limited to examining diurnal and circadian rhythmicity in positive affect, there are exciting avenues to explore in the possible associations between circadian genes and phase angles, and reward motivation.

Although outside the scope of the project, one limitation noted in the publication emerging from Study 1 (see Section 5.4.4) was that the study's review was largely limited to positive affect; however, sleep parameters may be affected by the *interaction between* negative affect and positive affect. While some studies included in the review accounted for negative affect in the relationship between sleep quality and positive affect by creating a ratio of positive affect to negative affect (Cousins et al., 2011; Garcia et al., 2014; von Känel et al., 2014; Wrzus et al., 2014), most reviewed studies did not examine negative affect (as it sat outside the scope of Study 1). The ratio of positive to negative affect may be more important in understanding how affect relates to other variables (Fredrickson & Losada, 2005). In the context of Study 1, accounting for negative affect in the positive affect and sleep quality relationship may explain more variance in the sleep quality and reward motivation relationship, relative to positive affect alone. In addition, given the proposed relationship between negative affect, BIS, and FFFS (see Carver & White, 1994; Corr, 2008), accounting for BIS and FFFS may be an important research direction in future studies of biological rhythms and reward motivation (see also Section 3.4.2. for how BIS and FFS may interact with BAS). Although raised in the publication emerging from Study 1, the limitation of not accounting for negative affect (and proposed behavioural manifestations of BIS and FFFS) is relevant to the other studies in this project. For example, depression may include components of decreased positive affect and increased negative affect (Watson, 2000b); however, the Depressed Mood scale of the SCRAM questionnaire did not partition positive from negative affect. In Study 3, performance on reward tasks may be affected by both approach motivation (BAS) and threat minimisation (BIS, see Section 11.4.1.4). Thus, accounting for negative affect is an important area of future examination to advance understanding of the relationship between biological rhythms and reward motivation.

11.2.4   Implications of Study 1. One of the conclusions of Study 1, based on the review of studies investigating circadian modulation of reward, is that there is preliminary evidence of biological rhythms modulating reward function in healthy individuals, and targeting biological rhythm functioning may be important for stabilising mood (see Section 5.5). Ehlers et al. (1988) introduced a social zeitgeber theory that hypothesised that major life events can destabilise biological rhythms which in turn may lead to depressive episodes. This theory was later extended to bipolar disorder and Frank and colleagues (E. Frank, 2007; E. Frank, Gonzalez, & Fagiolini, 2006; E. Frank et al., 1997; E. Frank, Kupfer, Ehlers, & Monk, 1994) have done important work in the biological rhythm-stabilising treatment of interpersonal and social rhythms therapy (E. Frank et al., 1994, see Sections 4.5.3 and 5.5). Interpersonal and social rhythms therapy aims to maintain biological rhythms through identifying and managing precipitating factors that may lead to destabilisation of biological rhythms (Grandin et al., 2006). Biologically, non-pharmacological interventions such as strengthening the circadian signal through zeitgebers such as sleep, social activity, light, and, exercise may help to promote temporal consistency between internal circadian rhythms and external light-dark cycles (see Lall et al., 2012 for reviews; Schroeder & Colwell, 2013). Strengthening the circadian signal may promote consistent circadian rhythm alignment to the light-dark cycle and consequently improve mood stability (Murray, Allen, Trinder, et al., 2002).

11.3   Study 2: Development and Validation of the SCRAM Questionnaire

Study 2 sought to advance the characterisation of biological rhythms and reward motivation through the development and examination of the validation of the new SCRAM questionnaire, with the aim of quantitatively separating diurnal preference, sleep quality, and mood using a psychometric approach. This section reviews the findings from Study 2a (see Chapter 6), Study 2b (see Chapter 7), and then considers the limitations, implications, and future research of Study 2 as a whole.

11.3.1   Study 2a: Development of the SCRAM questionnaire. Study 2a was designed to use psychometrics to quantitatively separate the parameters of diurnal preference, sleep quality, and mood. At the construct level, it was found that sleep quality, diurnal preference, and mood could be distinguished using a

psychometric approach. Following the generation of items developed from existing questionnaires measuring these domains separately, the latent factor structure was interrogated through EFA and CFA. A three-factor solution was the preferred number of factors; however other factor solutions were examined. Only a three-factor solution fitted the data with the final scales named: Morningness, Good Sleep, and Depressed Mood. A subsequent CFA supported this factor structure. While a fourth factor of *hypomania* items emerged; an insufficient number of items and relative lowered factor loadings did not warrant a fourth scale. One possible explanation for the lower factor loadings on a *hypomania* scale may be a reduced signal of abnormally elevated mood in the general population sample of Study 2a.

Despite the selection of items that mapped uniquely onto the Morningness, Good Sleep, and Depressed Mood scales and an orthogonal rotation method used for the EFA, the scales had interrelationships that were consistent with previous research (e.g., Barclay et al., 2016; Chan et al., 2014; Fernandez-Mendoza et al., 2016). Morningness and Good Sleep scales were positively related, aligning with previous evidence of a relationship between eveningness and poorer sleep quality (e.g., Barclay et al., 2016; Wittmann et al., 2006). Depressed Mood was negatively related to both Morningness and Good Sleep in the generation of the questionnaire. This is consistent with previous work that has found an association between higher levels of depressive symptoms and clinical depression in those with higher eveningness (e.g., Abe et al., 2011; Chan et al., 2014) and poorer sleep quality (e.g., Fernandez-Mendoza et al., 2016; Fernandez-Mendoza et al., 2015) respectively.

11.3.2   Study 2b: Psychometric investigation of the SCRAM questionnaire. A psychometric investigation on three datasets was conducted to interrogate the reliability and validity of the SCRAM questionnaire. In the first dataset, test-retest reliability was examined. The relationship between the SCRAM scales and well-validated measures of sleep quality, diurnal preference and depressed mood was examined in the second dataset. The third dataset was used to compare the association between the three SCRAM scales and objective sleep-wake behaviours through previously collected actigraphy data. Test-retest reliability was strong, suggesting these constructs were stable over a two-week period. The questionnaire's utility in measuring these three constructs separately was supported, with each SCRAM scale significantly associated with a well-validated measure of the construct

in bivariate analyses. In addition, using three separate regressions, the SCRAM scale that matched the well-validated measure (e.g., Good Sleep and the PSQI) explained the greatest variance (at least three times the variance relative to the other SCRAM scales) in the well-validated measure. These relationships were robust to the inclusion of the other two SCRAM scales in the regression analyses. The results from the regressions provide provisional support for the construct validity of the three scales; however, Study 2b found stronger support for the convergent validity of the SCRAM scales relative to divergent validity, as all three SCRAM scales were significantly related to the PSQI and CES-D.

Actigraphy data provided a third line of evidence to speak to the separation of these constructs. An existing data set (a subsample of from Study 3) provided the opportunity to examine the relationship between actigraphy data and the SCRAM questionnaire. As such, there was an 18-month time difference between collecting actigraphy data and completing the SCRAM questionnaire. Across a seven day/night data collection, sleep efficiency was positively related to Good Sleep, Morningness was positively associated with earlier sleep and wake times, and there were no associations between objective sleep-wake variables and the Depressed Mood scale.

In sum, Study 2b provided three lines of preliminary psychometric support for the SCRAM questionnaire. There was evidence of appropriate test-retest reliability, strong convergent validity with well-validated measures, and preliminary evidence that Morningness and Good Sleep are associated with objective measures of sleep times and sleep efficiency respectively. However, the evidence for divergent validity of the SCRAM scales was less strong (all three SCRAM scales were associated with the PSQI and CES-D), and Depressed Mood was not related to any measures of objective sleep-wake behaviours derived from actigraphy data. More work is needed to continue examination of the psychometrics of the questionnaire (see Section 11.3.3. and Section 11.3.4.).

11.3.3 Limitations of Study 2. Study 2a and Study 2b developed and provided preliminary validating data on the SCRAM questionnaire; however, there are limitations to consider. Two limitations are considered in this section: While the SCRAM questionnaire has assumed potential in clinical settings, it has not been validated in a clinical population. Secondly, there were limitations to how the external correlates were collected in Study 2a and Study 2b.

A limitation of the SCRAM questionnaire was that it was developed, and initial validation was conducted using a non-clinical sample. In the discussion of the paper emerging from Study 2a (see Section 6.7), it was highlighted that the SCRAM questionnaire may have clinical utility. In the instance that a patient presents with, for example, sleep complaints, it is also important to treat the commonly co-occurring circadian phase alignment and mood issues (e.g., Carney et al., 2009; Crowe et al., 2016; Harvey et al., 2005). An important step towards this potential clinical end is to assess the properties of the SCRAM questionnaire by generating normative data in different clinical groups (such as insomnia, bipolar disorder and major depressive disorder). Moreover, as discussed in Section 11.3.3 using a clinical sample can help assess the sensitivity and specificity of the SCRAM questionnaire in identifying different clinical groups. In addition, conducting a CFA using a clinical population would permit assessment of the factor loadings on each scale and confirm the adequacy of the three-factor model fit. For example, in the creation of the Depression Anxiety Stress Scales (DASS), Lovibond and Lovibond (1995) first assessed the factor structure in a large university sample, before examining the factor structure in psychiatric outpatients. Given the recommendation of a sample size between 100 (Muthén & Muthén, 2013) to 300 (Tabachnick & Fidell, 2013) participants for CFA, using relatively high prevalence psychiatric disorders such as major depressive disorder or insomnia disorder would be the most practical next step in providing additional psychometric validation of the SCRAM questionnaire (see also Section 11.3.4 for further ways to validate the SCRAM questionnaire in a clinical sample).

There were limitations to the collection of external correlate data in Study 2a and Study 2b. In Study 2a, external correlates of mental health behaviours were self-reported. Participants responded to dichotomous questions of "have you ever been diagnosed with a mental disorder"? and "have you ever been diagnosed with a sleep disorder"? Results of this analysis suggested that self-reported history of mental or sleep disorder were associated with increased score on Depressed Mood, and decreased scores on Morningness and Good Sleep. While this is consistent with previous research (e.g., Gershon et al., 2012; Levinson et al., 1999; Ohayon & Roth, 2003; Soehner et al., 2016), more systematic measurement of diurnal preference, sleep quality, and mood is needed to draw conclusions of the external validity of the

SCRAM scales. While Study 2b provided some measures of external validation, ongoing work measuring the SCRAM scales against other biological and psychological markers of diurnal preference, sleep quality, and mood, that do not rely on self-report, would improve external validation of the SCRAM questionnaire. For example, well-validated measures of diurnal preference such as the MEQ and MCTQ (see Section 2.1.3.2.2) have expected relationships with DLMO (evening preferences and later sleep times are associated with later DLMO; Kantermann & Eastman, 2018; Kantermann et al., 2015). It would be interesting for future work to examine whether the Good Sleep scale is related to objective markers of sleep quality. Previous research has found that the most widely used measure of sleep quality (Mollayeva et al., 2016), the PSQI is not associated with polysomnography outcomes including sleep continuity (SE, TST, WASO, and SOL), sleep architecture or sleep disorders (Buysse et al., 2008), or actigraphy measures of sleep continuity (Grandner et al., 2006). Furthermore, in addition to these important objective markers of sleep quality, it will be important to examine the SCRAM scores in populations where sleep is disturbed, for example in sleep apnoea and in anxiety disorders. Clinician ratings of mood disorders would be an important external correlate of the Depressed Mood scale (for example the Structured Clinical Interview for DSM-5; First, Williams, Karg, & Spitzer, 2015).

The actigraphy data used in Study 2b was collected 18 months before completion of the SCRAM questionnaire. Although expected relationships were found between earlier sleep onset and offset times and higher Morningness, and sleep efficiency and Good Sleep, other markers of sleep-wake behaviour were not related to Good Sleep and Depressed Mood was not related to any markers of sleep-wake behaviours. In previous research, lowered amplitude of daily activity rhythms has been identified as a marker of risk to, and course of, mood disorders and lowered positive affect more generally (Bullock & Murray, 2014; Merikanto et al., 2017; Murray, Allen, Trinder, et al., 2002). Future research should now investigate whether a relationship exists between 24-hour activity profiles and the SCRAM scales in healthy individuals, within the delay due to pragmatic considerations in Study 2b.

11.3.4 Implications and future research emerging from Study 2. As noted in Chapter 1, the present basic science project was motivated by the potential clinical importance of understanding the relationship between biological rhythms

and reward motivation. Several authors have considered the potential for concurrent biological rhythm and reward dysregulation to occur, and be causally important, in clinical populations (also discussed above in Section 11.2.4; Alloy, Nusslock, et al., 2015; Hasler et al., 2015; Logan, Hasler, et al., 2018; Wulff et al., 2010). The SCRAM questionnaire has potential clinical utility in reminding clinicians to pay attention to interacting sleep quality, diurnal preference, and mood processes in treatment planning and provides an easy tool for measuring the three domains.

A primary aim for developing the SCRAM questionnaire was to measure individual differences in interrelated, but separable sleep quality, diurnal preference, and mood constructs. This rationale was, in part, due to the observation that sleep, circadian, and affective phenomena interact in clinical populations (e.g., Murray & Harvey, 2010). If patients are experiencing sleep, circadian, *and* mood disturbances, only treating one process (e.g., sleep problems) leaves remaining circadian and mood disturbances which could serve as independent risk factors for future sleep, circadian, and mood problems (see Section 6.7.1; and Harvey et al., 2005 on the importance of adjunct treatments). In terms of clinical application, the SCRAM questionnaire has the potential to identify the relevant symptoms and level of symptomology across three processes to help guide treatment planning. One interesting consideration is that diurnal preference (while largely considered a trait measure) may also display state changes. For example, a shift towards morningness has been observed following psychoeducational and behavioural sleep interventions (e.g., Harvey et al., 2018; Hasler, Buysse, & Germain, 2016). For Hasler, Buysse et al. (2016) this shift towards morningness following a behavioural sleep intervention was associated with a decrease in depressive symptoms and increase in positive affect in military veterans. Understanding how interventions in one domain may concomitantly affect the other domains of sleep quality, circadian phase, and depressed mood offers an interesting research and clinical future direction.

The SCRAM questionnaire has the potential to create clinical profiles, e.g., how does someone with bipolar disorder score on the SCRAM questionnaire relative to someone with major depressive disorder? Future work should use Receiver Operating Characteristic curves to derive cut-off scores, to determine if the SCRAM scales can discriminate individuals with different clinical disorders. By dichotomising a continuous scale, respondents' scores on each SCRAM scale may

be able to provide a potential screen as a predictor of different clinical disorders (e.g., Cairney, Veldhuizen, Wade, Kurdyak, & Streiner, 2007; Carney et al., 2009). Given there are three scales on the SCRAM, the profile across the three different scales may be particularly informative to these ends. Through these analyses, future research can determine if the SCRAM scales are sensitive to detecting individuals with (for example) bipolar disorder, and whether the SCRAM scales can specifically identify *only* those with bipolar disorder (cf. Streiner & Cairney, 2007 for determining optimal cut points).

The properties of Morningness, Good Sleep, and Depressed Mood scales may be clinically informative for the stages of bipolar disorder. For example, in bipolar disorder, circadian rhythmicity and sleep have been pointed to as potential mechanisms for the onset and course of the disorder and as such have been targeted in the treatment of the disorder (Foster et al., 2013; E. Frank, 2013; E. Frank et al., 1997; E. Frank et al., 2005; E. Frank et al., 2000; Wehr et al., 1987). A questionnaire that can measure these variables has the potential to look at how each stage of the disorder (depression, euthymia, and mania) may relate to changes in this symptomology and whether residual symptoms in sleep quality, diurnal preference, and mood remain in euthymic states. Evidence from other sources suggests that mood (Aubert et al., 2016; Berghorst et al., 2016; Di Nicola et al., 2013; Gershon & Eidelman, 2015; Gruber, Eidelman, & Harvey, 2008; Pizzagalli, Goetz, Ostacher, Iosifescu, & Perlis, 2008; Roux et al., 2017), sleep (Gershon et al., 2017; Harvey et al., 2005; Kaplan et al., 2015; Samalin et al., 2017), and circadian (Gershon et al., 2015) dysregulations continue to occur in those with bipolar disorder even in euthymic states. With further validation in clinical samples the SCRAM questionnaire may have the potential to distinguish between subtypes of bipolar disorder. For example, one large study ($N = 3140$ patients with bipolar disorder) found sleep differences between bipolar disorder subtypes (Lewis et al., 2017). Measuring sleep quality, diurnal preference, and mood at different stages of disorders may help to elucidate current stage of the disorder, episode prodromes and trait characteristics of the disorder. Ultimately, more precise assessment of the symptoms may assist with treatment of clinical disorders. Together, the creation and validation of the SCRAM questionnaire appears to advance measurement of these

three separable but related constructs and provide a new tool for bringing these important relationships into the clinical domain.

11.4   Study 3: Examining Circadian Modulation of Berridge's Psychological Components of Reward

To advance understanding of what components of reward may be modulated by the circadian system, Study 3 (see Chapter 8) investigated Berridge and colleagues' three psychological components of reward (see Section 3.3; Berridge & Robinson, 2003) to guide task selection of "wanting", wanting, liking, and learning. The aim of Study 3 was to examine diurnal variation in these psychological components of reward.

Study 3 built upon work examining a diurnal and circadian waveform in positive affect (e.g., Murray, Allen, & Trinder, 2002; Murray et al., 2009) by testing whether variables measuring different facets of reward motivation operate similarly in the circadian context. To the present author's knowledge, Study 3 provides the first evidence that the psychological components of reward may be important to consider in a circadian context. To test for diurnal variation in psychological reward components, it was hypothesised that tasks measuring unconscious "wanting" and conscious wanting would display diurnal variation, fitting a waveform that peaks at 14:00h with nadirs at 10:00h and 19:00h. Diurnal variation of a waveform peaking in the mid-afternoon was explored for liking and learning. Results showed that measures of "wanting" and wanting significantly fit this waveform, consistent with previous evidence of a mid-afternoon peak in positive affect (Clark et al., 1989; Watson et al., 1999), with no evidence for this modulation in the tasks measuring liking and learning. It was concluded that these results offer preliminary evidence of diurnal rhythmicity modulating in part "wanting" and wanting. Study 3 provided evidence that the three psychological components of reward may be important to apply to a circadian context. Reward should not be treated as a unitary construct as the circadian modulation of psychological reward processes may differ systematically on different tasks aimed at distinguishing recognised components of reward motivation.

To the best of this author's knowledge, Study 3 was the first study that sought to measure diurnal and circadian variation (previously observed in positive affect; Murray, Allen, & Trinder, 2002; Murray et al., 2009; Watson et al., 1999) in

objective tasks tapping reward motivation. To compare the objective tasks to previous studies of diurnal and circadian variation in positive affect, Study 3 was designed to include the PANAS; however, due to experimenter error, PANAS data was not collected. Since the time of this publication (Byrne & Murray, 2017a), one study has investigated diurnal variation in an objective task of reward learning (Whitton, Mehta, Ironside, Murray, & Pizzagalli, 2018). In a secondary dataset, Whitton et al. (2018) found that between 09:00h and 17:00h (using hourly epochs) performance on a reward learning task displayed diurnal variation with lowest response bias to rewards at midday (viz. reward learning was lowest at midday). Thus, the reward learning findings of Study 3 sit in contrast to the work by Whitton et al. (2018) and evidence from animal studies showing circadian modulation of reward learning (Cain et al., 2004; Kurtuncu et al., 2004; Valentinuzzi et al., 2008). One possible explanation for the inconsistency is the ceiling effect observed during Study 3 on the IGT (see below Section 11.4.1.2).

11.4.1   Limitations of Study 3. An important sample limitation of Study 3 (and subsequently Study 5), was the restriction of the sample to healthy, young men. In the context of testing novel hypotheses, this project aimed to recruit a homogenous sample. Men were selected due to the replicated findings of the menstrual cycle affecting circadian and sleep variables (see Baker & Driver, 2007 for a review) and emotion processing (e.g., Guapo et al., 2009); however, this gender imbalance has limited generalisability of findings. The investigation of diurnal variation in the psychological components of reward in Study 3 also had a number of limitations. Firstly, selecting the timing and rate of sessions involved methodological choices with associated limitations (the limitation considered here is also relevant to Study 5). Secondly, the number of IGT trials may limit measurement of diurnal variation of reward learning. Thirdly, measuring diurnal variation of reward motivation may not be specific to reward (a limitation relevant also to Study 4 and Study 5), and lastly, there are limitations in using Berridge and colleagues' psychological components of reward to measure reward motivation in the human context. Study 3 also presented evidence consistent with, but not evidence for, circadian variation of reward motivation. This limitation is considered later in Section 11.7.2 and is relevant to many of the reviewed studies in Study 4 and Study 5.

11.4.1.1   Rate and timing of sampling in Study 3. Selecting three time points to measure diurnal rhythms presented a number of methodological choices in Study 3 (and Study 5, which used the same time-sampling strategy). To optimise the trade-off between participant burden, measuring diurnal variation, and desensitisation of reward stimuli with each session, three time-points were selected in Study 3. Previous diurnal and circadian studies have been able to use more frequent sampling rates when examining the circadian modulation of positive affect due, in part, to the relative brevity of positive affect measures and versatility in measurement; or resting-state fMRI studies (Blautzik et al., 2013; Blautzik et al., 2014) have not needed to account for task-related fatigue (see also Section 11.4.2).

Selecting times for testing was based on optimising the peak of diurnal variation and accounting for normal sleep-wake periods. The 14:00h time was selected to measure the peak (Study 3; and variation of the quadratic waveform in Study 5 [see Section 10.3]) based on previous research in positive affect finding peaks at 15:00h (Murray, Allen, & Trinder, 2002) and 11:00h-14:00h (Watson et al., 1999) in three hour epochs, and 14:00h in a study of two hour epochs (Murray et al., 2009). To capture the change in quadratic waveform, times were selected that were far enough apart to capture anticipated differences in the diurnal rhythm; however, would not curtail sleep offset, or onset for participants. Thus, 10:00h was selected as an early time in this young adult population, and 19:00h to capture an evening change without affecting sleep onset times. While these times may capture the gross changes of diurnal rhythmicity, clearly future research is still needed to examine fine-grained changes that may occur in this diurnal reward rhythm. One consideration is that the 14:00 timepoint sits at the approximate time of the mid-afternoon circadian dip (see Wertz et al., 2006), potentially blunting the observed peak of diurnal rhythmicity.

Set times of day were chosen for Study 3 (and Study 5) rather than staggering the timing of testing session by individual sleep times. By keeping times consistent across participants, an ecologically valid snapshot of how, on average, individuals respond to reward at different times of day under naturalistic conditions was observed. It should be noted that an important study on circadian modulation of neural reward functioning (Hasler, Forbes, et al., 2014) elected to control for sleep and wake times in staggering testing times to minimise individual differences in

circadian phase in the neural reward response. Although set testing times were chosen, adding circadian phase variables (mid-sleep on free days and self-rated chronotype) as confounding factors after testing did not alter results in Study 3. In sum, a series of decision making steps were used to optimise the timing and sampling rates in Study 3. Although individual differences in two circadian phase variables did not post-hoc relate to diurnal variation in reward motivation, future studies may benefit from staggering testing times relative to participants preferred timing of sleep and diurnal preference as previous research has done.

      11.4.1.2   Number of trials on the IGT. The IGT has been commonly used to measure learning in a reward context (e.g., Lawrence et al., 2009; X. Li et al., 2010); however, observing diurnal variation in reward learning in Study 3 may have been limited by the number of trials used. Previous research has typically used 100 trials on the IGT (e.g., Bechara et al., 1994; X. Li et al., 2010; Suhr & Tsanadis, 2007); in Study 3 due to experimenter error, participants completed 300 IGT trials at each time point. Although the quadratic waveform was in the expected direction for Study 3, with participants selecting more from the disadvantageous *risky* decks at 14:00h relative to 10:00h and 19:00h, this failed to reach significance. Using substantially more trials than previous research may have given participants a greater opportunity to learn the pattern of the four deck selections and this ceiling effect may have masked diurnal variation of reward learning. The prediction of diurnal variation in reward learning as measured by the IGT should be retested using accepted IGT protocols.

      11.4.1.3   The specificity of measuring diurnal variation in reward motivation. In Study 3, the measures of reward motivation may not have been specific to reward. Diurnal rhythms in any variable (e.g., alertness, body temperature, sleep-wake) are a complex amalgamation of interactions between circadian phase and prior wakefulness and other drivers (Dijk et al., 1992). Given this, it is impossible to determine whether the observed diurnal variation measured reward motivation in "wanting" and wanting, or whether extraneous variables (e.g., alertness) were being captured in these specific tasks that also display diurnal variation.

      11.4.1.4   Using the psychological components of reward to measure reward motivation in the human context. Although the chosen tasks in Study 3

were face-valid and defensible measures of "wanting", wanting, liking, and learning, doubts remain about both their sensitivity and specificity in this capacity. As it is the first time these measures have been applied to the psychological components of reward, there may be some contention as to whether these measures specifically capture "wanting", wanting, liking, or learning reward components. For example, Pool et al. (2016) highlighted in a review that some studies used the same questions to measure wanting in one study and liking in another. This same concern applies to Study 3. As one example, unconscious "wanting" was measured on the automatic BART. The BART captures varying levels of risk-taking behaviour across trials (Lejuez et al., 2002; Pleskac et al., 2008). Due to the association between risk-taking during the BART and reward motivation (in self-report inventories and neural correlates; see Section 3.5.4) it was thought that the BART may index "wanting". As noted in Study 3 (see Section 8.5) the selection of the BART may predominantly index "wanting" but individuals may moderate their "wanting" through a learned response of win or loss across a number of trials, and, individuals' conscious liking of rewards may also serve to increase or decrease the degree of "wanting" on any single trial. Additionally, this task may activate the BIS, with participants attenuating their "wanting" out of a threat response to minimise risk or loss (Demaree, DeDonno, Burns, & Everhart, 2008; see also Section 11.2.3 that reward motivation [positive affect] may not be distinct from the threat system [negative affect]).

While Study 3 provided preliminary evidence of the utility of applying the psychological components of reward to a diurnal context, concerns of applying these three components into the human context should be noted (Havermans, 2011, 2012). In looking at the human response to food rewards, Havermans (2011) argues that an individual's capacity to "like" food is not independent of "want" for food. For example, in a study examining stimuli-specific reward separation, the more someone liked chocolate the more someone wanted chocolate; similarly stimulus satiety (giving someone lots of chocolate) led to decreased subjective drive (want) and liking of chocolate, preferentially increasing drive towards other stimuli (chips; Havermans, Janssen, Giesen, Roefs, & Jansen, 2009). Thus, Havermans (2011) concludes that while abnormal reward behaviours (e.g., anorexia, binge eating disorder, drug and alcohol use disorders) may heighten neural sensitisation to increase "wanting" behaviour, without an associated rise in "liking" behaviour

(Berridge & Robinson, 2003), the phenomenon of "wanting" and "liking" co-vary to such an extent that partitioning them may not reflect normal reward behaviour. Although Study 3 sits outside of the appetite literature, it is important to acknowledge Havermans' (2011) concerns of parsing "wanting" and "liking" in the human context. Study 3 suggested that some tasks are able to separate Berridge and colleagues' psychological components of reward in a diurnal context. For example, while positive pictures (using the IAPS), displayed diurnal variation peaking at 14.00h for arousal ratings (wanting), this diurnal variation was not observed for the same images in pleasantness ratings (liking). Extending the findings of Study 3 to examine diurnal variation in appetite variables for "wanting" and "liking" may be important to advancing understanding of whether the psychological components of reward can be separated in healthy humans for appetite variables.

Future studies should continue to explore what behavioural measures might best capture "wanting", wanting, liking, and learning in a diurnal context in humans. Pool and colleagues' (2016) found that most reviewed studies measured both wanting and/or liking using quantitative questions or questionnaires, with brain activity, physiological, and behavioural measures less frequently used. Future studies that aim to advance measurement of the psychological components of reward should concurrently use measures that directly ask participant's wanting and liking while also measuring other behavioural, neural and physiological tasks that might index unconscious psychological components of reward (see also Section 11.4.2. for a discussion of whether conscious and unconscious processes of the psychological components of reward are the same construct measured differently). These steps may help to address Havermans' (2011) concerns that a lack of theory, and transparent, construct valid measures has added to the difficulty of distinguishing "wanting" and "liking" in the human context.

11.4.2 Implications and future research of Study 3. Within its limitations, Study 3 has furthered understanding of the human reward system by examining the three psychological components of reward in a diurnal context. Five implications are considered here: Study 3 advances understanding of how "wanting", liking, and learning can be separated in the human context, and secondly, has implications for considering conscious and unconscious measurement of the psychological components of reward. The separation of the psychological components of reward

may be important for addiction researchers, and diurnal variation of the psychological components of reward observed in healthy populations may have implications in clinical populations. Finally, the findings of Study 3 are important to considering the importance of counterbalancing start times due to reward habituation.

Study 3 offers alternative ways that the three psychological components of reward can be separated in the human context. In animal studies, the psychological components of reward have been most commonly distinguished through neural manipulation (e.g., D. C. Castro, Cole, & Berridge, 2015; Golani et al., 2014; Peciña et al., 2003; S. Robinson et al., 2005; Tadmor et al., 2017). In humans, separating wanting, liking, and learning has typically been assessed in cross-sectional studies (cf. Pool et al., 2016 for a review of wanting and liking studies in humans), with some work in abnormal reward behaviours (e.g., addiction) and imaging studies (see reviews by Berridge & Kringelbach, 2008; Berridge & Kringelbach, 2015; Kringelbach & Berridge, 2016). The findings of Study 3 are innovative as beyond cross-sectional work, imaging, and addiction studies, diurnal variation may be another way to separate the psychological components of reward in humans.

Measuring the psychological components of reward at different levels (e.g., self-report, behavioural tasks, neuroimaging paradigms), may help extend understanding of the distinct roles of different brain systems and advance understanding of broader human behaviour (Berridge & Kringelbach, 2008). Examining diurnal variation in heart rate during the Fowles task, and a dynamometer progressive-ratio task of reinforcement are two potential physiological measures to extend present research. To do this, future research could ask more nuanced questions to investigate the psychological component of reward. For example, how do these reward components influence each other in a diurnal context? By looking at subsequent reward behaviour following a loss (e.g., popping the balloon on the BART) future work could investigate if there is a learning and wanting interaction that moderates reward behaviour, and whether this modulating differs by time of day.

Study 3 also draws an important distinction between conscious and unconscious processes of human reward motivation. As the translation of Berridge's work in animals is brought into the human context, future work should focus on

whether circadian modulation of liking and learning reward stages can be observed in both unconscious and conscious processes. Also, unconscious "wanting" and conscious wanting was inferred by the nature of the task; however this was not directly tested in Study 3. Knutson et al. (2014) propose that fMRI paradigms have the potential to speak to unconscious reward processing, while self-report measures may complement fMRI data but remain limited by the capacity to reflect the conscious experience. Further examination is now needed to examine whether conscious wanting, liking, and cognitive learning are the same processes as unconscious "wanting", "liking", and associative learning (see Section 3.3 above for discussion on why quotation marks are not used for separating conscious and unconscious learning). Berridge and Kringelbach (2015) argue that while, for example, liking and "liking" often occur together, dissociation between conscious and unconscious levels of liking can occur. Alternatively, the conscious and unconscious psychological components of reward may represent distinct concepts (drawing on suggested differences in conscious and unconscious attitudes; e.g., Nosek, 2007; Rudman, 2004). As support for the latter, work by Winkielman, Berridge, and Wilbarger (2005) investigated unconscious priming with happy and angry faces. Priming of happy faces increased sugary drink consumption and willingness to pay for this drink in thirsty subjects, without altering the subjective experience of affective state. Advancing measurement of "wanting", "liking", and learning is clearly important to more clearly delineate the overlap and separation of these psychological reward components. The findings of Study 3 are a promising start to using diurnal variation as one such way to separate these components.

Separating wanting, liking, and learning may be of interest to researchers who investigate relationships between reward and other phenomena. For example, in the appetite literature there is debate over the role of "wanting" and "liking" in disordered eating (see above; Finlayson & Dalton, 2012; Finlayson, King, & Blundell, 2007; Havermans, 2011, 2012). Separating Berridge and colleagues' three psychological components of reward allows for more precise questions to be examined of the specific mechanisms that may drive or be affected by these underlying reward components. As one example, T. E. Robinson and Berridge (2000) review that addiction processes mediate the psychophysiological underpinnings of "wanting". As the three components of reward interact

continuously in everyday life they can be difficult to separate; however, when there is tension between them (e.g., someone who no longer likes drugs, can still unconsciously "want" them) the psychological components of reward can be distinguished (Berridge & Robinson, 2003).

Study 3 has taken the preliminary step of characterising diurnal variation in the psychological components of reward in healthy populations; examining diurnal variation of these reward components in clinical populations may have important implications. The pattern of diurnal variation in the psychological components of reward may be dysregulated in clinical populations, particularly in disorders related to reward motivation. Outside of bipolar disorder (see Section 4.5), circadian dysregulation of reward motivation has been proposed most comprehensively for alcohol and substance use (Hasler & Clark, 2013; Hasler, Franzen, et al., 2017; Hasler, Kirisci, & Clark, 2016; Hasler, Smith, et al., 2012; Hasler, Soehner, et al., 2014; Hasler et al., 2015), but also for binge eating disorder (Roveda, Montaruli, et al., 2017), and gambling (Adan, Natale, Caci, & Prat, 2010; Parhami et al., 2012). As one example, people with alcohol and substance use disorders may display increased "wanting" of substances, without concurrent liking of the stimulus (see T. E. Robinson & Berridge, 2000 for a review). Examining how diurnal variation in the psychological components of reward may be dysregulated may help refine treatment targets in these disorders. As one example: Is diurnal variation in all three psychological components of reward dysregulated in disorders related to reward motivation? Evidence to date suggests dysregulation of "wanting" (characterised by NAc and dopamine alterations) has the strongest support (cf. Berridge & Kringelbach, 2015; Linnet, 2014; T. E. Robinson & Berridge, 2000 for reviews). From the findings of Study 3, measuring diurnal variation in the psychological components of reward (particularly "wanting") may help to highlight differences between clinical and non-clinical groups. If clinical groups have altered diurnal variation of "wanting" (and potentially the other psychological components of reward), subsequent research questions could examine whether correcting circadian parameters (e.g., promoting regular sleep and wake times) normalises the "wanting" component in the management of reward-related disorders.

An important feature of the design of Study 3 (also relevant to Study 5, see Section 11.6) was the counterbalancing of times for measuring rewards across

participants. With multiple exposures to positive, rewarding stimuli, the acute state novelty response may be attenuated and begin to reflect a trait level of reward motivation (Brickman, Coates, & Janoff-Bulman, 1978; Diener, Lucas, & Scollon, 2006; Fredrickson et al., 2008). In Study 3, this effect may occur within each testing time-point, and across the testing sessions. The 'hedonic treadmill' effect states that relative responses to emotional events tend to be affected by repeated exposures, and this adaptation has been proposed to occur in cross-sectional and longitudinal studies (Diener et al., 2006). Consistent with this prediction, multiple studies show that repeated exposures to emotional and reward tasks displayed a habituated reward response (Breiter et al., 1996; Burger & Stice, 2014; Hasler, Forbes, et al., 2014; C. I. Wright et al., 2001). To account for this effect, Study 3 (and Study 5) counterbalanced the start times of the three testing sessions. This choice was important as when iteration alone was examined ratings of pleasure on the IAPS and positive emotions on the mDES, all decreased from Time 1 > Time 2 > Time 3 in Study 3 (this effect was also observed in putamen activation in Study 5). Hasler, Forbes, et al. (2014) found a similar effect whereby an attenuated reward response in the second scan relative to the first was observed (and interpreted by the authors as task habituation). In an fMRI study, Burger and Stice (2014) found that administration of Sweet Milkshake Receipt > Tasteless Solution Receipt led to an attenuated response in the putamen and ventral pallidum with increasing number of exposures to the milkshake. It is important for future studies to counterbalance start times so that diurnal variation is not obscured by the effects of repeated exposures. An additional suggestion is to compensate participants based on performance to sustain task-motivation, while this strategy was used in Study 5 (where participants were told they would be compensated for their highest performance on the Gambling task) no such strategy was used in Study 3.

11.5   Study 4: A Systematic Review of fMRI Studies Generating Data Concerning Circadian Modulation of the Reward System

To investigate neural aspects of the circadian modulation of reward motivation, Study 4 was a systematic review of studies generating data concerning circadian modulation of neural reward activation (see Chapter 9). As outlined in the protocol paper (see Section 9.2) studies were included in the Study 4 review if they measured a proxy for circadian functioning as a predictor variable and a reward

outcome variable using fMRI. As noted in the publication reporting on the findings of Study 4 (see Section 9.3), the broad inclusion criteria led to significant heterogeneity across identified studies. For example, some included studies were task-based measuring neural response to reward stimuli, while other studies examined circadian modulation of reward regions and networks in resting-state designs.

Across resting-state and task-based studies, 13 of the 15 identified studies generated evidence consistent with circadian modulation in multiple brain regions implicated in reward functioning. In terms of reward-related brain regions that appear to exhibit circadian modulation, the data reviewed suggest the subcortical VS (and less consistently the putamen) region, the cortical regions of the mPFC (and to a lesser extent the ACC), and the DMN may be involved. These results suggest that these brain regions (a) may exhibit circadian variation, (b) are most sensitive to circadian modulation, or (c) are the regions in which circadian modulation is most easy to demonstrate in fMRI. Given the relative immaturity of the reviewed literature, it was not possible to determine which of these possibilities are most likely, and indeed, they are not necessarily mutually exclusive. While patterns were consistent with modulation by proxies of circadian function in these reward brain regions, the direction of effect in each region was inconsistent across reviewed studies. For example, relative to a morning scan, one study found greater VS activation in afternoon hours in response to monetary rewards (Hasler, Forbes, et al., 2014) while another found attenuated VS activation in the afternoon to food rewards (Masterson et al., 2016). These findings constitute an initial step in understanding the specific mechanisms of circadian modulation of the reward system, but significant heterogeneity in the fMRI protocols weakens the qualitative synthesis that can be drawn across studies and limits definitive conclusions.

Reviewed studies in Study 4 were examined to interrogate whether circadian modulation was present for both reward anticipation and reward receipt (as discussed in Section 9.2.2 above, only studies employing event-related designs enabled this distinction). In studies using event-related designs, the mPFC and VS were the two regions identified as ROIs across the five reviewed studies (LeMoult et al., 2015 used only the VS as an ROI). In these five studies, there was evidence consistent with circadian modulation of both reward anticipation and reward receipt; however,

stronger evidence was observed for the latter. Only three of the five studies generated data consistent with circadian modulation of *reward anticipation*. There was evidence of the mPFC displaying circadian modulation in two studies (Hasler, Dahl, et al., 2012; Hasler et al., 2013) but not in two other studies (Forbes et al., 2012; Hasler, Casement, et al., 2017). There was evidence of VS activation being modulated by proxies of circadian function in two studies (Hasler, Dahl, et al., 2012; LeMoult et al., 2015), while circadian modulation of reward regions was not observed in three other studies (Forbes et al., 2012; Hasler, Casement, et al., 2017; Hasler et al., 2013). All four studies reporting on *reward receipt* found some evidence of circadian modulation. The effect of circadian modulation of reward receipt was observed in the mPFC (Forbes et al., 2012; Hasler, Casement, et al., 2017; Hasler, Dahl, et al., 2012) and the VS (Hasler, Casement, et al., 2017; Hasler, Dahl, et al., 2012; Hasler et al., 2013) although following reward receipt circadian modulation was not always correlated with activation in the mPFC (Hasler et al., 2013) and VS (Forbes et al., 2012).

Event-related designs can partition reward anticipation from reward receipt, which may be consistent with what Berridge and colleagues call "wanting" and "liking" respectively. A well-cited study (O'Doherty, Deichmann, Critchley, & Dolan, 2002) found in an event-related design that during food reward anticipation, activation in the VTA and striatum were increased relative to reward receipt. The brain region response may be different for reward anticipation and reward receipt, and O'Doherty et al. (2002) suggest the pattern of activation for reward anticipation is at least partially dissociable from reward receipt, which the authors indicate is consistent with what Berridge (1996) calls "wanting" and "liking". Other authors have also taken the theoretical step of suggesting "wanting" can be measured through reward anticipation, and "liking" measured through reward receipt in fMRI studies (e.g., Hasler et al., 2013; Nusslock & Alloy, 2017; Nusslock, Young, & Damme, 2014).

Berridge and colleagues' psychological components of reward have the potential to deepen understanding of examining the circadian modulation of reward functioning in future fMRI studies. Initially, the intention for the systematic literature review conducted in Study 4 was to investigate all three components of reward behaviour ("wanting", "liking" and learning); however, a preliminary

scoping of the literature found no fMRI studies looking at putative circadian modulation of reward learning. There is reason to think that neural underpinning of the learning component of Berridge and colleagues' psychological components of reward may in fact be more difficult to capture than "wanting" and "liking". Berridge et al. (2009) detail clear delineation of "wanting" and "liking" in the NAc while this same distinction is not made for learning. "Wanting" has been associated with dopaminergic function particularly in the core of the NAc, and "liking" related to Mu-opioid receptors particularly in the shell of the NAc (D. C. Castro & Berridge, 2014b; Peciña & Berridge, 2000). D. C. Castro et al. (2015) highlight that the brain circuitry involved in learning may be more complex, with a review of neuroimaging studies (O'Doherty, 2004) finding that the OFC, VS, and amygdala are involved in processes of encoding reward value, maintaining reward predictions, and may be involved in guiding future decisions based on these existing reward predictions. Future improvements in task-based fMRI may be important for capturing circadian modulation of learning. For example, X. Li et al. (2010) found that when the IGT was completed in the fMRI it activated a range of brain regions relevant to reward (mPFC, VS, ACC, dlPFC, insula, PCC, and OFC) in healthy individuals.

  11.5.1 Limitations of Study 4. Study 4 had some important limitations, one of which was the heterogeneity of studies that were identified by the review. As considered in the published protocol paper (see Section 9.2.3.1.3), it was decided that papers would be accepted if they used experimental or quasi-experimental quantification of some proxy of circadian functioning. For example, Forbes et al. (2012) was examining the moderating effects of a circadian gene (the *rs*2304672 allele) on the relationship between the timing of weekend sleep mid-point and neural reward response. Using circadian genes gave some insight into the origin of this circadian finding. In Hasler, Dahl, et al. (2012) the variable of sleep time shifts was used as a proxy for circadian misalignment (i.e., social jetlag). Using weekday-weekend changes in sleep times as a proxy of circadian function has the benefit of measuring actual sleep behaviour, relative to a self-reported diurnal preference; however a limitation of this approach is that social jetlag is closely associated with changing sleep durations across the course of the week (Wittmann et al., 2006). Sleep duration then becomes an additional confound in using social jetlag measuring the circadian modulation of neural reward (Skeldon, Phillips, & Dijk, 2017; also see

Section 11.7.2 for a discussion of the limitations of inferring circadian rhythmicity from naturalistic study designs). All circadian predictor variables that were included in the systematic literature review are limited by measuring downstream outputs of the circadian system (see Section 11.7.2 for further discussion). Proxies of circadian phase (timing of sleep and meal times, chronotype, external clock time) were used as the primary predictor variable of interest in the reviewed studies although, three studies examined diurnal variation in the context of neural reward response (Byrne, Hughes, et al., 2017; Hasler, Forbes, et al., 2014; Masterson et al., 2016), and two studies looked at the effect of circadian genes as a marker for circadian function (Baranger et al., 2016; Forbes et al., 2012). Ultimately, the review is limited by the various proxy measures of circadian function. Given this heterogeneity of studies, a meta-analysis was not appropriate, and estimates of the strength of evidence were not able to be determined. Further work is now needed to more systematically test how each of these circadian predictor variables may be related to neural reward outcomes, with replication studies an important starting point.

The systematic review of Study 4 aimed to capture studies collecting data on whether there was evidence in fMRI studies of a circadian signal in reward circuitry in healthy humans, irrespective of whether this was a stated focus of the publication. Indeed, with the exception of Yoncheva and colleagues (2016), none of the resting-state studies specifically referred to "reward". As the aim of the review was to seek a signal of the relationship of interest in the existing literature, articles were included if they collected data on the neural basis of reward function and the interpretation of the reward regions was broad with sensitivity prioritised over specificity. Thus, articles that measured reward-related brain regions (see Figure 11 for list of reward inclusion terms) were included in the review.

There is circumstantial evidence of DMN involvement in reward processing. In a systematic review, for example, Broyd et al. (2009) found altered DMN activity in individuals with mental illnesses. More recently, altered DMN activation has been observed in individuals with high trait reward sensitivity (Olivo et al., 2016), and those with a history of alcohol use disorders (X. Zhu, Cortes, et al., 2017). Similarly, the regions of the insula and amygdala were included as part of the review although the insula activates to both reward and loss anticipation (e.g., Knutson & Greer, 2008), and appetite and disgust (e.g., Britton et al., 2006). The amygdala also

activates to arousal for both positive and negative valence reward stimuli (e.g., Costa et al., 2010), although this effect is observed more consistently for negative relative to positive stimuli (see Zald, 2003 for a highly cited review). Given many of the included regions are not specific to reward motivation, it is possible that circadian modulation inferred by activation patterns observed in the neural reward regions may capture other mental processes. For example, circadian modulation observed in resting-state studies in frontal regions and the DMN (Blautzik et al., 2013; Coutinho et al., 2015; Hodkinson et al., 2014; Kyeong et al., 2017), could alternatively be attributed to the putative circadian modulation of cognitive (Wright et al., 2012) and attentional processes (Goel et al., 2013).

A key issue in interpreting the results of Study 4 is the nature of selected samples, and consequent uncertainty about generalizability of findings. The reviewed studies largely focused on convenience samples of university students who are typically young. Additionally, many of the included studies have only included one gender. While Study 5 and other studies elected to sample men only (Hasler, Casement, et al., 2017; Hasler et al., 2013; Hodkinson et al., 2014), others have recruited females only (LeMoult et al., 2015; Masterson et al., 2016). Similarly, age may affect both circadian (Duffy & Czeisler, 2002) and reward function (Deakin, Aitken, Robbins, & Sahakian, 2004; Somerville et al., 2010). Future research that investigates other samples (i.e., females, adolescent [<18 years of age], and mid-, older-adult samples) is warranted to examine the putative circadian variation in reward functioning for all individuals.

11.5.2 Implications and future research for Study 4. Some implications stemming from Study 4 have been mentioned elsewhere and are not repeated here: A discussion of applying Berridge and colleagues' psychological components of reward to examining circadian function was presented in Section 11.4.2, and the importance of controlling for diurnal variation in reward paradigms is discussed later in Section 11.8.3.

Given that the qualitative synthesis of Study 4 generated preliminary evidence of circadian variation in neural activation in both task-based and resting-state studies, considering time of day may be important for medical treatment planning. For example, transcranial magnetic stimulation is gaining prominence as a treatment for mood disorders, particularly depressive episodes (Dell'Osso et al.,

2002; Holtzheimer et al., 2010; Levkovitz et al., 2015; Mitchell & Loo, 2006). To date, there has been no investigation as to whether efficacy is more pronounced at different times of day, with time of day not reported in studies including in a Cochrane review (Rodriguez-Martin et al., 2001) and more recent reviews (Bersani et al., 2013). Expecting altered treatment responses with time of day is not unprecedented: Individuals receiving chemotherapy report an altered tolerance and different response rates depending on the time of day of administration (Kobayashi, Wood, & Hrushesky, 2002). There is some evidence that this time of day effect may have a circadian origin. Most recently, an animal study (Borniger et al., 2017) found that administration of a drug often used for localised breast cancer treatment displayed evidence of altered inflammatory gene response to chemotherapy medications dependent on circadian parameters. As the circadian system coordinates a broad range of physiological processes, it is critical to investigate further application of a wide range of biological interventions that may exhibit diurnal variation.

A potential implication of Study 4 is that it raises initial considerations for future research selecting potential reward ROIs in a circadian context. Given the findings of the systematic literature review, the VS, mPFC, ACC, and putamen appear to warrant inclusion as specific ROIs and the DMN as a network of interest in future research seeking to investigate circadian modulation of neural reward functioning. As noted in Section 11.5.1, however, these areas may be *false positives*. These findings should be considered in the context of the limitation that the brain region may not relate specifically to reward motivation, particularly relevant to the DMN. As this area is still new, to rule out *false negatives*, whole-brain secondary analyses remain important for more exploratory mapping.

11.6   Study 5: Diurnal Variation in Neural Reward Functioning

Study 5 (see Chapter 10) examined diurnal variation in neural reward function as a first step in further testing a longstanding hypothesis of circadian modulation of reward motivation. Study 5 took a subsample of the participants from Study 3 and conducted a repeated measures investigation of hypothesised diurnal variation in neural reward response. An advance over two other studies with a similar aim (Hasler, Forbes, et al., 2014; Masterson et al., 2016), was the use of three time-points to test for neural reward variation across the day (10:00h, 14:00h, and

19:00h). The 14:00h timepoint was expected to show marked differences in BOLD activity in response to rewards, but a direction of this rhythm was not predicted. The direction of the diurnal waveform was modelled to test either a peak or nadir of neural reward activation at 14:00h relative to earlier (10:00h) and later (19:00h). A peak at 14:00h would be consistent with the results of Study 3 and findings from Hasler, Forbes, et al. (2014). A nadir of the diurnal waveform at 14:00h would be consistent with evidence from Masterson et al. (2016) and *prediction error* findings in the neural reward responsivity literature (see below; Abler et al., 2006; Hare et al., 2008; McClure et al., 2003). Study 5 found decreased activation in the left putamen in response to monetary rewards at 14:00h relative to 10:00h or 19:00h. The finding was considered consistent with a prediction error explanation of the findings.

Drawing on the work of Schultz and colleagues, it was explored in Study 5 that diurnal creatures may have evolved to form reward predictions about the rewarding potential of certain times of day. For example, as humans were hunting creatures, food availability would be higher during the daytime due to improved visual acuity relative to night time (see Section 4.2). As a result, humans may have evolved to expect rewards during daylight hours. This is consistent with the observed peak in positive affect in the afternoon (Murray, Allen, & Trinder, 2002; Murray et al., 2009; Watson et al., 1999). In a neural context, by contrast, reward acquisition during daylight hours may generate less neural activation (as it is expected) in reward regions, relative to earlier and later when rewards are unexpected: a circadian prediction error. In sum, one explanation for the findings of Study 5 is that neural activation in reward regions may be increased when the timing of these rewards are surprising, viz. this *circadian prediction error* in the brain may reflect higher expectations of rewards at 14:00h (consistent with a circadian rhythm in reward response), compared to 10:00h and 19:00h.

The finding in Study 5 of decreased afternoon reward activation appears inconsistent with earlier findings by Hasler, Forbes, et al. (2014), suggesting that neural activation is highest in response to rewards (the same reward task that Study 5 employed; albeit with a different number of trials and included control blocks) in the afternoon relative to morning. Given the limited data in this field it is impossible to resolve these inconsistencies, most importantly it points to an urgent need for more systematic imaging studies to investigate these mechanisms further (see Section

11.6.2). As Study 5 is one of the first studies to examine diurnal variation in reward motivation, more systematic research (for example by controlling for multiple comparisons [see Section 11.6.1]) will help identify the brain mechanisms which may subserve healthy reward functioning in a circadian context. Identification of the neural mechanisms that underpin diurnal variation in healthy reward motivation may also advance knowledge of how reward and circadian systems may be dysregulated in mood disorders and disorders of addiction (see Section 11.8.2). To extend understanding of the reward brain mechanisms in a diurnal context, future work could compare diurnal variation of reward regions and networks in resting-state fMRI. Self-report measures of affective experience should also be collected to compare to neural data (discussed later in Section 11.7.1).

11.6.1   Limitations of Study 5. A general limitation of task-based fMRI is that a *reward task* may measure other processes not directly relevant to reward. The BOLD fMRI technique infers brain activation (and brain structure involvement) from the relative oxygenation to different brain regions; however, a task designed to measure "reward" may also measure other brain processes not related to reward (e.g., Delgado et al., 2000). For example, although seemingly simple, the task used in Study 5 (Delgado et al., 2000) displayed visual information and required a motor response from participants, requiring activation of visual and motor systems that were not part of the primary reward hypothesis of Study 5. Activation of visual and motor systems may account for the higher level of activation in the dorsal striatum in both Study 5 (Byrne, Hughes, et al., 2017) and in other studies using this task (e.g., Delgado et al., 2000; Forbes et al., 2009; May et al., 2004) as the dorsal striatum region, and putamen specifically, is important to both motor activity (e.g., McFarland & Haber, 2000) and reward processes (e.g., Valentin & O'Doherty, 2009). Thus, it is important to note that the activation in the left putamen in Study 5 may reflect broader neural processes than reward functioning.

Study 5 was limited to the measurement of diurnal variation in predefined reward regions in response to monetary stimuli. Future work should interrogate whether diurnal variation can also be observed in response to different reward stimuli. Money, measured largely through the HCP gambling task (Delgado et al., 2000), has been the most frequently used stimulus within (e.g., Forbes et al., 2012; Hasler, Dahl, et al., 2012; Hasler, Forbes, et al., 2014) and outside (e.g., Forbes et al.,

2009; Tricomi et al., 2004) of the circadian context; however this gambling task has been modified to measure anticipation and outcome, and administration between studies has varied by number of blocks (reward and punishment) and inclusion of control blocks. There has been one promising finding that diurnal rhythmicity is observed in neural responses to food stimuli (Masterson et al., 2016). Masterson et al. (2016) found diurnal variation in an fMRI study of high and low caloric food. It is also possible to administer substances (e.g., McCabe, 2016; McCabe et al., 2011) in the fMRI machine, which may have closer alignment to the liking, hedonic experience of rewards, relative to visual presentation of reward, which relies on the memories of expected pleasantness (Pool et al., 2016). Concurrent measurement of reward stimuli (including money and food, but also incorporating social and sexual reward [i.e., displaying erotica]) may be informative in extending knowledge of the diurnal variation in reward parameters in healthy individuals.

A critique of the publication from Study 5 (Byrne, Hughes, et al., 2017) was published by Steel, Thomas, and Baker (2018). Four specific criticisms raised by Steel et al. are addressed here. Firstly, Steel et al. suggest that Byrne, Hughes, et al. (2017) could have been clearer in stating whether the small volume corrections were based on anatomical or functional definitions of these regions (as recommended by Poldrack et al., 2008). ROIs were anatomically defined from the Automated Anatomical Labelling atlas (Tzourio-Mazoyer et al., 2002). Small volume corrections were applied to each region independently; however, multiple comparisons were not corrected raising the possibility of a Type I error (rejecting a true null hypothesis). Secondly, Steel et al. note that results not surviving correction were reported in Study 5. Given the exploratory nature of this work, journal reviewers had suggested investigating the contrasts for Reward > Loss. Although the clusters did not survive corrections, the location in the dorsal striatum (left putamen [-28 10 -8 peak voxel, 4 voxels] and left caudate [-12 14 14, 1 voxel]) were included in the published paper as they may inform potential ROIs in future work. Thirdly, Steel et al. note that the results of left putamen activation in the whole brain analysis were not presented in the published article. It can be assumed that the left putamen was significant given the voxel level thresholding was the same for whole brain analyses except for cluster extent. Twenty-three voxels were present in the small volume correction analysis and an arbitrary cluster threshold of 10 voxels was set in

the whole brain analysis (see Section 10.5). Lastly, Steel et al. stated that Byrne, Hughes, et al. implied diurnal modulation would be specific to the left putamen relative to the other ROIs, yet as Steel et al. note, this was not tested in Study 5. It was not the intention of the publication emerging from Study 5 to imply that diurnal variation would be observed in the left putamen to the exclusion of other reward regions in response to monetary stimuli. Rather, it was hypothesised that diurnal variation would be observed in neural activation in response to monetary stimuli in one or more reward regions, one potential area of which was the putamen. In sum, a rigorous critique of Study 5 methods highlights that the statistical approach taken could be improved by controlling for multiple comparisons and more careful wording of the imaging results.

   11.6.2 Implications and future research of directions stemming from Study 5. While implications of accounting for time of day in measuring reward motivation is considered elsewhere (see Section 11.8.3), the potential circadian prediction error (see Section 10.6.2) warrants more systematic investigation in future neuroimaging work. fMRI studies should report resting-state and task-based data, and self-reported affect to investigate more systematically the prediction error hypothesis that task-based neural response to reward may be lowest in mid-afternoon hours. Using food stimuli, Masterson et al. (2016) found that self-report measures of food wanting was lower when neural activation in reward regions was highest; while Hasler, Forbes, et al. (2014) found that self-reported affect (measured on the PANAS) did not significantly differ between the morning and afternoon time-point. Due to experimenter error PANAS data was not collected for Study 5 (or Study 3). As the PANAS has been the most commonly collected variable in examining self-reported positive affect especially in a circadian context (e.g., Clark et al., 1989; Murray et al., 2009; Watson et al., 1999), it would be helpful to collect to explore the cross-sectional relationship between self-reported affect and neural data.

   In the context of examining the circadian prediction error hypothesis, resting-state data may help extend what Masterson et al. (2016) and Hasler, Forbes, et al. (2014) have done with task-based results and self-report measures. Resting-state fMRI measures intrinsic and spontaneous activity of the brain capturing the functional connectivity of brain regions (see Cole, Smith, & Beckmann, 2010 for a review). Observing how resting-state patterns might relate to self-report and task-

based fMRI may be informative to the circadian prediction error hypothesis proposed here. For example, measuring functional connectivity between reward regions at rest may capture changes in preparedness to engage in reward activity. As one potential mechanism, some researchers have investigated the relationship between cross-sectional resting-state fMRI and dopaminergic functioning (e.g., Cole, Beckmann, et al., 2013; Cole et al., 2012; Cole, Oei, et al., 2013; Kaiser et al., 2017). Observing whether the relationship between dopaminergic availability and resting-state activation varies systematically across the day may be informative towards the proposed circadian prediction error.

11.7   Consideration of the Premises of the Project

In this General Discussion thus far, each study has been considered in isolation. In the present section, three important premises of the project as a whole are explicated. Firstly, it was a premise of the present project that reward motivation is a construct that can be measured at different levels (12.7.1). The second and third considerations are relevant to the project's investigation of circadian modulation of reward motivation (Study 3, Study 4, and Study 5). The second consideration is demonstrating diurnal variation was assumed a useful first step in demonstrating circadian variation (12.7.2). Lastly, the project chose to focus on the influence of circadian function on reward motivation, while the converse path (the influence of reward motivation on circadian function) has been given little attention here (12.7.3).

11.7.1   Measuring reward motivation. A major assumption of this project was that the construct of reward motivation can be measured usefully at different levels. This project measured reward motivation in a number of ways (summarised in Chapter 1 and Chapter 3). Study 1 measured reward motivation largely as self-reported positive affect. The Depressed Mood scale of the SCRAM questionnaire in Study 2 captures lowered positive affect (see Section 3.6 for how lowered positive affect may relate to anhedonia symptoms in major depressive disorder). Study 3 measured a variety of reward behaviours, and self-reported emotions, and Study 4 and Study 5 measured reward motivation through fMRI activity in resting-state (Study 4) and task-based (Study 4 and Study 5) neural response to reward stimuli.

Self-reported positive affect, approach behaviour, and reward-related brain regions captured in neuroimaging, may all measure the same construct: a higher-order construct called reward motivation (Knutson et al., 2014). Knutson et al.

(2014) proposed a mapping of the levels of analysis for reward motivation. In the affective space, dopamine (neurochemistry), NAc (fMRI activity), positive arousal (affective experience), and approach (motivated behaviour) are presented as the ascending levels of what has been labelled as reward motivation in the present project (see Figure 16 adapted from Figure 5 in Knutson et al., 2014).
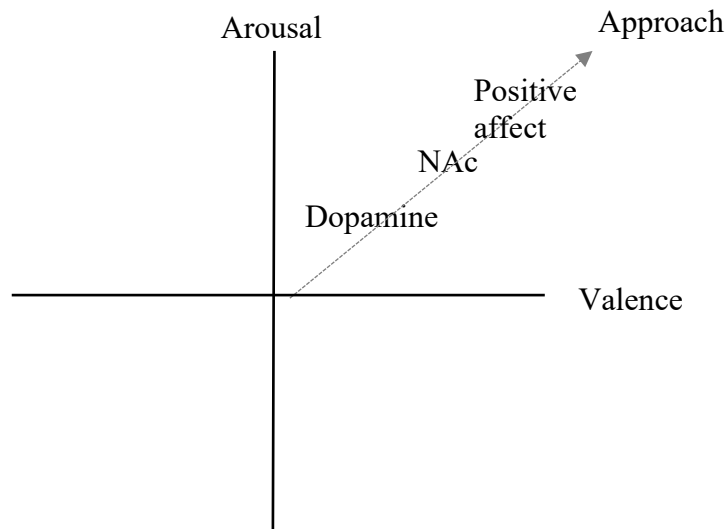
Figure 16. Proposed mapping of the levels of reward motivation. Adapted with permission from "Inferring Affect from fMRI Data" by B. Knutson, K. Katovich & G. Suri, G., 2014, *Trends in Cognitive Sciences, 18*(8), p. 427

Authors from positive affect (e.g., Watson et al., 1999), behaviour and physiology (e.g., Coan & Allen, 2003; Sutton & Davidson, 1997), and neuroscience (e.g., Colibazzi et al., 2010; Gerber et al., 2008) literatures argue that measures of positive affect, approach behaviours and activation in reward-related brain regions are highly correlated phenomena. In a highly cited meta-analysis, Wager, Phan, Liberzon, and Taylor (2003) found that positive valence and approach motivation have similar region-specific mappings and lateralisation in the brain. Another meta-analysis (Knutson & Greer, 2008) reviewed studies examining the correlation between anticipatory brain activation and self-reported positive arousal (the preferred circumplex rotation by Russell & Carroll, 1999b, see Section 3.6) finding the NAc was replicably activated in anticipation stages.

This project has worked from the assumption that the measures used in each study are part of a higher order reward motivation construct (see Figure 1, Section 1.1). The primary consequence of measuring reward motivation at the level of self-reported affect, behaviour, and neuroscience is that there is no straightforward way to synthesise findings of the relationship between reward motivation and biological rhythms across the five studies. As one example, it is unclear how the psychological

components of reward fit into the levels of analysis displayed in Figure 16. There is strong evidence for the relationship between "wanting" and dopaminergic projections, and NAc activation (e.g., Peciña & Berridge, 2013; Peciña et al., 2003; Wyvell & Berridge, 2000); however, it is less clear how "liking" and learning would fit into these levels of analysis. While the present project is not able to resolve this, future work should measure reward motivation in self-report, behavioural tasks, and neural imaging to continue work in exploring the cross-sectional relationship between subjective and objective facets of reward motivation.

   11.7.2   Diurnal variation as a step towards ultimate measurement of circadian function. This section looks at considerations of using time of day as a predictor variable in Study 3 and Study 5 and using various proxies of circadian functioning in included articles in the Study 4 review. The arguments presented in Study 3, Study 4, and Study 5 made the assumption that diurnal variation is consistent with circadian variation, and evidence for the former is a first step in testing the complex prediction of evidence for the latter (Murray et al., 2009).

   A major limitation is that the endogeneity of measured diurnal rhythms (Study 3 and Study 5) and proxies for circadian function (Study 4) remain unknown. As discussed in Section 2.3, complex laboratory techniques are required to unmask the endogenous circadian component of an observed diurnal rhythm in any process, and no attempt was made to achieve this in Studies 3 and 5. Rather, Study 3 and Study 5 used a repeated measures protocol to examine diurnal variation in reward functioning under naturalistic conditions. Measuring diurnal variation is suggestive of circadian modulation (Boivin et al., 1997); however, diurnal variation is not necessarily internally generated (Murray et al., 2009). Indeed, a primary motivation of the entire field of chronobiology is to determine the extent to which any observed 24-hour rhythms in physiology, behaviour and mental states can be attributed to endogenous circadian function (e.g., Czeisler et al., 1992; Duffy et al., 2001): Reliable 24-hour rhythms could equally be generated entirely exogenously, via 24-hour cycles in the physical and social world.

   Examining circadian physiology in humans is challenging, as direct outputs of the SCN cannot be measured *and* measurable downstream circadian rhythms can be influenced by other factors (such as sleep-wake cycles and changes to light exposure; Duffy & Wright, 2005). Specific protocols are needed to unmask the

circadian rhythm from potential entraining factors (viz. zeitgebers; Dijk & Czeisler, 1994). Circadian protocols (such as forced desynchrony and constant routine protocols, see Section 2.3) are the gold standard methods for unmasking the circadian rhythm from zeitgebers and homeostatic sleep influences (Herman, 2017). Study 3 and Study 5 could have been designed in a way that attempts to unmask the circadian component of the diurnal variation in reward. For example, CBT, DLMO, and heart rate could be continuously monitored in a time-free environment with reward tasks interleaved throughout the protocol to measure the proportion of variation in reward motivation that is attributable to circadian variables. To extend the work of Study 5 the challenge of collecting neural data of a reward rhythm in time-free circadian contexts remains. Firstly, a sleep laboratory that creates a time-free environment would be needed. Secondly, this sleep laboratory would need to be built around an MRI machine, to circumvent transporting a participant from the laboratory to the MRI and potentially exposing them to time-cues. While this procedure is possible there are clearly practical and financial challenges towards unmasking a circadian rhythm in neural reward motivation.

It is therefore important to consider the findings of Study 3 and 5, and the relevant reviewed studies in Study 4, through the lens of masking factors present for diurnal rhythms. Social factors and light intensity may be important masking factors in measuring the diurnal variation of reward motivation. The likelihood of rewarding events may systematically differ with time of day, which could mask the putative circadian modulation of reward motivation in Study 3 and Study 5 (and relevant studies included in the review of Study 4). For example, the end of the day is typically associated with socialising, relaxing, and meal times. These typically rewarding events may all increase propensity to rate pleasure as higher and endorse more positive emotions later in the waking day (e.g., Stone et al., 2006). In support of the evening being a time of high rewarding events, a pair of recent studies examined self-reported wanting and liking using an experience sampling method (Itzhacki et al., 2018; te Lindert et al., 2018). After controlling for light exposure and individual differences in self-report ratings, reports of liking and wanting were highest between 18:00h and 20:00h in healthy participants; importantly subjective levels of liking and wanting increased with light intensity. Interestingly, positive mood was also measured in these studies and was found to peak at 15:14h (te Lindert

et al., 2018) and 14:15h (Itzhacki et al., 2018). te Lindert et al. (2018) suggests that wanting and liking are more sensitive to light exposure relative to positive mood adjectives. By employing laboratory protocols, the diurnal variation in reward motivation observed in Study 3 and Study 5 can be measured controlling for important zeitgebers (including light intensity, social influences, and sleep-wake cycle) to unmask the putative circadian rhythm in reward motivation.

11.7.3 Considering the possible influence of reward motivation on circadian function. A limitation of the project is that Study 3, Study 4, and Study 5 invested in a single directional pathway, viz., that circadian function modulates reward motivation. As mentioned in Section 1.1, the interaction between circadian function and reward motivation is likely to be bidirectional (Alloy, Nusslock, et al., 2015), and it is useful (for completeness) to briefly consider evidence for this reciprocal pathway. To this author's knowledge, only one study in humans provides data relevant to the question of reciprocal relations between circadian function and neural reward functioning (Hasler, Casement, et al., 2017). Hasler, Casement, et al. (2017) examined whether circadian preference mediated VS and mPFC reward response, and whether VS and mPFC, in turn, reward response mediated circadian preference. Using cross-lag panel analyses, the study found that diurnal preference predicted neural reward activation to monetary reward receipt in the mPFC and VS two years later. Cross-lag associations between neural reward receipt predicting circadian preference, was not significant. No longitudinal relationship between circadian preference, VS, and mPFC activation was observed for reward anticipation.

Other outputs of the circadian system such as social rhythms, may be mediated by reward motivation. For example, volitional reward-seeking behaviour may disrupt circadian rhythms through zeitgebers (Alloy, Nusslock, et al., 2015). As discussed in Section 4.5, Alloy and colleagues (Alloy et al., 2017; Grandin et al., 2006) argue that reward-activating (e.g., job promotion) and reward-deactivating (e.g., divorce) life events tend to precede mood symptoms in bipolar disorders. Following, reward-activating or reward-deactivating events may mediate social rhythm disruption. In the social zeitgeber theory, social rhythm disruption may occur through loss of zeitgeber inputs such as neglect of routines (Alloy, Nusslock, et al., 2015). In a longitudinal study, Boland et al. (2015) recruited participants with no

diagnosis of bipolar spectrum disorders with high BAS ($n = 119$) and moderate BAS ($n = 85$) and measured BAS-activating and BAS-deactivating life events, and the social rhythm disruption of these events. At an average of 8.4 months follow-up, participants completed a measure of depressive and manic symptoms. Boland et al. (2015) found that individuals with high BAS levels experienced more BAS-relevant life events and had an increased social rhythm disruption to these events relative to moderate levels of BAS. In the path analysis, increased BAS-relevant events and resultant social rhythm disruption led to increased manic and depressive symptoms. In sum, the findings of Boland et al. indicate that BAS-relevant life events and social rhythm disruption may have important interrelationships that affect depressive and manic symptoms longitudinally, providing evidence of a circadian influence (social rhythm disruption) by reward motivation (BAS-relevant events). More longitudinal work is now needed in both clinical and healthy populations to better understand the pathways between circadian rhythms and reward motivation.

11.8   Integration

Three observations are made here which highlight some of the shared implications of the studies in the current project. This integrative section begins by considering potentially conflicting results in circadian modulation of reward receipt and liking (12.8.1.), followed by an examination of the potential clinical implications of the present project (12.8.2.), and an important implication of controlling for time of day in reward paradigms is outlined (12.8.3).

11.8.1   Measuring liking and reward receipt in a circadian context.

"Wanting" and "liking" are potentially measurable through reward anticipation and reward receipt in neuroimaging studies (see Section 11.5). In Study 4 the qualitative synthesis of findings from fMRI studies concluded that circadian modulation of reward receipt (i.e., unconscious "liking") was seen in the literature. However, the empirical data in Study 3 found no evidence of diurnal variation in self-reported conscious liking. Two potential explanations for this tension can be proposed.

Firstly, the two measures of liking in Study 3 (self-reported positive emotions and ratings of *pleasantness* to positive images) were intended to measure conscious liking, whereas fMRI activation during reward receipt may capture unconscious "liking". While it is also possible that the fMRI activation may capture conscious liking, reward receipt is generally suggested to capture "liking" (with quotation

marks) in event-related fMRI studies (e.g., Hasler, Casement, et al., 2017; Hasler et al., 2013; O'Doherty et al., 2002). This explanation suggests that conscious liking and unconscious "liking" may, at least to some extent, be separate processes. Kringelbach and Berridge (2009) have suggested that "liking" and liking can be separated at the neural level. Conscious liking may include brain circuitry of the cortical OFC, ACC, and insular regions, while unconscious "liking" is thought to involve circuitry including the subcortical NAc, ventral pallidum, periaqueductal gray, and amygdala (Kringelbach & Berridge, 2009). It is possible that the brain structures that support circadian modulation of "liking" either (a) do not exist for conscious liking, or (b) are not accessible using the methods of self-reported pleasantness and positive emotions.

A second explanation for finding evidence for circadian modulation of "liking" (Study 4) but not liking (Study 3) attributes the tension to the influence of other factors on the circadian system. As discussed in Section 11.7.2, time of day factors may affect recall of liking, external to the outputs of the biologically-driven endogenous circadian system. Visual inspection of the Figure 8c and 8d in Study 3 showed that both liking tasks increased across the day (10:00h < 14:00h < 19:00h). This is consistent with recent findings that showed an increase in liking in an experience sampling study (Itzhacki et al., 2018; te Lindert et al., 2018). Further work is now needed to investigate whether diurnal variation is different for unconscious "liking" from conscious liking. A preliminary step needed is administering tasks of liking in the fMRI (e.g., viewing IAPS images in the fMRI and rating the pleasantness of images) to examine whether, when measured at different levels of reward motivation, there is circadian modulation of reward "liking" and liking.

11.8.2   Clinical implications of circadian modulation of reward motivation. The diurnal variation in reward motivation observed in Study 3 and Study 5 may have clinical implications (see also Section 11.2.4). A range of evidence supports that abnormal circadian function of some form is part of the aetiological pathway to bipolar disorder (e.g., Alloy et al., 2017; Murray & Harvey, 2010; J. Scott et al., 2016). A downstream manifestation of this disturbance may be decreased amplitude of the 24-hour activity rhythm (Bullock & Murray, 2014; J. Scott et al., 2016; J. Scott et al., 2017).

Lowered amplitude of the 24-hour activity rhythm is often conceptualised as representing decreased stability in core circadian rhythms, or the circadian signal from the SCN itself (Aschoff & Pohl, 1978; Dosseville et al., 2013; Mairesse et al., 2014). Therefore, social perturbations that disturb this already vulnerable circadian system are hypothesised to increase the likelihood of a mood episode in those with bipolar disorder (E. Frank et al., 2014; E. Frank et al., 2007; E. Frank et al., 2000). Decreased circadian amplitude (measured through melatonin levels and CBT) has also been observed in individuals dependent on alcohol (see Hasler, Smith, et al., 2012 for a review). Chronic alcohol use may also disrupt circadian rhythms through attenuating the phase-resetting response to light. Two animal studies (Brager, Ruby, Prosser, & Glass, 2010; Ruby, Brager, DePaul, Prosser, & Glass, 2009) found that chronic alcohol administration attenuated the phase response to a light-pulse relative to water controls in hamsters (Ruby et al., 2009) and mice (Brager et al., 2010). Given these results, it is possible that diurnal variation in individuals with alcohol use disorder and bipolar disorder may display a diminished amplitude and disrupted circadian phases, relative to healthy controls. Thus, now that diurnal variation has been observed in behavioural (wanting and "wanting", Study 3) and neural reward regions (left putamen, Study 5), future work would benefit from sampling clinical group(s) to interrogate whether diurnal variation is altered in behavioural and neural reward motivation. Based on the findings of Study 3, future work should be mindful that diurnal variation may differ across the psychological components of reward.

11.8.3   Accounting for diurnal variation in studies of reward motivation. Tangential to the questions of this project, it is worth noting that data collected in Study 3, Study 4, and Study 5 point to the importance of accounting for time of day in studies examining reward parameters. Study 3 provided some evidence that accounting for diurnal variation may be particularly relevant to "wanting" and wanting components of reward seeking (i.e., diurnal variation was observed in "wanting" and wanting peaking at 14:00h). Study 4 reviewed a number of studies that found diurnal variation in reward-relevant regions (i.e., activation in the VS and putamen displayed diurnal variation, although the pattern of this diurnal waveform is unresolved, see Section 11.5), and Study 5 concluded that circadian priming might lead to a decreased neural response when rewards are accrued at expected times of day (i.e., a circadian prediction error, see Section 11.6). Irrespective of the direction

of the waveform, the data from Study 3, Study 4, and Study 5 suggests that a proportion of the reward response is accounted for by diurnal variation. Consistent with conclusions drawn by other researchers' (e.g., Hasler, Forbes, et al., 2014; Keith et al., 2013), future work looking at reward function are strongly encouraged to control experimentally (or at least statistically) for this factor.

11.9   Summary and Conclusions

The present project adds multiple pieces of additional evidence to the existing evidence for relationships between biological rhythm function and reward motivation in humans. Study 1 reviewed articles suggesting a relationship between biological rhythms and reward motivation considering four pathways: circadian modulation of positive affect, sleep modulation of next day positive affect, a daytime positive affect modulation of sleep quality, and biological rhythm dysfunction in bipolar disorder. Compared to sleep modulation of next day positive affect, the effect of positive affect on sleep quality was relatively weaker. Study 2 psychometrically quantified the separation of sleep quality, diurnal preference, and mood that led to the creation (Study 2a) and validation (Study 2b) of the SCRAM questionnaire with Morningness, Good Sleep, and Depressed Mood scales. The quick to administer questionnaire captures three clinically important processes and reminds clinicians to consider sleep quality, diurnal preference, and mood in treatment planning. Study 3 examined Berridge and colleagues' three psychological components of reward in a circadian context and found that "wanting" and wanting exhibited diurnal variation peaking at 14:00h with nadirs at 10:00h and 19:00h, while liking and learning did not display diurnal variation peaking at 14:00h. Study 4 reviewed fMRI studies of circadian modulation of reward motivation and found evidence of circadian modulation of neural reward in 13 of the 15 identified studies across resting-state and task-based studies. The VS, mPFC, and DMN were the brain regions and network most consistently demonstrating circadian modulation. In event-related designs using the mPFC and VS as ROIs, there was stronger evidence of circadian modulation of reward receipt relative to reward anticipation. Finally, Study 5 tested for the presence of diurnal variation in neural reward response in a repeated-measures fMRI study. In response to a well-validated monetary reward task, neural activation in the left putamen was lowest at 14:00h and highest at 10:00h and 19:00h. The nadir at 14:00h was interpreted as a circadian prediction error with

unexpected reward at 10:00h and 19:00h leading to greater levels of neural activation relative to 14:00h.

The work in this project provides further evidence of a relationship between biological rhythms and reward motivation in non-clinical samples and generates further questions in a number of areas. The present project has generated questions in considering how reward motivation is measured. For example, is a single reward motivation construct with multiple levels of measurement across self-report, behaviour, and neural levels a valid assumption? Also, how do Berridge and colleagues' psychological components of reward relate to the ascending levels of analysis of reward motivation presented by Knutson et al. (2014) and displayed in Figure 15? Dopamine and the NAc presented in Figure 15 most strongly relate to "wanting" (e.g., Peciña & Berridge, 2013; Wyvell & Berridge, 2000); but it is less clear where "liking" and learning would fit in this circumplex. A final question that emerged from Study 3 was whether unconscious "wanting", "liking", and learning are the same processes as conscious wanting, liking, and learning?

Similarly, questions have emerged from the project regarding circadian functioning. The present project has taken the first step of observing diurnal variation which is consistent with circadian modulation of behavioural (Study 3) and neural reward functioning (Study 5); however, does this diurnal variation or reward motivation have an endogenous origin? Study 4 reviewed studies using a broad range of proxies for circadian functioning. A remaining question is: how do each of these circadian predictor variables relate to neural reward outcomes?

The project therefore adds incrementally, at a greater level of detail than previous attempts, to the putative relationships between biological rhythm function and reward motivation. Broadly, expected links were observed, with important qualifications in each case. On balance, the project encourages further research in the broad area, and the lower level questions carved out and tested in this project warrant future refinement. A more systematic program of research is needed to advance findings of the relationship between biological rhythms and reward motivation. The SCRAM questionnaire of Study 2 has important potential clinical utility but validation in clinical samples is needed. The findings of Study 3, Study 4, and Study 5 are a promising advance towards a putative circadian modulation of reward

motivation. Ongoing work will need to examine the converse pathway of a reward motivation modulation of biological rhythm functioning.

In sum, in a number of specific and concrete findings, the present project advances understanding of the relationships between biological rhythms and reward motivation. In the context of important limitations, an exciting prospect of this project is that the SCRAM questionnaire provides an incremental advance over existing measures of sleep quality, diurnal preference, and mood which treat these measures as independent. A second important finding is that diurnal variation may modulate reward motivation at behavioural and neural levels in non-clinical samples. From here, questions remain as to the utility of the SCRAM questionnaire and findings of diurnal variation of reward motivation in clinical populations, and whether the diurnal variation of reward motivation has an endogenous origin. In line with its overarching aim, the present project finds that there is evidence for the relationship between biological rhythms and reward motivation which has been tested here at multiple biobehavioural levels. Future work should examine the clinical implications of the link between biological rhythms and reward motivation that this project's finding speak to, and basic science research should continue to interrogate the specific relationships that appear to exist between biological rhythm and reward motivation at various levels of the human system.

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Appendix A: Abbreviations and glossary of important terms

ACC, anterior cingulate cortex: Brain structure in the prefrontal cortex involved in effort-based reward decision-making

Actigraphy: A measure of the 24-hour activity rhythm

Amygdala: Brain structure, involved in emotion processes including emotional learning. Most known for role in indexing threat detection; however also activates in response to positive arousing stimuli

Amplitude: The peak-to-trough range of the observed circadian rhythm which may be measured in physiological processes such as core body temperature, melatonin, heart rate, or locomotor activity

aBART, automatic Balloon Analogue Risk Task: Across 30 trials, participants select how many times they want to pump up the balloon, with each pump earning 5 cents; if the balloon pops all winnings are forfeited and the trial ends. In the aBART, participants are told the explosion point of each balloon ranges from the 1st to the 128th pump. If the balloon does not pop, participants are told how many pumps they could have achieved for that trial. Task used to measure "wanting" in Study 3.

Biological rhythms: Circadian rhythm and sleep-wake processes

BAS, Behavioural Approach System: A system in Gray's Reinforcement Sensitivity Theory that organises behaviour in the context of reward and non-punishment, leading to approach motivation

BIS, Behavioural Inhibition System: A system in Gray's Reinforcement Sensitivity Theory that organises behaviour in the context of aversive stimuli, leading to avoidance and feelings of anxiety and worry

BOLD, Blood oxygen level dependent: fMRI technique that measures relative change to oxygenation within brain regions

Caudate: Brain structure that is part of the dorsal striatum, involved in reinforcing action in reward contexts

CES-D, Center for Epidemiologic Studies Depression Scale: The CES-D is a 20-item self-report measure of depressive symptomatology.

Chronotypes: Categorically grouped time of day preferences, most commonly divided into *morning, evening,* and *intermediate* chronotype

Circadian rhythm: Any biological process that exhibits a near 24-hour endogenous oscillation that is entrainable to the external environment

Constant routine: A protocol that unmasks the circadian system from exogenous influences by keeping participants awake for at least 24 (usually up to 60) hours, in constant light (or dark) conditions, with a controlled ambient room temperature, a semi-recumbent position and fed equally distributed, isocaloric meals

CBT, core body temperature: The internal temperature of the body which displays circadian rhythmicity and is used as a biological metric of the outputs of the circadian system (i.e., period, phase, and amplitude)

Depressed Mood: Name of a 5-item scale on the SCRAM questionnaire developed in Study 2

DLMO, dim light melatonin onset: The point at which melatonin begins to rise, as measured through levels present in saliva or plasma, typically this is 2-3 hours before habitual sleep onset

Diurnal preference: Dimensional time of day preference, ranging from higher scores on *eveningness* to higher scores on *morningness*

Diurnal rhythm: A 24-hour pattern in a physiological, behavioural or psychological variable which has not had the endogeneity of the rhythm confirmed

dlPFC, dorsolateral prefrontal cortex: Brain region in the prefrontal cortex important for engaging working memory in reward decision-making

DMN, default mode network: A network (including the mPFC and PCC) that is preferentially activated when an individual is at-rest and not performing a task

Dopamine: A neurotransmitter involved in reward-related motivation

Dorsal striatum: Area of the brain including the caudate nucleus and putamen relating to processes including integration of motor circuits, and anticipation of monetary and food rewards

Eveningness: A continuous measure of diurnal preference denoting a preference for sleep and activity at later times relative to those higher on morningness

Evening type: A dichotomous measure of chronotype denoting a preference for sleep and activity at later times relative to morning types

FFS, Fight-Flight System: A system in Gray's RST that manages behaviour in the context of an unconditioned aversive stimuli

FFFS, Fight-Flight-Freeze System: A system updated to include 'freeze' in the revised RST, upon revision this FFFS was proposed to organise behaviour in the context of all negative stimuli (conditioned and unconditioned)

Forced desynchrony: A protocol designed to uncouple the sleep homeostat process from circadian rhythms by imposing a (typically) 28-hour activity rest cycle to which the circadian oscillator cannot adapt, while still maintaining a 2/3 activity, 1/3 rest cycle

Good Sleep: Name of a 5-item scale on the SCRAM questionnaire developed in Study 2

IAPS, International Affective Picture System: A set of affective stimuli designed to separate pleasure and arousal responses. Task used to measure wanting (arousal ratings) and liking (pleasantness ratings) of positive images in Study 3.

IGT, Iowa Gambling Task: Participants select a card from one of four decks. Two decks contain greater gains but greater losses (net loss) and two decks contain smaller gains and smaller losses (net gain). Participants are explicitly told that the rewards and losses associated with each deck are not randomised, emphasising the learning component of the task. Task used to measure learning in Study 3.

Insula: A brain region in the prefrontal cortex important for indexing emotional arousal

Internal desynchrony: Abnormal phase relationship that occur when different clocks of the body are not aligned. For example, having a smaller phase angle between sleep onset and CBT minimum

ipRGC, intrinsically photoreceptive ganglion cells: Non-image forming photoreceptors containing melanopsin optimally sensitive to blue wavelengths (λ max = 479 nanometers)

IS, interdaily stability: Examines the pairing of the 24-hour activity rhythm to the broader activity pattern across time. A lower score is indicative of a relatively unstable activity rhythm across the sampling period

IV, intradaily variability: Measures the fragmentation of activity between rest and active periods. Higher fragmentation of daily activity patterns is indicative of a weaker circadian oscillator

Learning: Predictive cognitive understanding of reward reinforced by previous experience

"Liking": Unconscious hedonic association of the reward

Liking: Conscious experience of pleasure

mPFC, medial prefrontal cortex: A brain region in the prefrontal cortex important in encoding value of reward

MCTQ, Munich Chronotype Questionnaire: A questionnaire measuring actual timing of sleep-wake behaviours on work and free days

mDES, modified Differential Emotions Scale: Self-report emotion scale with 10 positive emotion adjectives (from 0 "not at all", to 4 "extremely"): amusement, awe, compassion, contentment, gratitude, hope, interest, joy, love and pride. Used to measure liking in Study 3.

MEQ, Morningness-Eveningness Questionnaire: A 19-item self-report questionnaire that measures chronotype focusing on ideal timing of sleep-wake and activity behaviours

Masking factors (circadian): Exogenous factors that obscure the true endogenous circadian component of a 24-hour rhythm

Morningness (scale): Name of a 5-item scale on the SCRAM questionnaire developed in Study 2

Morningness (construct): A continuous measure of diurnal preference denoting a preference for sleep and activity at earlier times relative to those higher on eveningness

Morning Type: A dichotomous measure of chronotype denoting a preference for sleep and activity at earlier times relative to evening types

MSF, mid-sleep on free days: Most commonly used variable derived from the MCTQ, measuring the mid-point of a sleep schedule when there are no morning commitments (e.g., work)

NA, Negative Affect: 10-item scale on the PANAS measuring negative affect, e.g., "ashamed", "irritable", "scared")

NAc, nucleus accumbens: A brain region in the VS involved in motivation and reward-seeking behaviour

OFC, orbitofrontal cortex: Brain structure in the prefrontal cortex involved in integrating motivation, sensory, and affective information to determine reward value

PA, Positive Affect: 10-item scale on the PANAS measuring positive affect, e.g., "interested", "active", "enthusiastic"

PANAS, Positive and Negative Affect Scales: The most commonly used measure to capture changes in affect

PCC, posterior cingulate cortex: Brain structure involved in attention regulation and internally directed cognition

Period: The length of one circadian cycle as measured in temporal isolation

Phase: The timing of the peaks and nadirs of an endogenous circadian process (such as core body temperature) relative to the external 24-hour time

Phase angle: The distance between a circadian rhythm (melatonin onset, CBT minimum) and timing of behavioural outputs, such as the timing of sleep or wake onset

PRC; Phase response curve: A plot of the degree and direction of a phase shift induced by zeitgebers plotted as a function of the circadian time at which the perturbation is given

PI, Primary insomnia: A sleep disorder characterised by difficulty initiating sleep, maintaining sleep, and/or early morning awakenings

Positive affect: High positive affect can be defined as positive emotional activation and strong goal-motivated engagement with the environment, whereas low positive affect is characterised by withdrawal from the environment

Prediction error: Dopaminergic signalling of the difference between reward expectations and received rewards

Primary reward: Rewards that have an innate value and are important to survival (e.g., food, shelter, procreation)

PSQI, Pittsburgh Sleep Quality Index: 10 item questionnaire that measures the quality and pattern of sleep over the past month, through seven domains: subjective sleep quality; sleep latency; sleep duration; habitual sleep efficiency; sleep disturbances; use of sleeping medication, and, daytime dysfunction

Psychological components of reward: Three dissociable components of rewards proposed by Berridge and colleagues: wanting, liking, and learning. Each component may have a conscious and unconscious component, distinguished by quotation marks: conscious wanting and unconscious "wanting", conscious liking and unconscious "liking", and conscious and unconscious learning.

Putamen: Brain region in the dorsal striatum involved in associating reward with action

RA, relative amplitude: Derived from a ratio of the most consecutively active 10 hours and least consecutively five hours in a 24-hour period. It is standardised

relative to predicted levels of total activity to normalise individual differences in activity. A higher ratio is indicative of a more robust circadian rhythm

REM, rapid eye movement: A stage of sleep characterised by paralysis of the body and rapid eye movements, involved in processing of emotional memories

Reward anticipation: During a trial it is the neural activation that occurs in the time when waiting for a reward (used in fMRI, event-related designs).

Reward motivation: Used in the present project to describe a higher order construct of reward processes

Reward receipt: During a trial it is the neural activation that occurs in the time when a reward is obtained (also called reward outcome, used in fMRI, event-related designs).

RST, Reinforcement Sensitivity Theory: A theory encompassing the biobehavioural processes (behavioural inhibition system, behavioural approach system, fight-flight system) that manages behaviour in the context of rewards and punishments.

rRST, Revised Reinforcement Sensitivity Theory: A revision to RST with minimal changes to the understanding of the behavioural approach system. Freeze was added to the fight-flight system (fight-flight-freeze system). The behavioural inhibition system was now conceptually considered to be a mediation system balancing behavioural approach – fight-flight-freeze conflicts.

SCN, suprachiasmatic nuclei: The central pacemaker that regulates the circadian rhythms of mammals, located in the anterior hypothalamus of the brain above the optic chiasm.

SCRAM, sleep circadian rhythms and mood: The questionnaire developed in Study 2

Secondary reward: Conditioned rewards that gain value through learning, most notably money

SE/SEf, sleep efficiency: Measured as a ratio of time asleep relative to time in bed

Sleep quality: A multi-component measurement of the degree to which the sleep period was restorative

Social jetlag: The shifts that occur between weekday and weekend sleep times that are largely driven by social and occupational commitments

SOL, sleep onset latency: The time taken to fall asleep

Striatum: A brain region including the dorsal and ventral striatum

Tau (τ): The length of the circadian period

TST, total sleep time: Time spent asleep

VS, ventral striatum: A brain region involved in reward processing and reward expectation

VTA, ventral tegmental area: A brain region involved in reward circuitry, with dopamine projections between the VTA and VS (particularly the NAc)

Wake maintenance zone: The circadian phase at which sleep propensity is very low coinciding with evening hours prior to melatonin onset

"Wanting": Unconscious drive towards rewards

Wanting: Conscious awareness of desire

Zeitgeber: German for *time giver*. Refers to stimuli that can entrain the circadian system to the external environment, e.g., light, food, and exercise

Appendix B: SCRAM Questionnaire

Instructions

The following questions ask about your sleep, mood and timing of daily activities.

Pick the answer which best describes you **over the past two weeks.**

		Strongly Disagree	Disagree	Somewhat Disagree	Somewhat Agree	Agree	Strongly Agree
1	I sleep soundly through the night						
2	People talk about 'morning' and 'evening' people, I'm a morning person						
3	I have lost interest in things that I used to enjoy						
4	I get very tired by 11pm						
5	I can laugh and see the funny side of things						
6	I wake up feeling refreshed, like I've had enough sleep						
7	All I want to do is cry						
8	I get the amount of sleep that I need						
9	Everything is going from bad to worse						
10	I wake up at least two hours later on a day off compared to a work day						
11	I work most efficiently before midday						
12	If I slept better at night my life would be drastically different						
13	I can't let things go, I find I ruminate a lot						
14	Waking up at 7am or earlier works really well for my natural body clock						
15	I fall asleep within 30 minutes of trying to sleep						

<u>Scoring</u>

Items 5, 10, and 12 are reverse scored.

Scores of Good Sleep, Morningness, and Depressed Mood are calculated by summing the scores for the relevant items following reverse scoring.

Good Sleep items: 1, 6, 8, 12 (R), 15

Morningness items: 2, 4, 10 (R), 11, 14

Depressed Mood items: 3, 5 (R), 7, 9, 13

Appendix C: List of preliminary item pool for SCRAM Questionnaire

1   On a day off, I struggle to sleep-in to a later time

2   If I had a task/event where I had to be at my physical, psychological and mental best
       I would want it to be between about 1-5pm

3   I feel rested when I wake up in the morning

4   To help my sleep, I am careful about when I drink coffee

5   I feel most energised and happy in the morning

6   I feel like the smallest disturbance will wake me during the night

7   I normally eat the same amount of meals at roughly the same time each day

8   I get very tired by 11pm

9   I feel drowsy after awakening, even after a good night's sleep

10   Even if things are bad now I know they're going to be better in the future

11   People know not to talk to me first thing in the morning because I'm so irritable

12   Even when good things happen I feel like nothing could make me happy

13   I usually need medicine to fall asleep at night

14   I can't predict whether I'll have a good or bad night's sleep

15   Bad dreams have caused me trouble sleeping

16   I remember more of my dreams than I used to

17   I'm so excited about everything, I feel like my thoughts are racing

18   Life is meaningless and I can't see the point in anything

19   I feel afraid, nervous or scared most of the time

20   It's been difficult for me to go to work and study

21   When sitting an exam, my peak performance time would be in the evening, after
about 5pm

22   I feel most energised and happy in the evening

23   Everything that I do takes a lot of effort

24   I feel relaxed when I go to bed at night

25   I don't feel refreshed in the morning even if I sleep well

26   I would consider myself an evening person

27   I feel most energised and happy in the afternoon

28   Using medication, alcohol or other drugs helps me get to sleep at night

29   I wake up throughout the night for no particular reason

30   I feel like I'm getting too much sleep

31   My sleep impacts on my ability to work and study during the day

32   Most days I have a nap that lasts at least 30 minutes

33   I care about my sleep

34   If I had a task/event where I had to be at my physical, psychological and mental best I would want it to be after about 5pm

35   I spend at least one and a half hours outdoors on a workday

36   My partner tells me that I disturb their sleep by snoring or other sounds and/or movements

37   When it's my usual bedtime I can't overcome sleepiness

38   I have nightmares and remember what they are about

39   I love sleeping

40   I'm satisfied with my current sleep

41   People have been saying I'm louder and more disruptive than normal

42   It takes a lot to get me angry or upset, little things don't bother me

43   I toss and turn in bed a lot

44   I can work just as easily during the day as at night

45   I would like to be more alert in the evening

46   I'm really satisfied with my sleep

47   I find it easy to find the motivation to get things done

48   Everything is going from bad to worse

49   I spend time in bed thinking about exciting things that have happened or are to come

50   I have felt much more self-confident than usual

51   I get the amount of sleep that I need

52   I worry about my sleep a lot

53   I have felt really enthusiastic, energetic and joyful

54   I can't let things go, I find I ruminate a lot

55   I don't think I'm a morning person or an evening person, I'm somewhere in the middle

56   I feel like I need a nap in the afternoon

57   I use my bed for lots of things: studying, eating, watching TV etc.

58   I can't stop thinking about whether people like me

59   I'd be more productive if I could start work later and finish later

60   The only time I use my bed is to sleep

61   I'm really satisfied with my life, things are really good

62   As soon as my head hits the pillow I'm asleep

63   I often fall asleep unintentionally or fight to stay awake during the day

64   I'd much rather start work earlier and finish earlier

65   All I want to do is cry

66   Compared to normal, I can't make simple decisions or concentrate

67   I've had restless or 'crawling' feelings in my legs at night that goes away if I move them

68   Compared to most people my age I have an early bedtime

69   I feel like I'm a burden to everyone around me

70   I feel like I am to blame for everything

71   If I've slept well it doesn't take me long to wake up

72   On holidays my sleep always drifts to later times

73   I would like to wake up earlier

74   I feel like I can't do anything without help

75   A 9-5 work-day suits me well

76   I normally leave the house at the same time each morning

77   I wake up feeling refreshed, like I've had enough sleep

78   I get enough sleep on weekdays, so I don't need to catch up on weekends

79   I look forward to seeing my friends and relatives who I care about

80   When I wake up on a day off I'm really hungry

81   I am more irritable and 'snappy' than usual

82   I'd be lucky to spend more than 30 minutes outside most days

83   If I had a task/event where I had to be at my physical, psychological and mental best I would want it to be before about 2pm

84   I sleep longer on weekends than workdays

85   I've noticed it takes me longer to fall asleep

86   Waking up at 7am or earlier works really well for my natural body clock

87   I think sleep is really important to my well-being

88   I feel so agitated and worried I can barely sit still

89   I have quite a regular schedule with work and social activities

90   When I have a day off, I would get less than 4 hours outside in daylight

91   No matter how much I eat, I'm still hungry

92   I'd describe my mood as calm and content

93   It takes me a long time to get to sleep

94   I spend a lot of time in bed at night worrying about bad things

95   I have felt so excited I can barely sit still

96   I feel so alone but I'm also pushing away people I love

97   My bedtime (including weekends) does not change by more than 2 hours

98   I have lost interest in things that I used to enjoy

99   Having regular times for daily activities helps me to sleep better

100   I don't want to be near anyone, even people who I care deeply about

101   My alarm clock is more of a safety net, I rarely need it

102   Once I fall asleep, I don't wake up throughout the night

103   When sitting an exam, my peak performance time would be in the afternoon, between about 1-5pm

104   I'm more likely to get emotional either crying or becoming irritable in the evening

105   When sitting an exam, my peak performance time would be in the morning, before about 1pm

106   I always get more sleep on the weekend

107   I feel really relaxed when I go to bed at night

108   I've been thinking I'm more important, talented and special than other people

109   I feel confident and secure in my relationships

110   I have found it really difficult to concentrate because I'm so sad

111   I fall asleep within 30 minutes of trying to sleep

112   I would struggle to stay awake until 1am

113   I have a lot of variation in what time I go to bed and wake up each day

114   I am worried that I will lose control over my sleep

115   My meal times vary dramatically, there are no set times

116   I'm relaxed and easy-going

117   I wake up at least two hours later on a day off compared to a work day

118   People see me as optimistic and cheery

119   I've been told I snore a lot

120   My sleep benefits from waking up at about the same time each day

121   If I had to stay up all night I could function the next day better than most

122   I think my sleep quality is awful

123   I could easily fall into a pattern of later bedtimes if I let myself

124   I don't understand people who 'snooze', when I wake up I'm awake

125   I've been thinking about sex more frequently than normal

126   I don't think much about sleep

127   I have no appetite at the moment

128   Sleeping badly one night means I'll sleep badly all week

129   If I do exercise I prefer it to be first thing in the morning

130   If I have work and study to catch up on, I'd rather wake up early than work late

131   Sleep is really low on my priority list

132   I've been patient with people whose words or actions are irritating

133   I can laugh and see the funny side of things

134   I feel lonely, down-hearted and blue

135   Exercising is part of my routine

136   I am so tired that I struggle to stay awake for meals, driving and social occasions

137   When I sleep badly I need to catch up the next day by napping or sleeping longer the next night

138   I'm particularly sensitive to any rejection or criticism

139   I feel like my future is hopeless and it will just get worse

140   I feel like I am in control of my sleep

141   I get really upset over little things

142   External factors (such as light, noise or temperature) make it really difficult for me to fall asleep

143   People say I'm easily distracted and that it's difficult to follow my train of thought

144   I always need an alarm clock to wake up in the morning

145   I don't enjoy eating in the morning, if I do it's out of habit

146   If I wake at 9am I would feel sluggish, slowly warming up throughout the day

147   I feel alert and most energetic in the morning, over the day my energy runs out

148   I have felt that others would be better off if I were dead

149   I think I'm most alert first thing in the morning

150   I can't manage the negative consequences of poor sleep

151   I feel weighed down, like I'm doing everything in slow-motion

152   People talk about 'morning' and 'evening' people, I'm a morning person

153   I sleep soundly through the night

154   When I go to bed at night I feel really calm

155   When I have a day off the following day I always stay up later

156   I can't schedule meetings or classes in the morning as I worry I'll sleep through them

157   I feel like I have really disturbed sleep at night

158   If I nap during the day I sleep badly that night

159   Sleep is a really important part of my life

160   I have a really depressed mood

161   I hate myself

162   7 hours sleep is more than enough for me

163   I stay up a lot later when I have no commitments the following day

164   I have been feeling unusually good, cheerful, or happy

165   I'm not willing to change my sleep during the week if it means I can't stay up as late on weekends

166   Some participants don't read questionnaires carefully, please select 'agree' for this question*

167   I have to set multiple alarms each morning

168   I feel more irritable, hostile and angry than normal

169   If I slept better at night my life would be drastically different

170   I work most efficiently before midday

171   When I've slept badly, I can hardly function the next day

*Please note this item was used as a validity question to measure mindless responding in participants

Appendix D: Certificates of ethical approval

To: Prof. Greg Murray

SHR Project 2014/170   Measuring sleep, circadian rhythm and mood function: The SCRAM Questionnaire
Prof. Greg Murray, Mr Jamie Byrne, Dr Ben Bullock - FHAD
Approved duration: 28-08-2014 to 31-03-2016 [adjusted]

I refer to the ethical review of the above project protocol by Swinburne's Human Research Ethics Committee (SUHREC). Your responses to the review, as emailed on 26 August 2014 with several attachments, were put to the Committee delegate for consideration.

I am pleased to advise that, as submitted to date, ethics clearance has been given for the above project to proceed in line with standard on-going ethics clearance conditions outlined below. In issuing this clearance, the understanding is that research or funding agreements entered into to cover the research are in accord with the research protocol submitted for ethical review.

-   All human research activity undertaken under Swinburne auspices must conform to Swinburne and external regulatory standards, including the *National Statement on Ethical Conduct in Human Research* and with respect to secure data use, retention and disposal.

-   The named Swinburne Chief Investigator/Supervisor remains responsible for any personnel appointed to or associated with the project being made aware of ethics clearance conditions, including research and consent procedures or instruments approved. Any change in chief investigator/supervisor requires timely notification and SUHREC endorsement.

-   The above project has been approved as submitted for ethical review by or on behalf of SUHREC. Amendments to approved procedures or instruments ordinarily require prior ethical appraisal/clearance. SUHREC must be notified immediately or as soon as possible thereafter of (a) any serious or unexpected adverse effects on participants and any redress measures; (b) proposed changes in protocols; and (c) unforeseen events which might affect continued ethical acceptability of the project.

-   At a minimum, an annual report on the progress of the project is required as well as at the conclusion (or abandonment) of the project. Information on project monitoring, self-audits and progress reports can be found at:
    http://www.research.swinburne.edu.au/ethics/human/monitoringReportingChanges/

-   A duly authorised external or internal audit of the project may be undertaken at any time.

Please contact the Research Ethics Office if you have any queries about on-going ethics clearance, citing the project number. Please retain a copy of this email as part of project record-keeping.

Best wishes for the project.

Yours sincerely.
Astrid Nordmann
Secretary, SUHREC

Dr Astrid Nordmann

To: Prof. Greg Murray, BPSRC

Dear Greg,

SHR Project 2014/211 Circadian rhythms and reward activation
Prof. Greg Murray, Mr Jamie Byrne (Student), Prof. Susan Rossell, Dr Mathew Hughes - BPSRC
Approved duration: 07-10-2014 to 07-10-2016

I refer to the ethical review of the above project protocol by Swinburne's Human Research Ethics Committee (SUHREC). Your responses to the review, as emailed on 22 September 2014 (with several attachments), and additional responses sent on 06 October 2014, were put to the Committee delegate for consideration.

I am pleased to advise that, as submitted to date, ethics clearance has been given for the above project to proceed in line with standard on-going ethics clearance conditions outlined below. In issuing this clearance, the understanding is that research or funding agreements entered into to cover the research are in accord with the research protocol submitted for ethical review.

- All human research activity undertaken under Swinburne auspices must conform to Swinburne and external regulatory standards, including the *National Statement on Ethical Conduct in Human Research* and with respect to secure data use, retention and disposal.

- The named Swinburne Chief Investigator/Supervisor remains responsible for any personnel appointed to or associated with the project being made aware of ethics clearance conditions, including research and consent procedures or instruments approved. Any change in chief investigator/supervisor requires timely notification and SUHREC endorsement.

- The above project has been approved as submitted for ethical review by or on behalf of SUHREC. Amendments to approved procedures or instruments ordinarily require prior ethical appraisal/clearance. SUHREC must be notified immediately or as soon as possible thereafter of (a) any serious or unexpected adverse effects on participants and any redress measures; (b) proposed changes in protocols; and (c) unforeseen events which might affect continued ethical acceptability of the project.

- At a minimum, an annual report on the progress of the project is required as well as at the conclusion (or abandonment) of the project. Information on project monitoring, self-audits and progress reports can be found at:
  http://www.research.swinburne.edu.au/ethics/human/monitoringReportingChanges/

- A duly authorised external or internal audit of the project may be undertaken at any time.

Please contact the Research Ethics Office if you have any queries about on-going ethics clearance, citing the project number. Please retain a copy of this email as part of project record-keeping.

Best wishes for the project.

Yours sincerely.
Astrid Nordmann
Secretary, SUHREC

To: Prof Greg Murray, FHAD

Dear Greg

SHR Project 2015/246– Measuring sleep, Circadian rhythm and Mood Function: The SCRAM Questionnaire
Prof Greg Murray, Ms Jamie Byrne (Student), Dr Ben Bullock - FHAD
Approved Duration: 22-09-2015 to 31-09-2017 [Adjusted]

I refer to the ethical review of the above project revised protocol by a Subcommittee (SHESC1) of Swinburne's Human Research Ethics Committee (SUHREC). Your responses to the review, as emailed on 16 September 2015 with attachments, were put to the Subcommittee delegates for consideration.

I am pleased to advise that, as submitted to date, the project may proceed in line with standard on-going ethics clearance conditions here outlined.

- All human research activity undertaken under Swinburne auspices must conform to Swinburne and external regulatory standards, including the current *National Statement on Ethical Conduct in Human Research* and with respect to secure data use, retention and disposal.

- The named Swinburne Chief Investigator/Supervisor remains responsible for any personnel appointed to or associated with the project being made aware of ethics clearance conditions, including research and consent procedures or instruments approved. Any change in chief investigator/supervisor requires timely notification and SUHREC endorsement.

- The above project has been approved as submitted for ethical review by or on behalf of SUHREC. Amendments to approved procedures or instruments ordinarily require prior ethical appraisal/clearance. SUHREC must be notified immediately or as soon as possible thereafter of (a) any serious or unexpected adverse effects on participants any redress measures; (b) proposed changes in protocols; and (c) unforeseen events which might affect continued ethical acceptability of the project.

- At a minimum, an annual report on the progress of the project is required as well as at the conclusion (or abandonment) of the project. [Information] on project monitoring and variations/modifications, self-audits and progress reports can be found on the Research Intranet pages.

- A duly authorised external or internal audit of the project may be undertaken at any time.

Please contact the Research Ethics Office if you have any queries about on-going ethics clearance. The SHR project number should be quoted in communication. Researchers should retain a copy of this email as part of project recordkeeping.

Best wishes for the project.

Yours sincerely,

To: Prof. Greg Murray, BPSRC

Dear Greg,

SHR Project 2014/211 Circadian rhythms and reward activation
Prof. Greg Murray, Mr Jamie Byrne (Student), Prof. Susan Rossell, Dr Mathew Hughes - BPSRC
Approved duration: 07-10-2014 to 07-10-2016; Modified October 2014 (x2), December 2014, March 2016.

I refer to your e-mail of 08 March 2016 in which you requested a modification to the project by recontacting participants and asking them to complete two additional questionnaires. The documentation was reviewed by a SUHREC delegate.

I am pleased to advise that, as modified to date, the project/protocol may continue in line with standard ethics clearance conditions previously communicated and reprinted below.

Please contact me if you have any queries about on-going ethics clearance, citing the SUHREC project number.   Copies of clearance emails should be retained as part of project record-keeping.

As before, best wishes for the project.

Kind regards,
Astrid Nordmann

Appendix E: Author indication forms

Swinburne Research

Authorship Indication Form
For PhD (including associated papers) candidates

NOTE

This Authorship Indication form is a statement detailing the percentage of the contribution of each author in each associated 'paper'. This form must be signed by each co-author and the Principal Coordinating Supervisor. This form must be added to the publication of your final thesis as an appendix. Please fill out a separate form for each associated paper to be included in your thesis.

DECLARATION

We hereby declare our contribution to the publication of the 'paper' entitled:

Positive affect and biological rhythms: Interactions in general population and clinical samples

First Author

Name: Jamie Byrne   Signature:

Percentage of contribution: 80%   Date: 22/6/2018

Brief description of contribution to the 'paper' and your central responsibilities/role on project:

 Wrote the first draft of the manuscript

Second Author
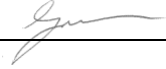
Name: Greg Murray   Signature:

Percentage of contribution: 20%   Date: 22 / 06 / 2018

Brief description of your contribution to the 'paper':

 Provided supervisory input into the manuscript

Principal Coordinating Supervisor: Name: Greg Murray   Signature:

Date: 22 / 06 / 2018

Swinburne Research

Authorship Indication Form
For PhD (including associated papers) candidates

DECLARATION

We hereby declare our contribution to the publication of the 'paper' entitled:

Development of a Measure of Sleep, Circadian Rhythms, and Mood: The SCRAM Questionnaire

First Author

Name: Jamie Byrne   Signature:

Percentage of contribution: 80%   Date: 22/6/2018

Brief description of contribution to the 'paper' and your central responsibilities/role on project:

 Contributed to the design of the study, collected and analysed the data, wrote the first draft of the manuscript

Second Author

Name: Ben Bullock   Signature:

Percentage of contribution: 5%   Date: 22 / 06 / 2018

Brief description of your contribution to the 'paper':

 Contributed to the design of the study, provided supervisory input into the manuscript

Third Author

Name: Greg Murray   Signature:

Percentage of contribution: 15   %   Date: 22 / 06 / 2018

Brief description of your contribution to the 'paper':

 Contributed to the design of the study, provided supervisory input into the manuscript

Principal Coordinating Supervisor: Name: Greg Murray   Signature:

Date: 22 / 06 / 2018

Swinburne Research

Authorship Indication Form
For PhD (including associated papers) candidates

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DECLARATION

We hereby declare our contribution to the publication of the 'paper' entitled:

A psychometric investigation of the SCRAM questionnaire

First Author

Name: Jamie Byrne   Signature:

Percentage of contribution: 80%   Date: 2 / 11 / 2018

Brief description of contribution to the 'paper' and your central responsibilities/role on project:

Contributed to the design of the study, contributed to data collection, and analysed the data, wrote the first draft of the manuscript

Second Author
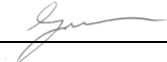
Name: Ben Bullock   Signature:

Percentage of contribution: 5%   Date: 2 / 11 / 2018

Brief description of your contribution to the 'paper':

Provided supervisory input into the manuscript

Third Author

Name: Aida Brydon   Signature:

Percentage of contribution: 5%   Date: 2 /11 / 2018

Brief description of your contribution to the 'paper':

Contributed to data collection

Fourth Author

Name: Greg Murray   Signature:

Percentage of contribution: 10   %   Date: 2 / 11 / 2018

Brief description of your contribution to the 'paper':

Contributed to the design of the study, provided supervisory input into the manuscript

Principal Coordinating Supervisor: Name: Greg Murray   Signature:

Date: 22 / 06 / 2018

Authorship Indication Form   1 of 1

Swinburne Research

Authorship Indication Form
For PhD (including associated papers) candidates

NOTE

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DECLARATION

We hereby declare our contribution to the publication of the 'paper' entitled:

A psychometric investigation of the SCRAM questionnaire

First Author

Name: Jamie Byrne   Signature:

Percentage of contribution: 80%   Date: 22/6/2018

Brief description of contribution to the 'paper' and your central responsibilities/role on project:

 Contributed to the design of the study, collected and analysed the data, wrote the first draft of the manuscript

Second Author

Name: Ben Bullock   Signature:

Percentage of contribution: 5%   Date: 22 / 06 / 2018

Brief description of your contribution to the 'paper':

Provided supervisory input into the manuscript

Third Author

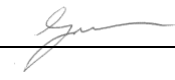Name: Greg Murray   Signature:

Percentage of contribution: 15   %   Date: 22 / 06 / 2018

Brief description of your contribution to the 'paper':

 Contributed to the design of the study, provided supervisory input into the manuscript

Principal Coordinating Supervisor: Name: Greg Murray   Signature:

Date: 22 / 06 / 2018

Swinburne Research

Authorship Indication Form
For PhD (including associated papers) candidates

NOTE

This Authorship Indication form is a statement detailing the percentage of the contribution of each author in each associated 'paper'. This form must be signed by each co-author and the Principal Coordinating Supervisor. This form must be added to the publication of your final thesis as an appendix. Please fill out a separate form for each associated paper to be included in your thesis.

DECLARATION

We hereby declare our contribution to the publication of the 'paper' entitled:

Diurnal rhythms in psychological reward functioning in healthy young men: 'Wanting', liking, and learning

First Author

Name: Jamie Byrne   Signature:

Percentage of contribution: 80%   Date: 22/6/2018

Brief description of contribution to the 'paper' and your central responsibilities/role on project:

Contributed to the design of the study, collected and analysed data, wrote the first draft of the manuscript

Second Author

Name: Greg Murray   Signature:

Percentage of contribution: 20%   Date: 22 / 06 / 2018

Brief description of your contribution to the 'paper':

Contributed to the design of the study, provided supervisory input into the manuscript

Principal Coordinating Supervisor: Name: Greg Murray   Signature:

Date: 22 / 06 / 2018

Swinburne Research

Authorship Indication Form
For PhD (including associated papers) candidates

DECLARATION

We hereby declare our contribution to the publication of the 'paper' entitled:

The sleep and circadian modulation of neural reward pathways: A protocol for a pair of systematic reviews

First Author

Name:___Jamie Byrne_____ Signature: _____

Percentage of contribution: 80%   Date: 22/6/2018

Brief description of contribution to the 'paper' and your central responsibilities/role on project:

 Contributed to the design of the review, wrote the first draft of the manuscript

Second Author

Name:_Greg Murray_____ Signature: _____

Percentage of contribution: 20%   Date: 22 / 06 / 2018

Brief description of your contribution to the 'paper':

 Contributed to the design of the review, provided supervisory input into the manuscript

---

Principal Coordinating Supervisor: Name:_Greg Murray_____ Signature:_____

Date: 22 / 06 / 2018

Swinburne Research

Authorship Indication Form
For PhD (including associated papers) candidates

DECLARATION

We hereby declare our contribution to the publication of the 'paper' entitled:

Circadian modulation of reward function: Is there an evidentiary signal in existing neuroimaging studies?

First Author

Name: Jamie Byrne   Signature: _____

Percentage of contribution: 80%   Date: 22/6/2018

Brief description of contribution to the 'paper' and your central responsibilities/role on project:

Contributed to the design of the review, searched and screened the articles, data extraction, quality evaluation, wrote the first draft of the manuscript

Second Author

Name: Hailey Tremain   Signature: _____

Percentage of contribution: 4%   Date: 22 / 06 / 2018

Brief description of your contribution to the 'paper':

Screened the articles, data extraction, quality evaluation, provided intellectual input into the manuscript

Third Author

Name: Nuwan Leitan   Signature: _____

Percentage of contribution: 4%   Date: 22 / 06 / 2018

Brief description of your contribution to the 'paper':

Contributed to the design of the review, provided intellectual input into the manuscript

Fourth Author

Name: Charlotte Keating   Signature: _____

Percentage of contribution: 4%   Date: 22 / 06 / 2018

Brief description of your contribution to the 'paper':

Provided intellectual input into the manuscript

Fifth Author

Name: Sheri Johnson   Signature:

Percentage of contribution: 4%   Date: 22 / 06 / 2018

Brief description of your contribution to the 'paper':

Provided intellectual input into the manuscript

Sixth Author

Name: Greg Murray   Signature:

Percentage of contribution: 4%   Date: 22 / 06 / 2018

Brief description of your contribution to the 'paper':

Contributed to the design of the review, provided supervisory input into the manuscript

Principal Coordinating Supervisor: Name: Greg Murray   Signature:

Date: 22 / 06 / 2018

Swinburne Research

Authorship Indication Form

For PhD (including associated papers) candidates

DECLARATION

We hereby declare our contribution to the publication of the 'paper' entitled:

Time of day differences in neural reward functioning in healthy young men

First Author

Name: Jamie Byrne   Signature:

Percentage of contribution: 80%   Date: 22/6/2018

Brief description of contribution to the 'paper' and your central responsibilities/role on project:

 Contributed to the design of the study, collected and contributed to analysis of the data, wrote the first draft of the manuscript

Second Author

Name: Matthew Hughes   Signature:

Percentage of contribution: 5%   Date: 22 / 06 / 2018

Brief description of your contribution to the 'paper':

 Contributed to the design of the study, fMRI analyses, provided intellectual input into the manuscript

Third Author

Name: Susan Rossell   Signature:

Percentage of contribution: 5%   Date: 22 / 06 / 2018

Brief description of your contribution to the 'paper':

 Contributed to the design of the study, collected data, provided intellectual input into the manuscript

Fourth Author

Name: Sheri Johnson   Signature:

Percentage of contribution: 5%   Date: 22 / 06 / 2018

Brief description of your contribution to the 'paper':

Contributed to the design and interpreting of the findings of the paper

Fifth Author

Name: Greg Murray   Signature:

Percentage of contribution: 5%   Date: 22 / 06 / 2018

Brief description of your contribution to the 'paper':

Contributed to the design of the study, provided supervisory input into the manuscript

Principal Coordinating Supervisor: Name: Greg Murray   Signature:

Date: 22 / 06 / 2018

Appendix F: Copyright waivers

I warrant that I have obtained, where necessary, permission from the copyright owners to use any third party copyright material reproduced in the thesis (such as artwork, images, unpublished documents), or to use any of my own published work (such as journal articles) in which the copyright is held by another party (such as publisher, co-author).

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