The influence of threat-induced anxiety on inhibitory control, sustained brain responses, and the changes associated with impulsivity and addiction

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Abstract

Anxiety and self-control are two features of many mental disorders. Yet these features are not often studied in experimental settings. The threat-of-shock procedure is a reliable way to induce anxiety. However, this procedure has not been used to assess the neuroelectrophysiological correlates of sustained anxiety in a way that is independent of task demands. Further, this procedure has not been fully applied to explore how anxiety and self-control (e.g., response inhibition and trait impulsivity) interact. Overall, the aim of the present thesis is to establish an understanding of how two key features of mental disorders (anxiety and self-control) interact and to explore this interaction in a disorder characterised by both features (addiction).

First, the influence of anxiety on response inhibition was explored. Previous evidence has shown that early sensory-perceptual processing is facilitated by induced anxiety, which often comes at the expense of later processing. Response inhibition sits in a unique position between early motor action and high order cognitive processes. Similarly, response inhibition is thought to involve the right inferior frontal gyrus (IFG), which sits anatomically between the stimulus-driven and goal-directed attention systems. The thesis reports on the behavioural and neurobiological changes relating to the relationship between induced anxiety and response inhibition, using the Stop-signal Task, and found that inhibitory performance was impaired by threat-induced anxiety. This impaired performance was underpinned by the disruption of key prefrontal cortex (PFC) regions that are involved in response inhibition, such as the right IFG.

Next, sustained oscillatory changes were monitored during threatening and non-threatening conditions across several passive and active tasks, providing a detailed picture of the neuroelectrophysiological changes that are associated with state anxiety. The results showed a robust reduction in beta power over the sensorimotor areas and right

frontal areas during sustained anxiety, which was interpreted to reflect a readiness for action. Further, there was a reduction in alpha power within the thalamus and the left intraparietal sulcus (IPS), thought to reflect changes in early sensory perception and sustained attention.

Next, the relationship between trait impulsivity and anxiety-induced impairments in response inhibition was explored. Previous literature has been unable to identify a clear relationship between behavioural and self-reported measures of self-control. However, a narrower measure of impulsivity and matching behavioural conditions to trait measures may reveal a relationship. Negative urgency, which reflects impulsive action during times of negative affect was significantly related to response inhibition (reflecting impulsive action) during induced anxiety (reflecting negative affect). These results showed that behavioural and self-report measures of impulsivity are related when their characteristics are aligned.

Finally, the thesis reports on a preliminary investigation extending the threat-of-shock paradigm and Stop-signal task to a group of participants with addiction problems. Addiction is a disorder that is characterized by impaired impulse control and heightened anxiety. Previous literature has demonstrated that those with addiction problems tend to perform more poorly on response inhibition tasks. Results showed that unlike in the healthy group, those with addiction problems showed significant slowing of responses during induced anxiety. Further, they did not show the typical behavioural adjustments seen during the stop-signal task (i.e., slowing after errors). However, they tended to have better behavioural adjustment in the threat than the safe condition. The preliminary nature of this study limits fully elucidating the relationship between anxiety and self-control in

those with addiction problems. Still, it was shown that those with addiction problems engage in more cautious deliberate responding during induced anxiety, despite having marginally poorer inhibitory control. This pattern may be due to the sample being "in recovery" (having had treatment and been abstinent for at least 2 weeks). Those in recovery from addiction may be utilising strategies to improve behavioural control during times of stress.

Overall, the current thesis demonstrated that anxiety is marked by adaptive changes in brain regions associated with action readiness, sensory perception, and sustained attention. However, these adaptive changes result in poorer inhibitory control underpinned by right IFG dysfunction. Further, this anxiety-induced weakened inhibitory control is more pronounced in those with greater trait impulsivity. Finally, those in recovery from addiction seem to engage in strategies to overcome anxiety-induced weakened behavioural control.

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Declaration

I, the candidate, declare that the contents of this thesis:

1. Contains no material which has been accepted by me for the award of any other degree at any other university or equivalent institution.
2. To the best of my knowledge, contains no material previously published or written by another person except where appropriate reference is made in the thesis.
3. Discloses the relative contributions of the authors on work that is based on joint research or publications (see Appendix A).

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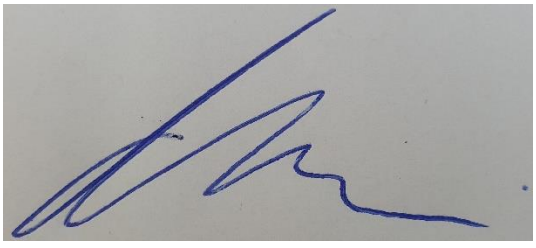
Ariel Roxburgh  12/05/2021

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Authorship Indication

I would like to acknowledge the contributions of all co-authors of the papers included in this thesis. The author indication forms for all published and submitted papers in this thesis are provided in Appendix. As demonstrated by the author indication forms, all co-authors approved the inclusion of the papers in this thesis. I confirm that the major contributions to research design, data analysis and the writing of all papers in this thesis were made by me, as indicated by my position as first author on all included papers.

List of Acronyms

SSRT	=	Stop-signal reaction time
MEG	=	Magnetoencephalography
EEG	=	Electroencephalography
SST	=	Stop-signal task
SSD	=	Stop-signal delay
IFG	=	Inferior frontal gyrus
SMA	=	Supplementary motor area
PFC	=	Prefrontal cortex
dlPFC	=	Dorsolateral PFC
AD	=	Addiction group
HC	=	Healthy control group
OFC	=	Orbitofrontal cortex
ACC	=	Anterior cingulate cortex
vmPFC	=	ventral medial PFC
UAMA	=	Uncertainty and Anticipation Model of Anxiety
BNST	=	bed nucleus of the stria terminalis
aMCC	=	anterior-medial cingulate cortex
STN	=	subthalamic nucleus
VTA	=	ventral tegmental area

ERP = Event-related potential

Chapter 1 - Introduction

Excessive anxiety is one of the most common features among the disorders listed in the DSM 5 (American Psychiatric Association, 2013). In fact, while the DSM 5 lists anxiety disorders, obsessive-compulsive disorders, and trauma and stressor-related disorders as separate categories, the DSM 4 included all these categories under 'anxiety disorders' (American Psychiatric Association, 2000). Just these three categories account for 28 different disorders and a large portion of mental health issues across the world (American Psychiatric Association, 2013; Bandelow & Michaelis, 2015). However, they are not the only disorders associated with excessive anxiety. Excessive anxiety and anxiety disorders are highly comorbid with other mental health disorders (Bandelow & Michaelis, 2015). Further, experiences of excessive anxiety often lead to worsening symptoms of other disorders such as relapse in addiction (Sinha, 2007), and verbal hallucinations in schizophrenia and other psychotic disorders (Ratcliffe & Wilkinson, 2016). Yet the study of anxiety is often limited to studying specific anxiety disorders and differences in anxious traits (Eysenck, Derakshan, Santos, & Calvo, 2007; Grupe & Nitschke, 2013), which does not fully reveal the cognitive and neurobiological changes associated with heightened states of anxiety. Recently however, more studies have begun exploring neurobiological and cognitive changes associated with the experimental induction of anxiety (Balderston, Hale, et al., 2017; O. J. Robinson, Vytal, Cornwell, & Grillon, 2013). Researching anxious states is key to our understanding of mental health problems and disorders, and this needs to be done with experimental induction to ensure findings are not subject to confounding variables (Shackman et al., 2006). For example, those with higher self-reported anxiety are likely higher on other variables that influence cognitive and neuroimaging outcomes such as quality of sleep (Alvaro, Roberts, & Harris, 2013).

Thus, non-experimental measures of anxiety are unable to disentangle anxiety-related, neural and cognitive changes from effects caused by other confounding variables. Further, the relationship between anxious states and other key features of mental health problems such as impulsivity should be explored.

Impaired self-control is another key feature of many disorders (American Psychiatric Association, 2013). Impulsivity or related terms such as 'loss of control' are mentioned as a diagnostic criterion in many mental disorders such as impulse control and addiction related disorders (e.g. gambling disorder, substance use disorder, intermittent explosive disorder, and trichotillomania); impulsive or aggressive disorders of personality (e.g. borderline, histrionic, antisocial, and narcissistic); attention deficit hyperactivity disorder (ADHD); and bipolar disorder (American Psychiatric Association, 2013; Kisa, Yildirim, & Göka, 2005). Excessive anxiety is also associated with many of these disorders (Bandelow & Michaelis, 2015). In fact, researchers are identifying concerns in the traditional category model of mental health taxonomy; noting problems with unclear boundaries between disorders and arbitrary distinctions between the normal and the pathological (Kotov et al., 2017); as well as problems in studying the disorders as a whole when compared to studying symptoms separately (Insel et al., 2010). Kotov and colleagues created and alternative model to the traditional disorder taxonomy that focuses on pathological syndromes in a more dimensional and hierarchical style. The model identifies disinhibition (related to impulsivity and compulsivity) as a key syndrome common to many of those with a mental disorder diagnosis. Given, the idea that there are key features common to many mental disorders, it is beneficial to study these features separately and their interaction. The discussed literature suggests poor self-control and anxiety are two of these key features. However, it is not clear how the two interact.

Mental disorders tend to be heterogeneous in nature (Wardenaar & de Jonge, 2013). Thus, grouping all patients in a particular category of disorder, regardless of their different pattern of symptoms, may interfere with our understanding of psychopathology (Grupe & Nitschke, 2013; Lanius, Bluhm, Lanius, & Pain, 2006; Nitschke & Heller, 2005). It is advantageous to study aspects of disorders separately, which also helps to align neuroscience findings with clinical presentations and develop targeted treatments (Insel et al., 2010). The current thesis will explore how anxiety relates to impulsivity and inhibition, which are two aspects of self-control (Bari & Robbins, 2013; Cohen & Lieberman, 2010; Dreves, Blackhart, & McBee, 2020; Gillebaart, 2018). Further, it will explore how this relationship manifests in those with addiction problems. Finally, the thesis aims to explore the neural underpinnings of these relationships and of anxiety more generally using magnetoencephalography (MEG). Anxiety is the key variable explored in this thesis and will be introduced first.

1.1 Anxiety

Anxiety can be conceptualised in several ways (Davis, Walker, Miles, & Grillon, 2010; Endler & Kocovski, 2001). However, the current thesis, which is interested in the neurobiological correlates of anxious states and on the interaction between anxiety and self-control, will focus on anxiety defined as a response to prolonged and unpredictable future threat (O. J. Robinson, Vytal, et al., 2013). This anxious response, sometimes explored by inducing anxiety in participants, is characterised by a number of physiological, psychological, and cognitive changes, such as an increase in heart rate, muscle tension, and startle reflex (Grillon, 2008). Anxiety can manifest from a real or perceived uncertain threat; for example, the knowledge that an electric shock could be delivered at random at any time (O. J. Robinson, Vytal, et al., 2013), or the belief that the individual may be judged negatively by others (Schlenker & Leary, 1982). While anxiety

is associated with deleterious consequences to individuals and society (Beddington et al., 2008; Olatunji, Cisler, & Tolin, 2007; Whiteford et al., 2013; Wittchen, 2002), the adaptive nature of anxiety has been explored by researchers highlighting its necessary role in the regulation of cognition and behaviour (Ekman & Davidson, 1994; O. J. Robinson, Vytal, et al., 2013). In the cognitive domain, anxiety can facilitate early sensory processing, which often comes at the expense of other cognitive processes (Eysenck et al., 2007; O. J. Robinson, Letkiewicz, Overstreet, Ernst, & Grillon, 2011).

The neural components of anxiety and its effects have been studied using a number of neuroimaging techniques (Andreatta et al., 2015; Coan & Allen, 2004; Cornwell, Mueller, Kaplan, Grillon, & Ernst, 2012; Grupe & Nitschke, 2013). Anxiety is associated with functional brain activity changes in many brain regions including regions associated with emotion, motor function, and cognitive, emotional, attentional, and motor control (Andreatta et al., 2015; Cornwell, Mueller, et al., 2012; Grupe & Nitschke, 2013; Klinkenberg et al., 2016). The changes in control regions such as those important for cognitive and motor control are important to consider as anxiety is thought to facilitate early processing, but this facilitation likely comes at the expense of higher order processes and functions requiring greater control both behaviourally and neurobiologically (Cornwell, Mueller, et al., 2012; Eysenck et al., 2007; O. J. Robinson, Overstreet, Charney, Vytal, & Grillon, 2013). One important function at the intersection between early and later processing is response inhibition.

This intersection between the deleterious and advantageous effects of anxiety is of interest to the current thesis and will be explored further in chapters 4 and 5. Specifically, the influence of anxiety on response inhibition will be explored in chapter 4, then the neural underpinnings of this relationship will be explored in chapter 5.

1.2 Response inhibition

Impulsivity is difficult to measure in a laboratory setting, making it hard to understand how states of anxiety and impulsivity interact at the neurobiological level. However, Bari and Robbins (2013) describe the failure of the inhibitory process as "impulsivity". A well validated way to measure the inhibitory process is through measuring attempts to inhibit motor responses, known as 'response inhibition' (Bari & Robbins, 2013). Response inhibition is the ability to suppress or interrupt pre-planned or ongoing motor activity that interfere with goal-direction (Bari & Robbins, 2013). Exploring how anxiety influences response inhibition will help reveal the broader topic of how anxiety and self-control interact. Further, induced anxiety (Balderston, Hale, et al., 2017) and response inhibition (Hege, Preissl, & Stingl, 2014) can both be manipulated or measured in a laboratory setting, while taking simultaneous brain recordings. Exploring the relationship between anxiety and response inhibition will also improve our understanding of disorders that are characterised by increased anxiety, poor impulse control, and impaired response inhibition. For instance, substance use disorders are associated with anxiety (Grant et al., 2004; Hodgson et al., 2016; Teichman, Barnea, & Rahav, 1989), greater impulsivity (Albein-Urios, Martinez-González, Lozano, Clark, & Verdejo-García, 2012; Coskunpinar, Dir, & Cyders, 2013; Kristine Rømer et al., 2018; Mitchell & Potenza, 2014; Torres et al., 2013; VanderBroek-Stice, Stojek, Beach, vanDellen, & MacKillop, 2017; Whiteside & Lynam, 2003), and impaired response inhibition (J. L. Smith, Mattick, Jamadar, & Iredale, 2014). As such, understanding the relationship between anxiety and response inhibition may improve our understanding of the mechanisms that contribute to substance use disorders and impulsivity more generally. The relationship between anxiety, self-control, and addiction will be explored in chapter 8.

1.3 Impulsivity

Before exploring addiction in chapter 8, impulsivity will be explored in chapter 7. Impulsivity is a term that describes a heterogeneous set of behaviours or traits. The definition cannot be written in a simple sentence as it has been conceptualised differently among researchers (Whiteside & Lynam, 2001). However, impulsive behaviours tend to be driven by a desire to obtain pleasure, arousal and gratification, or difficulties with patience or control (Hollander & Rosen, 2000; Whiteside & Lynam, 2001). Whiteside and Lynam (2001) note that impulsivity is the most common diagnostic criteria in the DSM after subjective distress. As such, impulsivity is important to the understanding of the influence of anxiety on mental health. One area of contention is the connection between behavioural measures of self-control such as response inhibition and self-report measures such as trait impulsivity, with some saying the two are not connected (Reynolds, Ortengren, Richards, & de Wit, 2006) and others saying they are (Wilbertz et al., 2014). Given that some aspects of impulsivity are thought to be driven by emotional states (Lynam, Smith, Cyders, Fischer, & Whiteside, 2007), chapter 7 will attempt to elucidate how the induction of anxiety might reveal the relationship between response inhibition and trait impulsivity. This will set up chapter 8, which will explore the impaired response inhibition in a disorder characterized by impulsivity; addiction, and how this relationship is influenced by induced anxiety.

1.4 Addiction

Addiction is a psychological disorder that is characterised by a loss of control (American Psychiatric Association, 2013), is associated with impaired response inhibition (J. L. Smith et al., 2014) and greater impulsivity (Mitchell & Potenza, 2014), and becomes more severe during times of stress or anxiety (S. A. Brown, Vik, Patterson, Grant, & Schuckit, 1995; Shaham, Erb, & Stewart, 2000; Sinha, 2001, 2007). Thus, what is learned through the experiments in this thesis will be extended to addiction in chapter 8.

When related to substance use, addiction is more formally known as Substance Use Disorder and is characterised by the continued use of substances despite significant substance related problems (American Psychiatric Association, 2013). However, the term "addiction" will be used in this thesis for simplicity and ease of reading. The disorder is also associated with a physiological adaption to the substance; tolerance and withdrawal, though these are not required nor sufficient for a diagnosis (American Psychiatric Association, 2013). Tolerance describes a change in the relationship between dose and effect where a higher dose is required to achieve the same effect; or similarly, a regular dose will produce diminished effects (American Psychiatric Association, 2013). Withdrawal describes a set of symptoms that occur as the concentration of a drug reduces in an individual. These withdrawal symptoms vary depending on the drug but are often distressing for the individual experiencing them (Camí & Farré, 2003). More central to the disorder are the psychological and behavioural aspects, which are categorised into three groups; risky use, social impairment, and impaired control (American Psychiatric Association, 2013). Risky use describes the continued use of a drug despite associated risks (e.g., physical harm or legal repercussions). Social impairment describes continued use despite consequences such as social disengagement and failure to fulfil social obligations (e.g., work). Finally, impaired control describes a loss of control over the consumption of drugs. For example, consuming more than intended, or unsuccessful attempts to cut down or stop (American Psychiatric Association, 2013). This 'loss of control' is often considered a key criterion for the diagnosis of a substance related disorder (American Psychiatric Association, 2013; Camí & Farré, 2003), and is often linked with impaired control during cognitive tasks (Morein-Zamir & Robbins, 2015) and has been associated with frontal lobe dysfunction (Lyvers, 2000).

Researchers have highlighted the importance of the frontal lobe for goal directed behavioural control (Beer, Shimamura, & Knight, 2004). Executive functions where the frontal lobe is implicated include, planning, motivation, rule shifting, initiating appropriate actions and inhibiting inappropriate actions (Crews & Boettiger, 2009). Lyvers (2000) and Koob and Volkow (2016) argued that frontal lobe dysfunction plays a key role in the development and maintenance of addiction. They argue that key aspects of 'volition' such as, self-control, delayed gratification, anticipation of future consequences, and selective attention are all controlled by this region. Koob and Volkow (2016) posit that, while the reward system plays a key role in the development of craving and drug seeking behaviour, frontal lobe dysfunction contributes to the 'loss of control' experienced by those with addiction. Indeed, people with addiction show structural (Ersche, Williams, Robbins, & Bullmore, 2013) and functional (Luijten et al., 2014) abnormalities in the frontal lobe. A meta-analysis demonstrated that those with stimulant dependence show reduced grey matter in the left insula, right inferior frontal gyrus, and left middle frontal gyrus (Ersche et al., 2013), which are key regions for the assessment of decision outcomes, and behavioural and cognitive control (Aron, Robbins, & Poldrack, 2004; Levy & Glimcher, 2012; Liu, Hairston, Schrier, & Fan, 2011; Medford & Critchley, 2010). While the causal nature of these abnormalities has been debated (Ersche et al., 2013), it is likely that both drug use (Yamamoto & Bankson, 2005) and addiction pre-dispositions (Ersche et al., 2012) contribute to frontal lobe abnormalities. Whether due to drug use or a pre-disposition, addiction is associated with a loss of control, which includes impaired response inhibition (J. L. Smith et al., 2014), and abnormalities in frontal inhibitory regions (Ersche et al., 2013). Thus, understanding inhibitory control and its associated neural underpinnings is an important goal for the advancement of our knowledge of substance related disorders.

Another important factor in substance related disorders is anxiety. Anxiety and addiction are both highly prevalent, chronic, and the two are highly comorbid (Grant et al., 2004). While they are considered separate disorders, there are many commonalities. Both are triggered by stress (Koob, 2009; McEwen, 2012) and have overlapping vulnerabilities and neural correlates (Avery, Clauss, & Blackford, 2016; de Graaf, Bijl, ten Have, Beekman, & Vollebergh, 2004; Kendler, Prescott, Myers, & Neale, 2003). The bed nucleus of the stria terminalis (BNST) plays a key role in the development and maintenance of anxiety and addiction disorders; playing a unique role in sustained anxiety and in withdrawal related anxiety and relapse (Avery et al., 2016). The current thesis will add to our understanding of how anxiety, addiction, and impaired self-control interact.

1.5 The relationship between anxiety, addiction, and response inhibition

1.5.1 Anxiety and inhibition

Anxiety facilitates early sensory processing but has a deleterious effect on some higher order processes (Eysenck et al., 2007; O. J. Robinson, Vytal, et al., 2013). Some argue that anxiety facilitates stimulus driven attention at the cost of impaired goal directed attention (Cornwell, Garrido, Overstreet, Pine, & Grillon, 2017; Cornwell, Mueller, et al., 2012; Eysenck et al., 2007). One process that highlights this intersection is response inhibition. When viewed in relation to early vs later cognitive process, response inhibition can be described as the ability to suppress or interrupt pre-planned or ongoing motor activity that interfere with goal-direction (Bari & Robbins, 2013). Through this lens, pre-planned or ongoing motor activity (e.g., a simple reaction to a stimulus) is governed by stimulus directed attention/processing; while the updated goal (to inhibit the

process) can be thought of as goal directed attention/processing. However, this inhibitory process is often triggered by a new stimulus. For example, a person might take a step forward but then notice a hole in the ground, so they adjust their step to avoid the hole. In this way, the line between stimulus and goal-directed processing/attention is blurred. Essentially, response inhibition happens when one process overrides the other. Indeed, Logan and Cowan (1984) described a race model where an ongoing or pre-planned response 'races' against an inhibitory response. The winner is decided by the speed and timing of each. This model has been validated by numerous studies using variations of the Stop-signal task; where participants are instructed to respond to a go-stimulus as quickly as possible; however, on a minority of trials, a stop-signal follows the go-stimulus instructing the participants to inhibit their responses (Verbruggen & Logan, 2009). While there may be some interaction between the go and the stop process, the processes are likely relatively independent (Verbruggen & Logan, 2009). Interestingly, the right inferior frontal gyrus (IFG) has been implicated as a critical node in the stopping network (Aron et al., 2004; Aron, Robbins, & Poldrack, 2014); and is anatomically situated between the stimulus (or ventral) attention and goal-directed (or dorsal) attention systems (Corbetta & Shulman, 2002; M. D. Fox, Corbetta, Snyder, Vincent, & Raichle, 2006). M. D. Fox et al. (2006) argued that although the dorsal and ventral attention systems have largely independent topography, the right IFG is a region that is correlated with both the dorsal attention system, involved in (top-down) orienting of attention, and the ventral attention system, involved in reorienting attention in response to sensory (bottom-up) stimuli. Given that anxiety is thought to facilitate stimulus driven processes while impairing goal-directed processes (Cornwell et al., 2017; Cornwell, Mueller, et al., 2012; Eysenck et al., 2007), response inhibition is an ideal process to explore the effects of anxiety upon cognitive functioning and to understand how anxiety impacts self-control.

Response inhibition sits in a unique position between processes that are typically facilitated by anxiety and those that are impaired. However, the nature of how anxiety will affect inhibitory processing is not clear, with some arguing anxiety will lead to cautious responding and thus improved inhibition (O. J. Robinson, Krimsky, & Grillon, 2013); while others, arguing that anxiety will facilitate stimulus driven responding at the expense of inhibitory control (Cornwell, Mueller, et al., 2012; Eysenck et al., 2007). While the behavioural evidence is mixed (Cornwell, Mueller, et al., 2012; O. J. Robinson, Krimsky, et al., 2013), various theories may shed light on how anxiety could affect response inhibition. Eysenck et al. (2007) suggest that early sensory processing and responses are facilitated by anxiety. If this were the case, it seems likely that response inhibition would be impaired; not because of a direct impairment, but because the thing that must be inhibited has been facilitated; making inhibition more difficult. Contrary to the hypothesis that anxiety would impair response inhibition, it is possible anxiety may lead to its facilitation. The Uncertainty and Anticipation Model of Anxiety (UAMA) describes anxious individuals as having a greater prediction of error and threat probability that manifests in the insula and dorsal medial prefrontal regions respectively (Grupe & Nitschke, 2013). This greater prediction of error and threat may facilitate the inhibition of responses as individuals slow down their responses in anticipation of inhibitory requirements. O. J. Robinson, Krimsky, et al. (2013) found improvements in response inhibition during induced anxiety, yet no change in the speed of go responses. They argued that response inhibition is improved during anxiety independently of slowed go responses. However, they note improvements may be due to increased arousal and attention (O. J. Robinson, Krimsky, et al., 2013; Torrisi et al., 2016). Conversely, the higher activity in the prefrontal regions associated with anxiety may interfere with the inhibition process, which is also thought to involve these regions (Aron, 2007).

Additionally, alterations in attention to facilitate threat detection (Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & Van Ijzendoorn, 2007) may divert attention away from a task requiring inhibition (towards threat monitoring) and lead to impaired inhibition. The impaired deployment of attentional resources and response selection mediated by anterior mid-cingulate cortex (aMCC; Shackman, Salomons, et al., 2011) may also lead to impaired response inhibition during the Stop-signal task. Evidence for impaired inhibition during induced anxiety is found in a mixed saccade task (Cornwell, Mueller, et al., 2012), where participants responded with saccadic eye movements more quickly to peripherally presented stimuli. However, inhibiting eye movements and instead looking away from stimuli is impaired. It is clear there is evidence and theoretical arguments supporting contrary ideas (that response inhibition is facilitated and that it is impaired by induced anxiety) making it difficult to determine the influence of induced anxiety on response inhibition. The relationship between anxiety and response inhibition will be explored further in chapter 4.

1.5.2 Anxiety, impulsivity, and response inhibition

Understanding the relationship between anxiety and response inhibition will improve our understanding of how cognitive processes are altered during anxious states; however, the link between response inhibition and pathological impulsivity must also be established to argue the relevance of this relationship to an argument about anxiety and self-control more generally. Firstly, it is noted that response inhibition is generally impaired in those with disorders of impulse control such as ADHD, OCD, and addiction (Chamberlain & Sahakian, 2007). It is also established that anxiety and stress worsen the symptoms of these disorders (Adams et al., 2018; Combs, Canu, Broman-Fulks, Rocheleau, & Nieman, 2012; Sinha, 2007). Finally, there is some evidence that anxiety impairs response inhibition (Cornwell, Mueller, et al., 2012; Eysenck et al., 2007), though stronger

evidence will be provided in chapters 4 and 5. Thus, the link between response inhibition and pathological impulsivity is established and response inhibition will be used as a laboratory model that is relevant to disorders of impaired control. However, due to some contention around the relationship between response inhibition and trait impulsivity (Reynolds et al., 2006) this relationship will be explored further in chapter 7.

1.5.3 Addiction and inhibitory functioning

There are several lines of reasoning for investigating response inhibition in substance use disorders. First, anecdotal reasoning suggests a possible link between response inhibition and addiction. Response inhibition is a measure of self-control. Similarly, a key feature of addiction is a loss of control, which leads to the continuation of behaviour despite negative consequences (American Psychiatric Association, 2013). Thus, reasoning suggests those with addiction would have impairments of inhibitory control. Supporting this hypothesis, the regulation of emotions, inhibition of cravings, and inhibition of motor responses are correlated in those with addiction (Tabibnia et al., 2011). Drug craving (Volkow et al., 2010), emotion regulation, and response inhibition have been associated with right IFG dysfunction (Tabibnia et al., 2011); supporting the connection between addiction and response inhibition.

A meta-analysis investigating the deficits in response inhibition in addiction examined 97 studies that used either the Go/No-go task or the Stop-signal task (J. L. Smith et al., 2014). The results revealed inhibitory deficits in those with cocaine, methamphetamine, MDMA, tobacco, and alcohol addiction. Evidence exists to support the assertion that this impaired response inhibition can be seen prior to onset of active addiction in humans (Ivanov, Schulz, London, & Newcorn, 2008; Nigg et al., 2006; Whelan et al., 2012) and rodents (Dalley, Everitt, & Robbins, 2011). Additionally,

evidence suggests that impaired inhibition remains after abstinence from stimulants (C. R. Li, Milivojevic, Kemp, Hong, & Sinha, 2006; Monterosso, Aron, Cordova, Xu, & London, 2005; Tabibnia et al., 2011).

The association between addiction and impaired inhibition has been demonstrated on a variety of tasks (Verdejo-García, Lawrence, & Clark, 2008). Inhibition of initiated behaviour has been associated with projections from the prefrontal cortex (PFC) to basal ganglia areas (Aron & Poldrack, 2006; Feil et al., 2010). Other fronto-striatal pathways involving the dorsolateral PFC (dlPFC), orbitofrontal cortex (OFC), and anterior cingulate cortex (ACC) have also been associated with inhibition. Additionally, addiction has been associated with diminished neural response and reduced grey matter in these fronto-striatal pathways (Verdejo-García et al., 2008; Verdejo-García, Rivas-Pérez, López-Torrecillas, & Pérez-García, 2006; Yücel & Lubman, 2007). Thus, the pathways involved in inhibitory control and the regions impaired in those with addiction overlap. Furthermore, impaired inhibition has been associated with poor treatment outcomes in patients with addiction (Brewer, Worhunsky, Carroll, Rounsaville, & Potenza, 2008; H. C. Fox, Axelrod, Paliwal, Sleeper, & Sinha, 2007). Further, Hester and Garavan (2004) found that impaired inhibition in stimulant dependant participants was associated with reduced right prefrontal and ACC activity, areas also implicated in the response inhibition network (Hung, Gaillard, Yarmak, & Arsalidou, 2018). Taken together these findings suggest that addiction is associated with impaired inhibition and dysfunction in brain areas associated with inhibition (for a review see: Feil et al., 2010).

1.5.4 Addiction, anxiety, and inhibitory functioning

The link between anxiety and addiction is well established. Those with addiction are more likely to be diagnosed with an anxiety disorder (Grant et al., 2004) and tend to score higher on self-report measures of anxiety (Comeau, Stewart, & Loba, 2001; Dixon,

Stevens, & Viana, 2014; Wedekind et al., 2013). Finally, relapse after periods of abstinence is triggered by stress (S. A. Brown et al., 1995; Shaham et al., 2000; Sinha, 2001, 2007). The link between addiction and inhibitory control (described in part 1.5.3) may be influenced by anxiety. Impaired response inhibition is reported during induced anxiety (Cornwell, Mueller, et al., 2012) and is a phenotype of addiction (J. L. Smith et al., 2014). However, the interaction of anxiety and inhibition in those with addiction is unclear as it has not been tested directly. This will be explored further in chapter 8.

1.6 Aims

The aims of the present thesis are: 1) To investigate the influence of threat-induced anxiety on response inhibition; 2) to investigate the neuroelectrophysiological activity that underlies the relationship between threat-induced anxiety and response inhibition; 3) to investigate the neuroelectrophysiological changes associated with threat-induced anxiety generally; 4) to investigate how trait impulsivity relates to changes in response inhibition during anxiety; and 5) to investigate whether the relationship between threat-induced anxiety and inhibitory control differs in individuals with addiction problems. Overall, the aim of the present thesis is to establish an understanding of how two key features of mental disorders (anxiety and self-control) interact and to explore this interaction in a disorder characterised by both features (addiction).

1.7 Thesis structure

The rationale behind the current thesis is to fill in several gaps in our understanding of key features of mental disorders. While it is established that impaired self-control and anxiety are common among mental disorders, studying these concepts in a laboratory setting has proven difficult. The current thesis aims to operationalise these variables in a way that allows for their exploration in a neuroimaging laboratory. Thus, the current studies will provide an understanding of the brain networks that underpin disorders characterised by poor impulse control and excessive anxiety such as addiction.

Before exploring the findings of each study, further background on each variable will be given to equip the reader with a broader understanding of the key variables in the thesis: anxiety, impulsivity, inhibition, and addiction. This will be done in chapter 2.

Additionally, the methodology of the key manipulations, procedures, and recording techniques will be explained in detail before exploring the findings of each study. This will provide the reader with a deeper understanding of the procedures in each experiment. The findings of five studies will then be presented, which together establish a deep understanding of anxious states, how these states manifest in the brain and how they influence response inhibition and impulsivity. This will provide insight into two key features of mental disorders (anxiety and impaired self-control). Chapter 4 will present the first of the five studies. This study introduces the relationship between threat-induced anxiety and response inhibition, by investigating the relationship between the two at the behavioural level. Chapter 5 expands on chapter 4 by showing how the relationship between threat-induced anxiety and response inhibition is reflected in the brain. The chapter will outline previous evidence for this relationship before introducing the second experimental study showing how the relationship between threat-induced anxiety and inhibitory control are reflected in magnetoencephalography (MEG) signal (for background on MEG, see part 3.4 of the method section). Chapter 6 will expand on the results from chapter 5 by combining them with results from other MEG threat-induced anxiety studies. This chapter will include a paper that shows the neuroelectrophysiological activity that underlies sustained state anxiety regardless of the task participants are engaged in. This chapter will provide a greater understanding of how anxious states manifest in the brain. Chapter 7 will link the findings so far to impulsivity, and thus demonstrating the relationship between anxiety and self-control more generally by exploring how trait impulsivity relates to changes of inhibitory control during induced anxiety. Chapter 8 will build on the knowledge of the preceding chapters and on previous literature to make predictions about how threat-induced anxiety would affect response inhibition in people with addiction problems. This chapter will also explore some

preliminary data on 9 participants with addiction problems, to further explore the future directions of research in this field. Chapter 9 provides a general description of the findings and a discussion of the overall conclusions, limitations, and implications.

Chapter 2 - Understanding the variables

2.1 Anxiety

Anxiety has been conceptualised in a number of ways; being described as a state, a trait, a category of disorders, and a type of response (American Psychiatric Association, 2013; Endler & Kocovski, 2001; O. J. Robinson, Vytal, et al., 2013; Spielberger, 1972). Spielberger (1966) distinguished trait anxiety from state anxiety – defining the former as a predisposition to anxious responses; and the latter as a transitory emotional state typified by physiological arousal and feelings of apprehension, tension, and dread. More recently, the American Psychiatric Association (2013) simply define anxiety as the anticipation of future threats. While others who aim to focus on the measurable aspects of anxiety, define it as a response to prolonged, unpredictable, future threat (O. J. Robinson, Vytal, et al., 2013). To understand what anxiety is, its characteristics must first be explored.

The anxious response is associated with an increase in startle response, where animals and humans show a stronger reflexive response to aversive stimuli including components such as eye blinks (Grillon, 2008). The response is also characterised by several physiological changes such as an increase in heart rate and galvanic skin response (Davis et al., 2010; Lang, Davis, & Öhman, 2000). Finally, induced anxiety is associated with a number of cognitive changes such as the facilitation of early sensory processing and subsequent impairment of some later processes (O. J. Robinson, Vytal, et al., 2013). Physiologically, anxiety has similarities to fear, in that both have overlapping physiological characteristics; however, fear is associated with stronger autonomic arousal with greater increases in heart rate and galvanic skin response; while anxiety is associated with muscle tension, greater and more prolonged increases in startle response, and hypervigilance – which is the sensitization of early sensory processes and an attentional bias towards cues signalling potential danger (American Psychiatric Association, 2013; Cornwell et al., 2017; Davis et al., 2010; Öhman, 1993). In addition to the physiological components, anxiety

is associated with cognitive components such as worry and poorer controlled concentration (Steptoe & Kearsley, 1990). The distinction between anxiety and fear is important to any definition of anxiety and has been addressed by a number of researchers (for a review see, Davis et al., 2010; Öhman, 1993). Fear is a phasic response to imminent threat. It begins rapidly and quickly dissipates after the removal of threat. Anxiety is a prolonged response to more uncertain and more physically or psychologically distant threat. Anxiety takes longer to dissipate and is centred around apprehension and uncertainty. Anxiety can manifest from a real or perceived uncertain threat; for example, the knowledge that an electric shock could be delivered at random at any time (O. J. Robinson, Vytal, et al., 2013), or the belief that the individual may be judged negatively by others (Schlenker & Leary, 1982). Throughout this paper, the term anxiety will be used to refer to a psychological and physiological state that is a response to uncertain threat. This state or response is characterized by physiological, affective, behavioural, and cognitive changes.

A number of psychological disorders, known as 'anxiety disorders', are characterised by excessive anxiety (American Psychiatric Association, 2013) and can have a significant negative impact on individuals and society (Beddington et al., 2008; Costa e Silva, 1998; Olatunji et al., 2007; Whiteford et al., 2013; Wittchen, 2002). For example, anxiety disorders are calculated to incur a significant economic cost (Beddington et al., 2008; Wittchen, 2002) and significantly reduce individuals' quality of life, which includes domains such as social functioning, mental health, and physical health (Olatunji et al., 2007). However, at its core, anxiety is believed to serve an adaptive function – facilitating the detection of and responses to threats (Bateson, Brilot, & Nettle, 2011; Eysenck et al., 2007). Evidence for anxiety's adaptive nature comes from research on animals and humans (Gutiérrez-García & Contreras, 2013; O. J. Robinson, Charney, Overstreet, Vytal, & Grillon, 2012). Early sensory processing is enhanced during anxious arousal, with greater perceptual neural responses to stimuli (Cornwell et al., 2007; Cornwell et

al., 2017). Furthermore, during anxious arousal compared to non-anxious, threat related stimuli are detected more rapidly than stimuli related to happiness (O. J. Robinson et al., 2011). This pattern of early sensory facilitation and bias for cues indicating potential danger is known as 'hypervigilance' (Grupe & Nitschke, 2013). Increased hypervigilance during anxious arousal fits with an adaptive explanation of anxiety. For example, if an individual enters a situation where harm is more likely (e.g., walking through the territory of a predator or enemy), they need to be more focused on possible threat and be more sensitive to changing stimuli. While anxiety serves an adaptive role, its negative effects are also clear (Beddington et al., 2008; O. J. Robinson, Vytal, et al., 2013). Apart from the personal and societal impacts of maladaptive anxiety, anxious arousal can impair cognitive functioning. While anxiety facilitates early sensory processing, many high order processes are more likely to become impaired as a result (Eysenck et al., 2007; O. J. Robinson, Vytal, et al., 2013; Shackman et al., 2006).

Induced anxiety facilitates early sensory perception and sensory gating, while it selectively facilitates emotional perception favouring threat related stimuli (O. J. Robinson, Vytal, et al., 2013). For example, fearful faces are recognised more rapidly than happy faces during induced anxiety conditions (O. J. Robinson et al., 2011). The story becomes more complex when looking at non-emotional and later processes. For trait anxiety or anxiety disorders, anxiety is associated with poorer performance for higher order tasks such as those that involve working memory, cognitive control, or decision making (Eysenck et al., 2007). However, induced anxiety sometimes facilitates higher order processes and other times impairs performance or has no effect (O. J. Robinson, Vytal, et al., 2013). For example, induced anxiety impairs the ability to exert conscious control over reflexive eye movements (Cornwell, Mueller, et al., 2012), impairs short term memory (Shackman et al., 2006; Vytal, Cornwell, Arkin, & Grillon, 2012), but can facilitate sustained attention (O. J. Robinson, Krimsky, et al., 2013), and there is some evidence of improved long term memory (O. J. Robinson, Vytal, et al., 2013).

Finally, induced anxiety is associated with changes in decision making where some aspects such as loss aversion and early responding are favoured over others (Keinan, 1987; Starcke & Brand, 2012).

Unlike studies exploring anxiety traits and disorders, studies using induced anxiety are better able to explore the adaptive changes associated with states of fluctuating anxiety and how these changes lead to physiological, psychological, and cognitive changes that both facilitate and impair functioning. While this intersection between the deleterious and advantageous effects of anxiety have been explored (Eysenck et al., 2007; O. J. Robinson, Vytal, et al., 2013), more research is needed to understand exactly how adaptive enhancements lead to maladaptive consequences and how this relationship is represented at the neural level. Firstly, the neural mechanisms behind anxiety must be explored.

2.1.1 Neural correlates of anxiety

Studying the neural correlates of anxiety comes with difficulties due to the complexity of anxiety. Many studies have compared patients with anxiety disorders to healthy controls (for a review see: Grupe & Nitschke, 2013) but the neural correlates of induced anxiety have only begun to be explored in the past decade, with only a relatively small number of studies (Balderston, Hale, et al., 2017; Balderston, Liu, Roberson-Nay, Ernst, & Grillon, 2017; Bijsterbosch, Smith, & Bishop, 2015; Cornwell, Arkin, Overstreet, Carver, & Grillon, 2012; Davis et al., 2010; Herrmann et al., 2016; McMenamin & Pessoa, 2015; O. J. Robinson et al., 2016; Torrisi et al., 2016; Vytal, Overstreet, Charney, Robinson, & Grillon, 2014) exploring this area, and even fewer exploring the sustained, non-task specific aspects of anxiety (Balderston, Hale, et al., 2017; Vytal et al., 2014). Before exploring the findings of induced anxiety studies, the common theories of anxiety discovered mostly through the exploration of anxiety disorders might help inform how anxious states manifest at the neural level. The Uncertainty and

Anticipation Model of Anxiety (UAMA) describes the neural processes that reflect anxiety (Grupe & Nitschke, 2013). The model describes 5 elements of anxiety that may lead to anxiety disorders. 1) Inflated estimates of threat likelihood and cost are hallmarks of anxiety and are associated with increased dorsal medial pre-frontal cortex (dmPFC), and orbital frontal cortex (OFC) activation respectively (Knutson, Taylor, Kaufman, Peterson, & Glover, 2005; Peters & Büchel, 2010; Plassmann, O'Doherty, & Rangel, 2010; Volz, Schubotz, & Von Cramon, 2003). 2) Increased attention to threat and hypervigilance are key characteristics of anxiety (Bar-Haim et al., 2007) and are associated with amygdala activation (for a review see: Grupe & Nitschke, 2013). The amygdala is thought to facilitate attention to threat and reinforce learning related to negative stimuli (Grupe & Nitschke, 2013). 3) Anxiety is associated with an impaired ability to recognise and respond to safety cues and is associated with disruption in ventral medial PFC (vmPFC) functioning, which is an area important for the extinction of conditioned anxiety cues (Phelps, Delgado, Nearing, & LeDoux, 2004; Schiller, Levy, Niv, LeDoux, & Phelps, 2008). 4) Anxiety leads to behavioural and cognitive avoidance. The learning of avoidance behaviour is associated with striatum and amygdala activity (Delgado, Jou, LeDoux, & Phelps, 2009). 5) At its core, anxiety is characterised by threat uncertainty. Heightened activity in the anterior insula is associated with uncertainty of threat. That is, when threat is less certain individuals tend to show greater physiological signs of anxiety such as a greater startle responses (Grillon, Baas, Lissek, Smith, & Milstein, 2004) and this is associated with anterior insula and bed nucleus of the stria terminalis (BNST) activity (Davis et al., 2010; Grupe & Nitschke, 2013). Finally the previous factors are thought to contribute to increased threat expectancies, impaired control and action in times of uncertainty is associated with anxiety (Grupe & Nitschke, 2013). The anterior-medial cingulate cortex (aMCC) is thought to integrate affective and motivational information to respond to uncertainty (Shackman, Salomons, et al., 2011). The aMCC is thought to project to the dorsolateral PFC and parietal regions to facilitate the allocation of attentional resources and response selection (Shackman, Salomons, et al., 2011). Disrupted functioning of the aMCC in

anxiety likely results in exaggerated automatic responses (Grupe & Nitschke, 2013). This model explains many aspects of anxiety and builds an understanding of how anxiety disorders manifest. However, the research used to create this model tends to focus on particular behavioural or cognitive aspects of anxiety (e.g. avoidance), differences between individuals that vary in diagnosis or anxiety trait, or animal models (Grupe & Nitschke, 2013). For example, animal models reveal that the amygdala responds to threat and projections from the amygdala are sent to centres that mediate the stress response (Lang et al., 2000). Animal models reveal that stimulating the amygdala can produce such effects artificially. For example, leading to activation of the lateral hypothalamus and subsequent changes to heart rate, blood pressure, and Galvanic skin response (Lang et al., 2000). Fewer studies have explored more general sustained neurobiological changes associated with induced anxiety in humans. For the purposes of this thesis, sustained anxiety will be defined as state-related shifts in neurophysiology and cognitive and behavioural functioning induced by the anticipation of uncertain threat. The term "sustained" is used to differentiate more general prolonged state-related changes as opposed to immediate changes in response to a stimulus or phasic changes such as the initial fear response.

The neural correlates of sustained state anxiety are still unknown as many functional studies explore discrete time windows that are time locked to an anxiety inducing stimulus or a task related stimulus (e.g. Cornwell, Mueller, et al., 2012). However, some studies have explored neural responses to sustained anxiety in healthy participants (Andreatta et al., 2015; Balderston, Hale, et al., 2017; Vytal et al., 2014). Exploring sustained responses in healthy individuals helps to determine how anxiety manifests in general (rather than immediate changes in neural signatures following stimuli exposure) in a non-pathological way. Andreatta et al. (2015) used 30 second blocks of threatening context compared to a non-threatening context in a VR environment. In the threatening context participants could receive an aversive electrical shock at any moment. This triggers an uncertain distal threat and thus operationalises an anxious state

(Davis et al., 2010). In the study by Andreatta et al. (2015), participants learnt that one room was associated with the possibility of shock and the other was not. They then had to take a pre-determined path through the VR shock and no-shock rooms, while simultaneous functional Magnetic Resonance Imaging (fMRI) recordings were made to measure cerebral blood flow. This was done over a number of 30 second blocks in each condition. The authors then explored initial and sustained responses. For the initial response (when participants were first exposed to the context) there were BOLD changes in the left motor area 1 (M1), left OFC, and left dlPFC. For the sustained response (the 30sec duration that participants were in the anxiety provoking context), there was activation in left M1, and right amygdala and right hippocampus. These results suggest sustained state anxiety may be associated with changes in brain activity in emotional, navigational (though this may be related specifically to anxiety inducing locations), and motor areas. Other studies have also explored sustained anxiety related activity.

Hasler et al. (2007) looked at cerebral blood flow (using PET) during threat of unpredictable shock and during the cue signalling an imminent shock. In the cue condition, left amygdala, ventral prefrontal, hypothalamus, ACC, left insula all showed increased blood flow. During the sustained condition, right hippocampus, left amygdala, mid-cingulate gyrus, midbrain periaqueductal gray, subgenual PFC, thalamus, parieto-occipital cortex, and bilateral ventral striatum showed increased blood flow. Suggesting, sustained anxiety caused a number of changes in brain activity in areas involved in sensory processing and executive control.

Finally, Vytal et al. (2014) explored sustained state anxiety in fMRI during threat of shock and safe conditions. The authors found increased coupling between amygdala and dmPFC during sustained anxiety. These amygdala dmPFC coupled regions were thought of as “anxiety seeds” and coupling to these seeds was explored to see what other regions might be involved in sustained anxiety (e.g. emotion regulation, action readiness etc.). Correlations between these two seed regions and other brain regions were explored and whole brain corrected for threat-safe

comparisons. In general, they found increased coupling between this seed network and areas involved in defensive responding (e.g. insula, OFC, dorsal ACC, basal ganglia, and thalamus) and decreased coupling between the seed and areas involved in emotional control (e.g. ITG). These findings suggest that induced anxiety is associated with a sustained change in motor, cognitive, affective, and emotional control areas. A number of induced and clinical anxiety studies have led to an fMRI model of anxiety that implicates key regions underlying anxiety; including left and right insula/inferior frontal regions, and a large region encompassing the medial frontal cortex and cingulate cortex (Chavanne & Robinson, 2020). Most of the research presented so far has focused on brain activity measuring haemodynamic changes via fMRI. However, neural activity is a electrophysiological phenomenon and blood flow is only a secondary measure of neural activity (E. L. Hall, Robson, Morris, & Brookes, 2014). Further, anxious arousal alters cerebrovascular function (Giardino, Friedman, & Dager, 2007). Giardino et al., argue that states of anxious arousal are often accompanied by respiratory changes that alter arterial CO2 tensions and create changes in cerebral blood flow. Thus, changes in cerebral activity measured using fMRI between anxious and non-anxious conditions may be confounded by anxiety-induced changes in cardiovascular function. To better understand brain related changes during anxiety, electrophysiological changes must be explored.

2.1.2 Neuro-electrophysiological components of anxiety

The brain produces electrical currents, which are thought to be the summation of excitatory and inhibitory post synaptic potentials, which (in comparison to action potentials) are long lived enough to overlap in time with surrounding neurons and lead to a summated change in potential (Hämäläinen, Hari, Ilmoniemi, Knuutila, & Lounasmaa, 1993). This electrical activity can be detected through electrodes placed in the brain or on the surface of the scalp. Further, the magnetic fields associated with these currents can be detected using magnetoencephalography (MEG). As the signature detected by MEG and EEG are a summation of activity of billions of cells, and because of the sensitivity of these tools to other sources of signal, there is often a lot of

noise in these measurements (Hämäläinen et al., 1993; Jackson & Bolger, 2014). Due to the oscillatory nature of the observed activity, one of the most common techniques used to study the brain activity measured with MEG and EEG is to decompose the data into the frequency domain, and characterize changes in activity within frequency bands over time (Pardey, Roberts, & Tarassenko, 1996). Frequency describes how many oscillations occur in a given time period. The five most common frequency ranges explored in neuroimaging literature are delta (0 – 4Hz), theta (4 – 8 Hz), alpha (8 – 13 Hz), beta (13 – 30 Hz), and gamma (30 – 100 Hz), which have each been extensively studied and attempts have been made to associate each with different neurobiological functions (Başar-Eroglu, Strüber, Schürmann, Stadler, & Başar, 1996; Başar, 2012; Schmidt et al., 2019; Thut & Miniussi, 2009).

Anxiety has been associated with gamma activity reflecting worry and anticipation (Miskovic et al., 2010; Oathes et al., 2008). Various lines of evidence suggest that anxiety is associated with greater right frontal EEG activity compared to left. For example, right frontal EEG activity is associated with high cortisol, defensive behaviour, and corticotrophin releasing hormone in rhesus monkeys (Kalin, Shelton, & Davidson, 2000). Greater right frontal activity has been associated with social phobia (Davidson, Marshall, Tomarken, & Henriques, 2000) and panic disorder (Wiedemann et al., 1999). Indeed, a large body of evidence suggests a relationship between anxiety and right frontal alpha EEG asymmetry (for a review see: Coan & Allen, 2004), with more recent findings showing that improvements in functioning in SAD after CBT are related to a reduction in right lateralised asymmetric frontal EEG (Moscovitch et al., 2011). Research into this field using MEG is scarce; Balderston, Hale, et al. (2017) showed a reduction in alpha in the left intraparietal sulcus (IPS) during threat-of-shock conditions; which were interpreted to mean induced anxiety increases excitability of a key attentional control region. Another neuroelectrophysiological marker of anxiety is found in beta oscillations. Cortical beta oscillations are thought to be generated by interactions between interneurons and

pyramidal neurons within the deep layers of the cortex (Schmidt et al., 2019). Changes in beta activity have been associated with anxiety, although the exact nature of this relationship is still unclear. For example, anti-anxiety medication increases beta activity (van Lier, Drinkenburg, van Eeten, & Coenen, 2004). Additionally, anxiety has been associated with cross-frequency coherence (or coupling) between beta and delta activity (Knyazev, Schutter, & van Honk, 2006; Putman, 2011). It is clear that the electrophysiological research on anxiety is still growing. However, very few studies have looked at the neuroelectrophysiological features of anxiety induced by threat. Klinkenberg et al. (2016) found that participants had increased signal amplitude (measured by MEG event related field (ERF) analysis) over dlPFC in response to neutral and fearful faces during unpredictable threat. The authors suggested the activity was related to emotion regulation. Other studies have shown increased processing of stimuli modulated by event-related potential (ERP) activity (Bublatzky & Schupp, 2012; Chattopadhyay, Cooke, Toone, & Lader, 1980), increased activity in inferior parietal regions in response to stimulus deviance (Cornwell et al., 2007), and altered theta and beta activity relating to stimulus driven attention and motor suppression (Cornwell, Arkin, et al., 2012) during threat conditions. Taken together these studies suggest that induced anxiety produces measurable neuroelectrophysiological effects, particularly in the processing of early sensory information. However, to our knowledge, only one study has explored sustained changes in neuro-electrophysiological activity during induced anxiety using MEG (Balderston, Hale, et al., 2017). The study found reduced alpha in the left IPS, but the study did not explore beta. Beta is important in action/thought stopping in the right IFG and basal ganglia (Castiglione, Wagner, Anderson, & Aron, 2019; Nicole Swann et al., 2011; N. Swann et al., 2009; Wagner, Wessel, Ghahremani, & Aron, 2017; Zavala, Zaghloul, & Brown, 2015), which as described earlier, is likely influenced by anxiety. It has also been shown that differential beta in the inferior parietal cortices underlies a greater readiness to perform anti-saccades during safety and to perform pro-saccades during threat (Cornwell, Mueller, et al., 2012). One aspect of beta that has been

extensively studied is sensorimotor beta (Kilavik, Zaepffel, Brovelli, MacKay, & Riehle, 2013). Kilavik et al. suggest that sensorimotor beta increases are associated with rest and stable postures; while decreases are associated with motor action and action readiness. Stable postures and rest (associated with beta increase in sensorimotor areas) is the opposite of what is needed for survival during anxious arousal. Indeed, the opposite (which is associated with movement) is required. This suggests that anxiety might reduce sensorimotor beta activity to facilitate readiness for action. This area will be explored further in chapter 6.

The reviewed literature presented defines anxiety and summarises relevant research on the representation of anxiety at the neural level. The adaptive and deleterious effects of anxiety have also been discussed. The present thesis will further explore the electrophysiological, neural representations of anxiety. Similarly, the intersection between the advantageous and deleterious effects of anxiety upon cognition and behaviour will be explored. One variable that may help to explore this intersection is response inhibition.

2.2 Inhibition

In his book, R. Smith (1992) describes the history of the word inhibition. Smith says the definition of the word has been shaped by language and culture but essentially describes mental and physical control. The concept of inhibition has a long history with many influential thinkers such as William James, Plato, Descartes, and Franz Joseph Gall commenting on it (R. Smith, 1992). A common concept from these earlier commentators is the notion of "will", mental competition, or mental hierarchy, where lower order concepts like passion and impulses are controlled by higher order (or opposing) concepts (R. Smith, 1992). While many of the earlier ideas about inhibition focused on the concept of "will" and linked the idea to consciousness (e.g., exerting will is an exercise in conscious control), more recently the concept started to be used to describe peripheral cellular interactions. Such interactions include the inhibition of motor neurons by adjacent neurons, or central inhibition such as the stimulation of central nervous

system regions causing the inhibition of motor reflexes (Bari & Robbins, 2013; MacLeod, Dodd, Sheard, Wilson, & Bibi, 2003; R. Smith, 1992). This later idea separated the concept into physiological inhibition (where neurons can have excitatory and inhibitory functions) and psychological inhibition (MacLeod et al., 2003). While recognizing that the two concepts are somewhat intertwined and aspects of psychological inhibition likely involve the physiological inhibition (e.g., response inhibition), this thesis will focus on the psychological concept of inhibition.

The Stroop task was an early example of what might be called psychological inhibition (Stroop, 1935) but is also an example of how the definition of inhibition changes with different researchers. The task involves trying to name the colour ink that a word is printed in, which becomes difficult when the word spells out an incongruent colour (Stroop, 1935). The task was generally referred to as an interference task rather than inhibition, with researchers describing a tug of war between the two processes (MacLeod & Dunbar, 1988; Stroop, 1935). However, some described the Stroop effect as an inability to "switch off" or inhibit the automatic process of reading (MacLeod, 2007). The use of the term "inhibition" became more frequent in the literature in the later part of the 20th century (MacLeod et al., 2003). However, MacLeod et al. (2003) argues that the ubiquitous use of the word inhibition has become troublesome with many researchers using it to describe any kind of response slowing such as negative priming and inhibition of return. Negative priming is where responses are slowed when responding to a stimulus that had to be ignored in a previous trial (Tipper, 1985). Inhibition of return describes suppressing the processing of stimuli that have recently been the object of attention; in this way the brain's search for novelty is aided (Klein, 2000). However, MacLeod et al. (2003) argue that these two phenomena are more related to memory and attention rather than cognitive/behavioural inhibition.

The term inhibition has been used to describe a large number of physiological and psychological phenomena (Bari & Robbins, 2013). However, this broad use of the word will be narrowed in the current thesis. The present thesis aims to explore inhibition as a basis for understanding disorders characterized by poor impulse control (see chapter 1). The inability to suppress or stop thoughts and responses is of key interest to the present study. Thus, a qualifying adjective is needed to bring consensus to the varying uses of the word "inhibition" (Bari & Robbins, 2013). Bari and Robbins used the terms "behavioural inhibition" and "cognitive inhibition". Behavioural inhibition is the withholding, cancelation, or suppression of a behaviour or response (Bari & Robbins, 2013). This type of inhibition is often cited in examples demonstrating the face validity of the existence of inhibition; people must be able to update and override their responses as new information in the environment becomes available (Bari & Robbins, 2013). Cognitive inhibition is defined as the suppression, stopping, or overriding of mental processes (MacLeod, 2007).

Cognitive inhibition includes the inhibition of emotions, craving, and thoughts. The authors also break behavioural inhibition into response inhibition, deferred gratification, and reversal learning, each with subdivisions. Response inhibition is the cancelation, postponing, or withholding of a response. The authors describe this as relating to "impulsive action". Deferred gratification relates to "impulsive choice" and includes delay discounting and other decision making problems (Bari & Robbins, 2013). Found to be higher in those with addiction, delay discounting is where a smaller immediate reward is favoured over a larger but more temporally distal reward (Amlung, Vedelago, Acker, Balodis, & MacKillop, 2017). Finally, reversal learning describes inflexibility or compulsivity. A typical task, such as discrimination reversal, involves participants learning a response that is associated with a reward; then having to learn a new response once rewards are changed. Participants have difficulty inhibiting the previously learned response and adapting the new response, and this difficulty is thought to be related to the

pathological reward seeking and inability to modify behaviour in those with addiction (Izquierdo & Jentsch, 2012). It is clear that the umbrella term "inhibition" has a range of cognitive and behavioural aspects that are related to addiction and other impulsive and compulsive disorders (Bari & Robbins, 2013). Interestingly, there is additional overlap in these phenomena. ERP studies show that both the cognitive and behavioural aspects of the Go/No-go task showed similar neural responses (Bruin & Wijers, 2002). Emotional, cognitive and behavioural inhibition have overlapping neural correlates (Hung et al., 2018). Furthermore, the regulation of emotions, inhibition of cravings, and inhibition of motor responses are correlated in those with addiction (Tabibnia et al., 2011).

Given the relationship between performance on tasks measuring inhibition and disorders characterised by impaired impulse control (Chamberlain, Fineberg, Blackwell, Robbins, & Sahakian, 2006; Clark et al., 2007; J. L. Smith et al., 2014; Verdejo-García et al., 2008), the study of inhibition is important. One of the easiest aspects to measure is response inhibition. This is because measuring responses is easier than measuring thoughts. Thus, a large amount of research has been done on response inhibition. Two key tasks have been used in this area: the Go/No-go task and the Stop-signal task. The Go/No-go task typically asks participants to press a button quickly in response to a stimulus (go stimulus) presented on screen (Gomez, Ratcliff, & Perea, 2007). Occasionally, a different stimulus (no-go stimulus) is presented indicating participants should withhold their responses (Gomez et al., 2007). The go stimulus is presented on the majority of trials, typically two thirds or above, conditioning the participant to respond quickly after the presentation of a stimulus (Gomez et al., 2007). This responding becomes automatic and must be withheld when the participant recognises a no-go stimulus. An analogy can be found in the game Time Crisis, where the player must shoot enemies that appear on screen but must not shoot civilians. There is some debate whether the Go/No-go tasks involves action withholding, action cancelation, or something else (Bari & Robbins, 2013). It has been

suggested that the presentation of the no-go stimulus does not unambiguously initiate a response that must be stopped (MacLeod, 2007). Nevertheless, many researchers believe the Go/No-go task measures some aspect of inhibitory control. Performance on the task is impaired in a number of disorders (Dong, Lu, Zhou, & Zhao, 2010; Kamarajan et al., 2005; J. L. Smith, Johnstone, & Barry, 2004; Wright, Lipszyc, Dupuis, Thayapararajah, & Schachar, 2014). A number of neuroimaging studies have attempted to elucidate the neural network underpinning response inhibition by using the Go/No-go task, and have found a network of structures including the pre-supplementary motor area (preSMA), the right, and sometimes left, inferior frontal gyrus (IFG) and a number of other structures (Chikazoe, 2010; Rubia et al., 2001; D. Zheng, Oka, Bokura, & Yamaguchi, 2008). However, some argue that it is difficult to determine if the regions typically activated are involved in inhibition or other processes involved in performance of the Go/No-go task, such as attention (Criaud & Boulinguez, 2013). The Go/No-go task has been extensively studied and is easy to use in neuroimaging studies due to the consistent timing of stimulus presentation. Conversely, the Stop-signal task has greater variation in the timing of stimulus presentation (Logan & Cowan, 1984). The Stop-signal task has also been researched extensively partly due to the unambiguous initiation of a go process, which must be subsequently inhibited (MacLeod, 2007).

The Stop-signal task typically involves a simple two-choice reaction time task, where participants are asked to quickly respond to two possible stimuli (e.g. press left when a left arrow appears and right when a right arrow appears; Logan & Cowan, 1984). On a small portion of trials (typically one third or less), a stop-signal (e.g. a tone or change to the go-signal) follows the presentation of the go-signal (Logan & Cowan, 1984). Participants are instructed to withhold their responses on stop-signal trials. The Stop-signal task has the benefit that go-signals are presented before stop-signals, so researchers can be confident a response has been initiated before needing to be inhibited (MacLeod, 2007). This assertion is supported by studies using

lateralized readiness potentials, which is an ERP signal believed to reflect motor activity preparation. Studies using this measure show evidence that the motor system is often inactive during no-go trials in the Go/No-go task; however, the motor system is active during the Stop-signal task (van Boxtel, van der Molen, Jennings, & Brunia, 2001). The Stop-signal task also has the benefit of measuring the speed of the stopping process (outlined in chapter 3). However, the task requires adaptive changes in the timing of the stop-signal, making it harder to code and making neuroimaging more difficult (due to the variability of the stop-signal presentation in relation to the beginning of a block, it is somewhat harder to properly epoch Stop-signal task windows – which may explain why the Go/No-go Task seems to be more popular in neuroimaging studies). Like the Go/No-go task, the Stop-signal task has been associated with preSMA and right IFG activation, along with a number of other areas (Aron et al., 2014; Hung et al., 2018; Nachev, Wydell, O'Neill, Husain, & Kennard, 2007). A slower stopping process (known as the stop-signal reaction time; SSRT) has been found in a number of disorders of impulse control such as ADHD, OCD, and addiction (Chamberlain & Sahakian, 2007). Given the strong link between disorders and the Stop-signal task, and the validity of the task procedure (go signals are unambiguously initiated before the stop-signal – reflected in readiness potentials), the present thesis will use this task to explore inhibitory control. Inhibitory control is important to study, particularly for when it is impaired.

2.3 Inhibition and Impulsivity

Bari and Robbins (2013) describe the failure of the inhibitory process as "impulsivity". The authors explain that impulsivity requires not only an impairment of the inhibitory process, but also, strong impulses – for one is meaningless without the other. Impulsive traits are a key descriptor of many psychological disorders such as ADHD, OCD, and addiction (American Psychiatric Association, 2013). For example, those with ADHD have difficulty waiting and often interrupt or respond before an appropriate interval (American Psychiatric Association, 2013). Those with OCD have trouble inhibiting intrusive thoughts and compulsive actions

(American Psychiatric Association, 2013). Finally, those with addiction often have trouble inhibiting cravings and drug seeking/using behaviour despite the desire to abstain from drugs (American Psychiatric Association, 2013). These impulsive traits often lead to impaired functioning and psychological distress (American Psychiatric Association, 2013). However, this relationship is not only characteristic of psychological disorders, but is descriptive of healthy adults too. Impulsivity measured with the self-report Barratt Impulsiveness Scale (Patton, Stanford, & Barratt, 1995) is significantly correlated with social functioning, where those with higher impulsivity have poorer social functioning (Dawson, Shear, & Strakowski, 2012). Impulsivity measured with the Urgency, Premeditation, Perseverance, and Sensation Seeking (UPPS; Whiteside & Lynam, 2003) scale is associated with increased drinking behaviour (Magid & Colder, 2007), aggression (Miller, Zeichner, & Wilson, 2012), and other negative externalizing behaviours (Carlson, Pritchard, & Dominelli, 2013) in healthy populations. In this thesis, the term impulsivity will describe a heterogeneous and multi-factorial set of behaviours or traits driven by a desire to obtain pleasure, arousal and gratification, or difficulties with patience or control (Hollander & Rosen, 2000; Whiteside & Lynam, 2001).

Impulsivity has been described as comprising multiple factors. Patton et al. (1995) broke impulsivity into three domains: attentional impulsiveness (difficulties focusing on tasks, and cognitive instability), non-planning (difficulties with self-control and cognitive complexity), and motor impulsiveness ("acting on impulse", and showing low perseverance). However, Barratt Impulsiveness Scale measures impulsivity unidimensionally. Lynam et al. (2007) described five aspects of impulsivity in their UPPS-P impulsivity scale: negative urgency (describing impulsive action during times of intense negative affect), (lack of) premeditation (describing a lack of prior thinking or planning), (lack of) perseverance (describing seeing things through or persevering as opposed to easily giving up), sensation seeking (describing a tendency to seek new and exciting experiences and sensations), and positive urgency (describing impulsive action during times of

positive affect). Scores on both the Barret Impulsivity Scale and the subscales of the UPPS-P are higher in disorders of impulse control (Petry, 2001; Um, Hershberger, Whitt, & Cyders, 2018) and higher scores also lead to poorer social outcomes in healthy people (Carlson et al., 2013; Savci & Aysan, 2016).

The evidence presented shows that both response inhibition and trait impulsivity are related to disorders of impulse control and poor social functioning in non-clinical populations. Furthermore, face validity suggests a relationship between the two – impulsivity is described as a problem with inhibitory control (Bari & Robbins, 2013). Despite this, researchers have argued that response inhibition is simply a measure of the inhibition of motor responses, suggesting it is not a legitimate measure of impulsivity (Reynolds et al., 2006). Reynolds et al. (2006) claim that response inhibition is not related to self-reported trait impulsivity. Thus, they argue the common impairment of these two attributes in impulsive disorders does not mean the two are directly related. An alternative explanation for the lack of association between impulse control scales and response inhibition could be found in the scales used to measure impulse control. Predominant scales used for measuring impulsivity such as the Barratt Impulsivity Scale (Patton et al., 1995) and the Behavioural Inhibition Scale (Carver & White, 1994) have a broad range of questions that reduce the specificity found in tasks that measure response inhibition. For example, one question in the Barratt Impulsivity Scale requires a Likert response to the statement “I am happy-go-lucky” (Patton et al., 1995). As described earlier, the alternative UPPS scale, has broken impulsivity down into four (and later five) distinct categories (Lynam et al., 2007; Whiteside & Lynam, 2001), with specificity in each category better conceptualizing the heterogeneity of the concepts that comprise self-control (Rochat, Billieux, Gagnon, & Van der Linden, 2018; Sperry, Lynam, Walsh, Horton, & Kwapil, 2016; Whiteside & Lynam, 2001). One specific example is the category of “urgency”, which describes the inclination to perform regrettable or impulsive actions when experiencing negative affect (Whiteside & Lynam, 2001).

The questions in this scale are distinctive and relate to impulsive *actions*, including questions such as "When I get upset I often act without thinking" (Whiteside & Lynam, 2001). This category appears to be more closely related to response inhibition than other categories such as sensation seeking. Indeed, urgency is correlated with errors in the Go/No-go task (Gay, Rochat, Billieux, d'Acremont, & Van der Linden, 2008) and stopping speed in the Stop-signal task (Wilbertz et al., 2014). Wilbertz et al. did not find the same relationship when using the Barratt Impulsivity Scale, showing that the non-specificity of the Barratt Impulsivity Scale may be the reason it does not correlate with behavioural measures. In addition to the correlation between trait and behavioural measures, Wilbertz et al. showed that urgency was negatively correlated with stop-signal inhibition (stop>go) in the right IFG (a key node in the inhibitory network).

Overall, inhibition is a term that describes the suppression, withholding, or delaying of thoughts and behaviours. The term has been used broadly; however, qualifying adjectives can help researchers reach a consensus. Many tasks and questionnaires have been used to measure cognitive inhibition, behavioural inhibition, and impulsive traits. The present thesis is interested in response inhibition, which will be measured using the Stop-signal task, and its relationship to impulsive traits, which will be measured using the UPPS-P scale. The present thesis will also explore the role of induced anxiety in this relationship. The relationship between impulsivity, inhibition, and anxiety will be explored in chapter 7.

2.4 Addiction

Substances of addiction, such as alcohol, have been present in human society for thousands of years and have appeared in writings of ancient Egyptian, Chinese, Greek, and many other cultures (Nathan, Conrad, & Skinstad, 2016). Similarly, the negative effects of overconsumption have been documented for thousands of years. The Christian and Hebrew bible/Torah, mention

wine and its effects frequently; generally with acceptance of moderate consumption, condemnation of drunkenness, and cautionary tales of the negative consequences of overindulgence (Nathan et al., 2016). Similar ideas have been found written in other religious texts (Nathan et al., 2016). The negative effects of alcohol were generally recognised, and different advice was given for how to combat this. In the bible, Paul claims that wine is a gift from god but recommends abstinence for individuals who have difficulty controlling their consumption; however, the Koran forbids alcohol in any form (Nathan et al., 2016). Similarly, Buddhist writings generally condemn the use of alcohol (Nathan et al., 2016). Throughout history, the use of substances and the negative consequences have been discussed. Similarly, the ideas around the causes, and subsequently, what addiction is, have been debated for years (Nathan et al., 2016; T. E. Robinson & Berridge, 2003). The temperance movement (1784 to 1883) in the United States viewed alcohol consumption as a moral and social problem; however, psychiatrists Philippe Pinel and Benjamin Rush (circa 1800) described alcoholism as a psychiatric disease (Nathan et al., 2016). This debate around the classification of addiction has not abated with modern researchers describing the conditions as both a disease (Campbell, 2003; Hyman, 2005; Leshner, 2001; Volkow, Koob, & McLellan, 2016) or something else such as maladaptive learning, or simply an expected consequence of the way humans evolved (W. Hall, Carter, & Forlini, 2015; Heather et al., 2018; Lewis, 2017, 2018). Whether a disease or a consequence of normal functioning, few researchers still argue that addiction is a moral failing (Heather, 2017). The next sections will outline some of the common theories about the causes of addiction.

2.4.1 Pleasure and Withdrawal

One of the more intuitive explanations for addiction is that addiction is a consequence of the pleasure (caused by consumption) and the withdrawal (caused by cessation) of substance use (Solomon, 1977). This idea of pleasure and withdrawal has gone by many names (T. E.

Robinson & Berridge, 2003); however, Solomon (1977) name the theory "opponent-processes theory" similarly named as the theory of colour vision, because of the opposing conditions of withdrawal and pleasure. Solomon describes two opposing processes behind the experience of pleasure and withdrawal: the "A-process" and the "B-process". The A-process is linked to pleasure. Solomon describes this process as occurring when the drug is consumed. This A-process triggers feelings of euphoria in the brain's reward circuit. However, the brain, seeking homeostasis, engages the B-process to decay the A-process and bring the brain back to a normal state. This decay process is initially mild; however, after continued use, the B-process is strengthened leading to tolerance and a reduction in the euphoria from drug use. The strengthening of the B-process continues with further use resulting in the B-process lasting longer than the A-process and leading to withdrawal. Solomon puts it simply by stating if A is greater than B, the individual feels euphoria; however, if the opposite is true the individual experiences withdrawal. There is support for this theory by researchers who have elucidated the underlying neurobiological mechanisms of addiction (Koob, Caine, Parsons, Markou, & Weiss, 1997). The opponent process theory views addiction as being driven by hedonic states. Individuals initially take drugs for the pleasurable effects but develop addiction when the negative effects of cessation develop, where continued use is the only way to abate this negative state.

The pleasure and withdrawal theories are compelling but there are some limitations. When looking at patients given pain killers, a large portion of those who develop withdrawal symptoms do not develop an addiction and are able to stop using after the pain improves (Martin et al., 2011). Further, when withdrawal is induced in rats, drug seeking behaviour is relatively low compared to the effects of environmental stress (Stewart & Wise, 1992). Put simply, stress seems to be a stronger driver of addiction than withdrawal. This leads to another factor that is not well captured in the pleasure and withdrawal theories; those with past trauma are more likely

to develop addiction (Garami et al., 2018; Khoury, Tang, Bradley, Cubells, & Ressler, 2010; Najavits, Weiss, & Shaw, 1997). One study found that more than 66% of drug court participants had significant past trauma, and those without trauma were more likely to have successful outcomes such as clean urine screens (Wolf, Nochajski, & Farrell, 2015). The other major limitation with the pleasure and withdrawal theory is that those with addiction who have recovered often relapse despite initially overcoming the withdrawal phase of recovery (Sinha, 2007). Finally, the pleasure and withdrawal model does not have a strong explanation for the genetic link to addiction (Legrand, Iacono, & McGue, 2005; M. D. Li & Burmeister, 2009) or the link between addiction and impoverished environments (Caprioli, Celentano, Paolone, & Badiani, 2007; Nawaz et al., 2017; Wang et al., 2018). Particularly, the link between trauma and addiction has prompted another genre of explanations for addiction.

2.4.2 Trauma

Trauma models of addiction developed from the need for better treatment for individuals who have addiction and past trauma, and to explain the link between the two (V. B. Brown, Harris, & Fallot, 2013; Padykula & Conklin, 2010; Potter-Efron, 2006). There are multiple explanations for why trauma is linked to addiction, but the theories tend to offer causal explanations for addiction in those who have experienced trauma without offering an explanation for the causes of addiction in those who have not experienced trauma. Nevertheless, with estimates for the co-occurrence of trauma and addiction ranging between 50% and 99% (Garami et al., 2018; Khoury et al., 2010; Medrano, Zule, Hatch, & Desmond, 1999; Najavits et al., 1997; Oyefeso, Brown, Chiang, & Clancy, 2008; Wolf et al., 2015), trauma informed theories offer a compelling explanation for a large portion of those with addiction. One trauma related theory of addiction that will be covered as an example of the area is the self-regulation model (SRM) of addiction (Padykula & Conklin, 2010). This model tries to explain addiction through the lens of trauma and attachment (Padykula & Conklin, 2010). The model describes people with addiction having

experienced interpersonal trauma, which has led to attachment system dysfunction. This dysfunction results in difficulties of self-regulation especially in the face of self-defeating attempts to maintain normality (Padykula & Conklin, 2010). The authors of the SRM claim that those screened with addiction tend to have trauma; claiming that most comorbidity studies only look at addiction and trauma related disorders such as PTSD resulting in the underestimation of the comorbidity between the two. Padykula and Conklin state that when all interpersonal trauma is captured, co-occurrence rates of addiction and trauma are closer to 99%. The authors state that this interpersonal trauma leads to attachment style dysfunction, which leads to problems with self-regulation. Interpersonal trauma is thought to create distress and an impaired ability to deal with that distress through the management of one's own behaviour and emotions, or to "self-regulate" (Allen, 2001). The SRM posits that when faced with greater distress and impaired self-regulation, individuals use substances to cope (Padykula & Conklin, 2010). As stated by the authors: "*The SRM views the impact of interpersonal trauma as sustaining an injury to one's attachment system, resulting in a client's diminished capacity for self-regulation. Substance use/abuse is an attempt at self-regulation in the service of adaptation*" (Padykula & Conklin, 2010, p. 351). The SRM is a compelling model but it has some limitations. For example, interpersonal trauma is not as strongly linked to addiction as non-interpersonal trauma (Garami et al., 2018). Further, the theory does not account for the development of addiction in individuals who have not experienced trauma. Finally, the theory overlooks a large body of research demonstrating other strong drivers of addiction such as aberrant learning (Hyman, 2005).

2.4.3 Learning

The word 'learning' is often associated with something beneficial such as studying for an exam. However, the transition from first drug use to addiction can also be viewed as a form of learning based on the principles of classical and operant conditioning and based on

neurobiological changes (Hyman, 2005; Hyman & Malenka, 2001; O'Brien, Childress, McLellan, & Ehrman, 1992). Learning theories of addiction often reference one of the most researched neural mechanisms of addiction; the reward circuit, where addiction related neuroadaptations alter the salience of rewards (Hyman & Malenka, 2001; Koob & Volkow, 2010). The reward circuit comprises a number of key structures including the: amygdala, dorsal anterior cingulate cortex (dACC), dorsal prefrontal cortex (dPFC), hippocampus, lateral habenula, hypothalamus, orbital frontal cortex (OFC), pedunculopontine nucleus, substantia nigra pars compacta, subthalamic nucleus (STN), thalamus, ventral pallidum, ventral tegmental area (VTA), and ventral medial prefrontal cortex (Haber & Knutson, 2010).

Early experiments by Olds and Milner (1954) began the research into this reward system. The researchers placed electrodes in the brains of rats and then presented the rats with a leaver that would administer a shock to the intracranial electrode. The placement of the electrode was changed, and the researchers found that when the electrode was placed in a particular location, the rats would continuously press the leaver. After continued research these deep brain areas involved in reinforcing behaviours became known as the reward circuit (Wise, 2002). Stimulation of the reward circuit seemed to override all other motivations for the rats, with the animals choosing stimulation over food and other rewards, and exposing themselves to painful shocks in order to self-stimulate their reward circuit (Routtenberg & Lindy, 1965). Substances of addiction strongly influence the reward circuit (Koob, 2009) and when given these substances, rats are less motivated to self-stimulate their reward circuit (Kornetsky & Esposito, 1979). This suggests that drugs of addiction influence a circuit that plays a large role in reward and motivation; furthermore, there are neural adaptations that occur in the reward circuit that favour drugs as a reward over other rewards such as food and sex (Koob & Volkow, 2010).

Operant conditioning tells us that a reward reinforces behaviour (Staddon & Cerutti, 2003); interestingly, researchers of addiction believe that the ‘reward’ can be implicit without a

conscious pleasurable effect (Stolerman & Jarvis, 1995). This separates the 'learning' theory from the pleasure and reward theories. More modern learning theories have a stronger basis in implicit learning and habit forming without the need for 'pleasure' to be the primary driver (Hyman, 2005). A good example of this is nicotine, which is highly addictive but has no obvious hedonic pleasure (Stolerman & Jarvis, 1995). Researchers believe all drugs of addiction act on the reward circuit (Di Chiara et al., 2004; Pontieri, Tanda, Orzi, & Chiara, 1996) and that changes happen in this circuit so that not only drugs but drug related cues activate the circuit (Childress et al., 1999; Knutson, Adams, Fong, & Hommer, 2001; Schultz, 1998; Volkow et al., 2006), occasionally even better than the reward itself (Schultz, 1998).

Better than expected rewards. Schultz et al. (1997) showed that reward circuit dopaminergic neurons respond to changes in reward prediction rather than to reward itself. Schultz et al. recorded the firing rates of these neurons in monkeys. When the monkeys were given juice unexpectedly, there was an increase in the firing rate of these dopaminergic neurons. The researchers then presented a cue just before giving the monkeys the juice. After the monkeys associated the cue with the juice, dopaminergic neuron firing rate increased after the presentation of the cue and then returned to normal when the juice was presented, which the monkeys expected from the cue. This study demonstrated how these dopaminergic neurons in the reward circuit adapt and learn. Specifically showing that dopaminergic neuron firing does not increase with a natural reward that is expected. In this sense, an increase in dopamine, resulting from the firing of these neurons, would indicate a "better than expected" reward (Hyman, 2005). Unfortunately, addictive drugs always increase dopamine levels in the reward circuit through various mechanisms unique to each addictive drug, regardless of the organisms expectations (Hyman, 2005). Hyman and Malenka (2001) argue that the reward circuit becomes tuned to drugs and drug related cues due to the 'usurping' properties that stimulates the reward circuit more than any natural rewards.

Other goals lose importance. The implicit motivation to obtain drugs then becomes as strong or stronger than most natural rewards. In this way, craving can be related to a very strong hunger. When someone is hungry, food becomes a primary concern to the detriment of other goals. Thus, the brain changes that cause this craving are a type of aberrant learning. However, other regions are implicated in the addictive properties of drugs and are thought to be part of the reward system. For example, nondrug goals become devalued within the prefrontal cortex (PFC) in those with addiction (Montague, Hyman, & Cohen, 2004). At the heart of learning theories of addiction is the concept that drugs overtake the natural reward system and the brain 'learns' to value drugs over all other rewards (Hyman, Malenka, & Nestler, 2006). Hyman (2005); Hyman et al. (2006) described three aspects to addiction related learning. After the consumption of rewards (e.g., food, sex, drugs) hedonic consequences (pleasure) are produced that begin the process of learning in the following ways: (a) reward enjoyment, (b) learning of cues that predict reward availability and actions that facilitate its consumption, and (c) allocating value and motivational rank to the reward, which the organism uses to choose among numerous behavioural options; ultimately informing decisions about the allocation of resources towards obtaining various goals. This value is often experienced as craving, hunger, or drive. The stronger the hunger/craving, the more likely the organism will follow a set of behaviours aimed at obtaining the targeted reward. The more the behaviours lead to the reward, the greater the reinforcement of those behaviours. Learning theories of addiction focus on the organisms learned value of drugs, but tend to overlook the cognitive deficits and impaired inhibitory functioning seen in those with addiction.

Impaired decision making and inhibitory control

One of the key criterion for addiction is impaired control (American Psychiatric Association, 2013; Camí & Farré, 2003), which describes a loss of control over the use of drugs. The American Psychiatric Association (2013) gives examples such as using more than intended,

or unsuccessful attempts to reduce consumption. Naturally, this 'loss of control' has been investigated as a possible cause for the development or maintenance of addiction (Jentsch & Taylor, 1999). While the reward circuit explanation provides some answers to why those with addiction experience a loss of control, there is another aspect that helps explain why those with addiction have trouble overriding the strong impulses to consume drugs. Evidence exists for dysfunction in decision making in those with addiction (Jentsch & Taylor, 1999; J. L. Smith et al., 2014), and evidence suggests this impairment in decision making might be related to frontal lobe dysfunction or damage (Crews & Boettiger, 2009). The frontal lobe is a key region involved in decision making and the ability to make judgments about future consequences (Bechara, Damasio, Damasio, & Anderson, 1994; Bechara & Van Der Linden, 2005; Beer et al., 2004). However, dysfunction in this region likely plays a role in the development and maintenance of addiction (Lyvers, 2000). The learning described earlier plays a key role in the development of drug seeking behaviour and craving and likely explains the loss of control to some extent (Hyman, 2005); however, the 'loss of control' experienced by those with addiction, is likely also influenced by impairments in the very parts of the brain that help humans make good decision about the future and to weigh up consequences (Lyvers, 2000). Indeed, structural and functional abnormalities in the frontal lobe are common in those with addiction (Ersche et al., 2013; Luijten et al., 2014). Thus, structural and functional abnormalities might contribute to the 'loss of control' experienced by those with addiction. Though this theory does little to explain why environmental factors play such a big role in addiction.

A combination of theories

It is likely that all of the theories mentioned play some role in the development and maintenance of addiction. Certainly, pleasure and withdrawal contribute to learning (Hyman, 2005). Furthermore, past trauma and current stress are strongly linked to addiction, but are not sufficient to develop an addition. For example, regardless of trauma, people are unlikely to

develop an addiction to substances that do not have a strong influence on the reward system (Hyman et al., 2006). Finally, a well-functioning frontal lobe likely protects against the development of addiction due to a stronger ability to make judgments about future consequences and the ability to inhibit cravings and reduce impulsive actions (Crews & Boettiger, 2009). There are likely interactions between these systems. For example, stress might further impair an organism's inhibitory ability. This possibility will be explored further in chapter 4.

Chapter 3 - Methodology

This chapter presents the methodology for the thesis and the theoretical background for the methodology. This will be presented by first introducing the major methodological components that are common to most of the studies and then presenting methodologies specific to individual studies. Section 3.1 outlines the threat-of-shock paradigm, section 3.2 outlines the stop-signal task, section 3.3 outlines the physiological and questionnaire measures, and section 3.4 outlines the MEG methodology.

3.1 Threat-of-shock

The threat-of-shock procedure operationalizes anxiety allowing for distal and unpredictable threat, enabling it to be differentialized from fear (Davis et al., 2010; Grillon, 2002). The procedure (Figure 1) comprises a threat and a safe condition enabling the comparison of induced anxiety and non-anxious conditions within subjects. During the Safe condition, participants are informed that they are "safe" and will not receive aversive stimuli, usually in the form of electric shocks (Cornwell, Echiverri, Covington, & Grillon, 2008; Grillon, 2002). During the Threat condition, participants are informed that they "may receive a shock at any time" (Cornwell et al., 2008; Grillon, 2002).

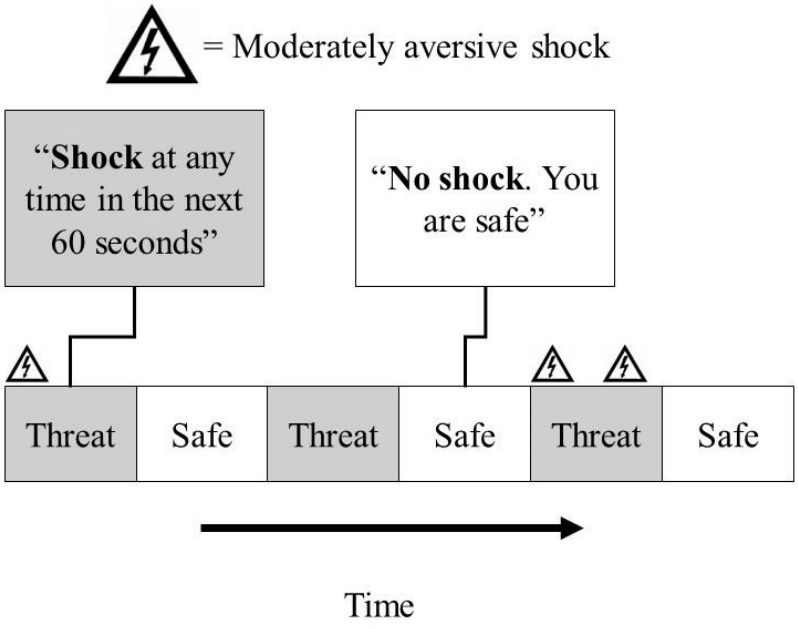

Figure 1. The threat-of-shock procedure switches between threat and safe conditions over a number of blocks ensuring both conditions are encountered throughout the duration of the experiment. Blocks have either one, two or no shocks (Cornwell et al., 2008; Grillon, 2002).

3.1.1 Background

The procedure allows for the defining characteristics of anxiety. The threat is distal and unpredictable rather than imminent (Davis et al., 2010). The threat-of-shock procedure is unique from anxiety inducing techniques used in animal models where aversive stimuli are paired with a conditioned stimuli to create fear or anxiety within the context of the conditioned stimulus (Davis et al., 2010). During the threat-of-shock procedure, aversive stimuli are only delivered to maintain credibility; it is the idea that a shock may be delivered that induces anxiety instead of the shock itself. Indeed, some studies have successfully induced anxiety with few (Baas et al., 2002) and even no delivery of shock (Hodges & Spielberger, 1966), relying on verbal warnings alone. This also mimics anxiety in real life where the verbal warning of threat is what induces anxiety (e.g. avoiding shark infested waters due to a warning sign) rather than the physical presence of threat. Threat-of-shock increases heart rate, Galvanic skin response, startle response, subjective anxiety, and leads to a number of cognitive and behavioural changes consistent with models of anxiety (O. J. Robinson, Vytal, et al., 2013). Importantly, the threat-of-shock procedure has a number of benefits when compared to other devices used to research anxiety in humans.

Many studies attempt to measure the influence of anxiety by recording responses on an anxiety questionnaire and comparing these with a dependent variable (e.g. reaction time) or by comparing participants with and without a diagnosis of anxiety (Eysenck et al., 2007). While this allows for an understanding of the relationship between trait/pathological anxiety and other measures, it does not allow causal inference due to the correlational nature of the studies.

Furthermore, these techniques are not ideal for understanding the adaptive changes associated with short live, anxious states. Other studies have tried to address these limitations by inducing anxiety through exposure to emotionally laden stimuli (e.g. movies, pictures, or music) prior to testing (Gray, 2001). However, without the continued threat imposed by the threat-of-shock producer, participants are likely to return to a neutral state during testing (Garrett & Maddock, 2001), especially if performing an experimental task, which can distract from previously induced anxiety (Erber & Erber, 2000). Finally, the threat-of-shock procedure allows experimenters to measure the influence of task irrelevant anxiety on task performance; unlike tasks that use emotional stimuli within their procedures (Shackman et al., 2006). Tasks with embedded emotional stimuli measure emotional perception rather than the influence of anxiety on performance (Shackman et al., 2006). In summary, the threat of shock procedure allows for the manipulation of anxiety that mirrors the unpredictable and distal nature of anxious arousal; furthermore, anxiety induced by this method last for the duration of testing (as long as the warning is present), and has shown to model anxiety well (Davis et al., 2010; Shackman et al., 2006).

3.1.2 Procedure

The studies reported within this thesis used similar threat-of-shock procedures. Each had multiple threat and safe conditions, each lasting for approximately 72 seconds, and presented one after the other, alternating across the duration of the experiment. Multiple alternating blocks were chosen instead of having two longer blocks for two reasons. First, anxiety wanes over time and shorter blocks ensure participants do not become desensitised to the anxiety condition (Shackman et al., 2006). Second, the alternating of blocks multiple times ensures there will be less within-subjects variance due to practice effects as each subject has multiple blocks from each condition at the beginning and at the end of the experimental paradigm. To further improve variance, the starting block alternated across participants with approximately half starting with a threat block and half starting with a safe block. Experiments typically consisted of ten threat and

ten safe blocks, with experiment 2 containing an additional 5 blocks of each during an "ignore tone" task. Each threat block had either zero, one, or two shocks, with no more than 10 shocks being delivered during testing. Shocks were delivered pseudo-randomly to allow for control over several timing aspects. Firstly, pseudo randomization allowed for shock timing to be separated from the presentation of the stop signal ensuring no contamination. Secondly, shocks were not delivered toward the end of the experiment. The purpose of delivering shocks was so participants believed shocks could come at any time. The purpose was to induce anxiety from the knowledge that a shock could come. This means there is no reason to deliver a shock at the end of the experiment. Pseudo-randomization ensured there were no unnecessary shocks being delivered. Prior to testing participants underwent a "shock workup" procedure where the intensity of the shock was individually calibrated, following previously established protocols (Cornwell et al., 2008). An initial weak shock was delivered followed by shocks of increasing intensity until the participant judged the shocks as "moderately aversive". The participants had full control over the intensity of the shock they received with full knowledge of the shock intensity before testing. Participants were also instructed they could reduce the shock at any time. This ensured that participants could provide informed consent and had control over their experience. Various measures were taken to check the credibility of the threat-of-shock manipulation. Some or all of the following measures were obtained during the studies: Galvanic skin response, heart rate, and subjective anxiety. These were used as a manipulation checks to ensure that the threat-of-shock procedure successfully induced anxiety in participants.

3.2 Stop-signal task

The Stop-signal task (Figure 2) involves the presentation of a stimulus indicating the need for a choice reaction (e.g. left or right stimuli) where participants must respond with the correct button as quickly as possible (e.g. press the left or right key). On a minority of trials (approximately

30%) a stop signal is presented after the presentation of the go signal. On these trials participants must not respond.

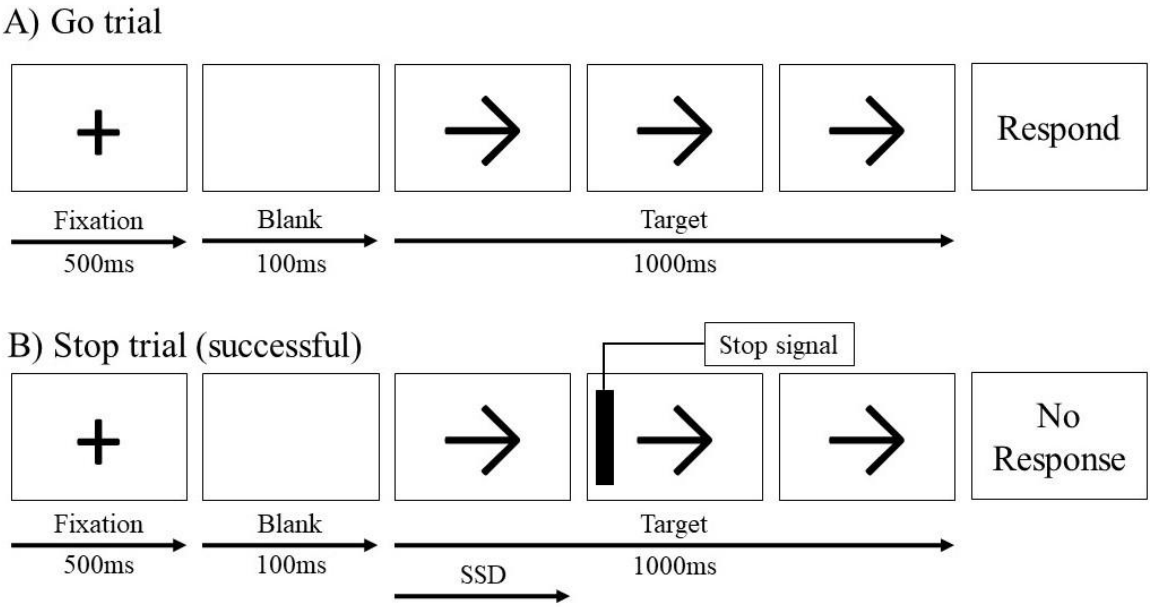

Figure 2. Representation of the stop-signal task procedure used in the studies. A) Go trial – where participants are required to respond to either a left or right arrow with the corresponding button. The go signal is represented by a rightward facing arrow. B) Stop trial – where a stop-signal (auditory tone) is presented after the go signal. Participants must not respond after hearing the tone. The delay between the presentation of the go signal and the stop signal changes across trials. This varying stop signal delay (SSD) is increased by 50ms following a successfully inhibited trial (making it harder to inhibit the next trial) or decreased by 50ms following an unsuccessfully inhibited trial (making it easier to inhibit the next trial).

3.2.1 Background

Withholding or interrupting a response is considered to be an important function of human behaviour and cognition (Bari & Robbins, 2013). While various tasks such as the Go/No-go task aim to measure response inhibition (O. J. Robinson, Krimsky, et al., 2013), the stop signal task is unique in that it ensures responses have been unambiguously initiated before the presentation of the stop signal (Logan & Cowan, 1984); addressing limitations of other inhibitory tasks (MacLeod et al., 2003). Furthermore, the Stop-signal task allows for the

measurement of the speed of the stopping process known as the stop-signal response time (SSRT; Logan & Cowan, 1984).

Logan and Cowan (1984) describe a metaphorical horse race between the go process and the stop process. The go process includes everything from the detection of a stimulus to the subsequent completion of a motor response. The stop process includes everything from the detection of the stop-signal to the inhibition of a motor response. While it is easy to measure the speed of the go process (time between stimulus presentation and motor response), the stop process cannot be directly measured as it is the absence of a response (Logan & Cowan, 1984). However, Logan and Cowan (1984) developed a way to calculate an estimation of the stopping process. They noted the distribution of go reaction times that is found in individuals; an individual will respond faster on some trials and slower on others. If the stop-signal reaction time (SSRT) is racing against the response to the go signal, it is more likely to 'lose' when participants have a quick go response and succeed when participants have a slow go response. Logan and Cowan (1984) suggested that if a task was manipulated so that participants always failed 50% of trials, the SSRT would be able to be calculated. They dynamically varied the delay between the stop signal and the go signal for each individual so that participants ended up with approximately a 50% probability of inhibition. They then subtracted the average stop-signal delay (SSD; the delay between the presentation of the go-signal and the stop-signal) from the median go RT. Figure 3 shows a graphical representation the model used to calculate SSRT.

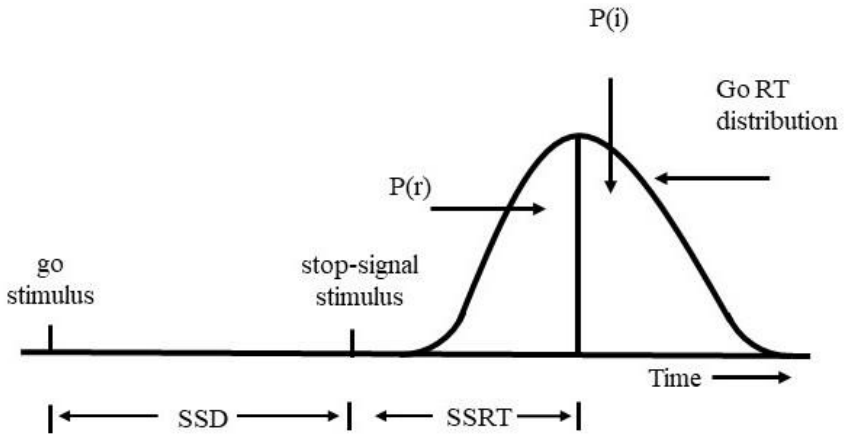

Figure 3. Logan and Cowan (1984)'s race model. The go signal reaction time distribution corresponds to the probability of responding (P(r)) and probability of inhibition (P(i)). Slower reaction times (right side of the curve) tend to be inhibited; while faster reaction times (left side of the curve) tend to not be inhibited. The Stop-signal Delay (SSD) indicates the time between the go signal and the stop-signal, which is varied across trials. The speed of the inhibitory process is the stop-signal Reaction Time (SSRT).

As can be seen in Figure 3, the stop signal reaction time is the time it takes to inhibit a response following the stop signal. Quick go reaction times will be harder to inhibit (left side of RT distribution curve), while fast go reaction times will be easier to inhibit (right side of RT distribution curve). According to the model, the point where a response is equally likely to be inhibited as to not be inhibited represents the average "finish line" for the stopping process. Using this theory, the SSRT can be calculated by subtracting the SSD from this cut-off point (mean go RT). Essentially marking the beginning of the stopping process (when the stop signal is presented) and the end of the stopping process (where the chance of inhibition is 50%).

3.2.2 Procedure

To achieve a 50% chance of responding, the delay between the go-signal and stop-signal is varied. When a stop signal is presented shortly after the go signal it is easier to inhibit a

response; however, when the stop signal is presented later, it is hard to inhibit as the go process is well underway (Logan & Cowan, 1984). The stop signal can be dynamically altered based on the performance of the previous stop trial. Every time a participant successfully inhibits a trial the SSD is increased making it harder to inhibit the next trial. The opposite is done following failed trials where the next stop trial becomes easier to inhibit.

The studies in the present thesis adjusted the SSD using two staircase algorithms independently adjusted for threat and safe conditions giving a total of four staircases. One staircase began with a high stop signal delay (e.g. 250ms) the other began with a low SSD (e.g. 50ms). Each SSD was increased by 50ms following a successful stop-signal trial, and decreased following a failed trial. This allowed for a relatively quick convergence on a SSD that achieved close to a 50% chance of inhibition. Unfortunately, it is not always possible to manipulate the SSD well enough to achieve a perfect 50% chance of inhibition. A number of techniques have been developed to account for variations in probability of inhibition (Logan & Cowan, 1984; Verbruggen et al., 2019). Verbruggen et al. (2019) recommends using the integration method where the cut of point in the go RT distribution corresponds to the probability of responding (rather than simply taking the mean); this is done individually for each participant to calculate the SSRT for that participant. For example, if a participant has a probability of responding of 40% the n^{th} highest go RT would be taken corresponding to .4 probability of responding. For example, if there were 160 go trials the 64^{th} fastest go trial would mark the cut-off point (160 x .40 = 64). The mean SSD would then be subtracted from this RT to give the SSRT. Verbruggen et al. (2019) also recommends replacing missing values (i.e. when a participant does not respond during a go trial) with the maximum go RT for that participant as this provides a more accurate estimation of SSRT and compensates for go omissions.

The stop-signal tasks used in the two experiments in the present thesis meet all nine recommendations from Verbruggen et al. (2019) for experimental design and analysis of results:

1) an appropriate go task was used – a simple two-choice reaction time task; 2) the stop signal was salient – a simple auditory tone; 3) the stop signal was presented on a minority of trials – approximately 30 percent; 4) a tracking procedure for SSD was used – see above; 5) participants were instructed not to wait for the stop signal and were reminded of this between runs; 6) at least 50 stop trials were used in each condition – there were approximately 100 stop trials in each condition for each experiment; 7) race model assumptions were not violated in any of the tasks – see individual chapters for more detail; 8) the integration method with replacement of go omissions was used to calculate SSRT; 9) participants with large deviations in probability of responding were removed – see individual chapters for more details.

A new model of stop-signal analysis has been developed that attempts to factor in 'trigger failures' into the estimation of SSRT (Matzke, Hughes, Badcock, Michie, & Heathcote, 2017). These 'trigger failures' are thought to represent attentional lapses rather than inhibitory control deficits. The assumption is that occasional attentional lapses may result in an overestimation of SSRT due to participants inadvertently successfully inhibiting a stop-signal (Matzke et al., 2017). While this technique is interesting, it has not yet been developed for within-subjects design, which is the design used in the current thesis. Developing a new statistical analysis is beyond the scope of the current thesis. Thus, the thesis uses the integration method recommended by Verbruggen et al. (2019).

3.3 Physiological and questionnaire measures

3.3.1 Heart rate

Heart rate refers to the speed at which the heart beats and is typically measured in beats per minute (Achten & Jeukendrup, 2003). The induction of stress or the presence of threat increases heart rate (Suess, Alexander, Smith, Sweeney, & Marion, 1980). This is thought to occur through increased sympathetic nervous system activity (AX, 1953; Palomba, Sarlo, Angrilli, Mini, & Stegagno, 2000). Heart rate was used as a manipulation check to determine if the threat-

of-shock procedure reliably induced anxiety in participants. This manipulation check has been used in a number of other threat-of-shock studies (e.g. Lavric, Rippon, & Gray, 2003; Shackman et al., 2006).

Heart rate was recorded utilizing Labchart software (ADInstruments, 2012) and collected using a bio amp (AD Instruments ML4856) and Meditrace electrodes, which were placed on each wrist. The ground electrode was placed on the left ankle. A band-pass filter of 50Hz was applied to remove interference from mains powerlines. To ensure heart rate changes were not due to a physiological response to shock delivery, only blocks containing no shocks were used in heart rate analysis. Heart Rate Variability (HRV) is another measure that is often used to reveal differences between stressful and non-stressful states (Quintana, Alvares, & Heathers, 2016). However, the current thesis chose to use heart rate given the susceptibility of HRV to be distorted by noise from motor tasks (Quintana et al., 2016) and the regularity of motor responses in the SST. Further, the nature of the tasks used in this thesis can change respiratory variability (Vlemincx, Van Diest, & Van den Bergh, 2012), which in turn can affect HRV (Quintana et al., 2016).

3.3.2 Galvanic skin response (GSR)

The Galvanic skin response is an electrophysiological measurement used to assess the resistance of the skin, which is thought to alter depending on the state of the sweat glands (Kucera, Goldenberg, & Kurca, 2004; Montagu & Coles, 1966). As sweat is controlled by the sympathetic nervous system (Kucera et al., 2004), the GSR has been used as a measurement of anxiety and stress (e.g. Bradley, Zlatar, & Lang, 2018; Bridger & Mandel, 1964; Horvath, 1978; Kurniawan, Maslov, & Pechenizkiy, 2013). The present paper used GSR as a manipulation check to ensure threat-of-shock reliably induced anxiety in participants.

GSR was recorded utilizing Labchart software (ADInstruments, 2012) and collected using a bio amp (AD Instruments ML116) and electrodes, which were placed on the index and ring fingers of participants. A band-pass filter of 50Hz was applied to remove interference from mains powerlines. To ensure GSR changes were not due to a physiological response to shock delivery, only blocks containing no shocks were used in heart rate analysis.

3.3.3 UPPS-P

The UPPS-P (Lynam et al., 2007) comprises 59 Likert-type items (Appendix B) and is designed to measure five areas of impulsivity: negative urgency ("I have trouble resisting my cravings (for food, cigarettes, etc.)"), (lack of) premeditation ("My thinking is usually careful and purposeful"), (lack of) perseverance ("I generally like to see things through to the end"), sensation seeking ("I generally seek new and exciting experiences and sensations"), and positive urgency ("When I am very happy, I can't seem to stop myself from doing things that can have bad consequences"). A 4-point scale was used for rating items from 1 (*strongly agree*) to 4 (*strongly disagree*). Higher subscale scores indicate greater impulsivity. Scores can range from 1 to 4 and some items are reverse coded. Convergent and discriminate validity has been shown between the subscales and analyses support the 5 factor model (Cyders & Smith, 2007; G. T. Smith et al., 2007). The UPPS-P has also shown predictive validity for impulsive disorders (Cyders & Smith, 2007). Each subscale of the UPPS-P has a reliability of above .80 (Cyders, 2013).

3.3.4 STAI

The STAI (Spielberger, 1983) comprises 40 Likert-type items (Appendix C) intended to assess state and trait anxiety. State anxiety assesses how participants feel "right now" using items such as "I am tense" and uses a 4-point scale from 1 (*not at all*) to 4 (*very much so*). Trait anxiety assessed how participants feel "in general" using items such as "I feel nervous and restless" uses a 4-point scale from 1 (*almost never*) to 4 (*almost always*). Higher scores on either scale indicate

greater anxiety. The STAI has shown discriminant and convergent validity (Oei, Evans, & Crook, 1990; Spielberger, 1983) and has shown a stable reliability (Barnes, Harp, & Jung, 2002).

3.3.5 Addiction Severity Index "Lite"

Due to the heterogeneous nature of addiction, a simple severity scale such as the STAI for anxiety is difficult to deliver in the short space needed for research purposes. The ASI-lite is a measurement of drug use and severity that is short and is often used by researchers and clinicians (Cacciola, Alterman, McLellan, Lin, & Lynch, 2007). The lite version of the ASI focuses mostly on substance use frequency and administration method (Appendix D). The ASI (Lite) was used in the current thesis to determine participants predominant drug/drugs of dependance.

3.3.6 Other self-report measures

The current thesis collected several measures that were not based on established scales. Participants were given a questionnaire focused on the demographic questions: age, gender, handedness, and level of education (Appendix E). Participants were also verbally asked to give a subjective anxiety score ranging from zero (indicating no anxiety) to 10 (indicating extreme anxiety). This question was asked after each block or run to determine how anxious participants thought they were in each condition. Scores for safe and threat blocks were compared as a manipulation check to ensure the threat-of-shock procedure reliably induced anxiety. Finally, participants were verbally asked to rate how uncomfortable shocks were during the shock workup procedure. Participants were told that zero indicated no discomfort while 10 indicated extreme discomfort. Participants had the choice to increase or decrease shock level and would indicate how uncomfortable the shock was. Scores on this scale tended to sit around five out of ten.

3.4 Magnetoencephalography (MEG)

3.4.1 Background

MEG is a noninvasive brain recording tool used to detect magnetic fields generated by neurophysiological electrical current flow (Hämäläinen et al., 1993). These currents are thought to be the summation of excitatory and inhibitory post synaptic potentials, which (in comparison to action potentials) are long lived enough to overlap in time with surrounding neurons and lead to a summated change in potential (Hämäläinen et al., 1993). It is thought that the pyramidal cells have a unique topological arrangement so that input to multiple cells does not cancel each other out, rather the combined input leads to a net current flow in the same direction, which can be detected using MEG (Hämäläinen et al., 1993). With each electrical current there is an associated magnetic field, which is what the MEG detects (Bao, Ammari, & Fleming, 2002). The magnetic fields produced by the brain typically have extremely small amplitudes, which do not exceed a few hundred femto tesla (10^{-15} T; Singh, 2014). When compared with the magnetic field of the Earth (10^{-4} to 10^{-5} T) or MRI (usually 1.5-3 T), the relative size of the brain's magnetic field becomes apparent (Singh, 2014). The MEG employs superconductive sensors (SQUID coupled to magnetometer/gradiometer) that are able to detect these very small magnetic fields (Hämäläinen et al., 1993). However, the existence of other magnetic field sources and the small magnetic fields of the brain necessitate the use of shielding. Typically, MEG data recording takes place in a magnetically-shielded room that filters the magnetic fields from other sources such as the Earth's naturally-occurring magnetic field, fields generated by equipment and power sources, or hardware such as elevators and air-conditioning (Puce & Hämäläinen, 2017). Further, devices used in the shielded room must be MEG-compatible; for example, tubular insert earphones (Puce & Hämäläinen, 2017). The MEG sensors are not attached to the participant's head like is typically done in EEG; rather, the sensors are placed in a fixed array in a helmet like structure where participants can place their heads (Singh, 2014). The fixed position of the sensors relative to each other allows for easier calculation of signal source compared to placing sensors on the scalp where relative distance varies (Singh, 2014). Unlike electrical signal

detected with EEG, magnetic signal detected with MEG is able to move through any empty space between scalp and sensors (Hämäläinen et al., 1993). However, the disadvantage of this system compared to sensors placed on the head is MEG is sensitive to participant head movements (Puce & Hämäläinen, 2017). Nevertheless, continued monitoring of head location relative to sensors has allowed for mathematical corrections of head movements and partially overcome this problem (Puce & Hämäläinen, 2017).

The MEG has several advantages over other imaging techniques such as fMRI, especially when imaging anxious responses. Blood flow, which is what fMRI detects, is only a secondary measure of neural activity (E. L. Hall et al., 2014). Further, anxious arousal (the primary manipulation of this thesis) alters cerebrovascular function (Giardino et al., 2007). Giardino et al., argue that states of anxious arousal are often accompanied by respiratory changes that alter arterial CO2 tensions and create changes in cerebral blood flow. Thus, changes in cerebral activity measured using fMRI between anxious and non-anxious conditions may be confounded by anxiety-induced changes in cardiovascular function. Unlike fMRI, MEG has a high temporal resolution allowing differentiation of brain activity on a sub-millisecond scale (Baillet, 2017). While this is also true of electroencephalography (EEG), unlike EEG, MEG is able to resolve activity across brain regions with high spatial resolution and without the signal distortion caused by intervening tissue (Baillet, 2017). In the present thesis, high spatial resolution is realised through a source analytic technique called adaptive beamforming.

3.4.2 Beamforming

While functional magnetic resonance imaging (fMRI) is the most common brain imaging method in cognitive neuroscience, MEG research is growing (Gross et al., 2013), which may be due to the development of new techniques such as beamforming (Hillebrand, Singh, Holliday, Furlong, & Barnes, 2005). Before the application of beamforming techniques, MEG research relied heavily on time-domain averaging of brain responses across many trials, limiting empirical studies to evoked responses that are strictly time-locked to stimulus and/or response

onsets (Hillebrand et al., 2005). Overcoming this constraint, allows for the measurement of activity that may be linked to higher-level cognitive processes (Hillebrand & Barnes, 2005). At the beginning of the 21st century, more researchers began using beamforming to analyse MEG signals in more flexible ways (e.g.Cheyne et al., 2003; Furlong et al., 2004).

Originally developed for radar use (Van Veen & Buckley, 1988), beamforming selectively weights the contribution of each sensor to an overall output. This, combined with a constructed "source model" can be used to focus on signals from a location of interest while attenuating signals from other locations; creating a "virtual electrode" (Hillebrand & Barnes, 2005). The weights for this "virtual electrode" are defined completely by the forward solution and the data covariance matrix (lead field) for the point's source (Hillebrand et al., 2005). To reconstruct the source of each signal, a source space must first be defined by forming a volumetric grid of target locations (Hillebrand & Barnes, 2005). The translation of a two-dimensional signal into three dimensional space is an example of "the inverse problem", where there is no perfect solution (Hillebrand & Barnes, 2005). However, by making some assumptions (e.g. that no two distinct locations show perfectly correlated signals), researchers are able to overcome the inverse problem (Hillebrand & Barnes, 2005). Hillebrand et al. (2005) provide evidence that the assumptions used to solve the inverse problem are empirically justified.

Beamforming involves several steps. First, a volume conduction model or "source model" is constructed. One step needed to solve the inverse problem is the creation of a "lead field". The lead field is a geometrical description that combines the sensor array and the volume conduction model (Hillebrand & Barnes, 2005). This model is essentially a representation of a grid over the brain. This grid is often created by co-registering structural MRI data to MEG coordinates (Hillebrand & Barnes, 2005).

Due to the high sensitivity of MEG sensors, environmental noise and patient artefacts must be eliminated by shielding, sensor design, and filtering (Hämäläinen et al., 1993). The

studies in this thesis did not employ active shielding due to the ability of beamformer to mathematically filter out artefact not originating from the head. Sensors are designed so that differences between signals hitting each loop of the sensor are detected. This helps to filter out external noise as distal signals will typically have no variation when detected by coils that are close to each other.

3.4.3 MEG Procedure used

3.4.3.1 Acquisition

We used a 306-channel Elekta Neuromag® TRIUX magnetometer system (Helsinki, Finland) to obtain MEG recordings. A sampling rate of 1000Hz was used to digitize the magnetic flux density. This was done in a magnetically shielded room with internal active shielding disengaged. Head position relative to the sensor array was tracked using five continuous head positioning indicator (cHPI) coils (one on each mastoid and three across the forehead). The three fiducial positions (nasion and pre-auricular points) and cHPIs were digitized with a Polhemus FASTRAK head digitizing system (Polhemus Inc., Colchester, VT, USA) and marked for later identification during MRI scanning. After MEG acquisition, a T1-weighted MRI obtained using a Siemens TrioTim 3-T system was acquired. The MRI acquisition used the following parameters: TR = 1.9s, TE = 2.5 ms, sagittal slice thickness = 1 mm, matrix = 256 x 256. Vitamin E capsules were attached to the three, pre-marked, fiducial points during the MRI scan to facilitate spatial co-registration. Chapter 6 included previously gathered data, which used different MRI parameters. These details are described in chapter 6.

3.4.3.2 Analysis

Using Fieldtrip Software (Oostenveld, Fries, Maris, & Schoffelen, 2011), analysis began with the construction of a volume conduction model. DICOM data were first assembled into 3d volumes and fiducial points were marked to spatially align MRIs to the MEG sensor array. The

co-registered MRI data were then re-sliced and segmented into the three tissue types (brain, skull, and scalp), and a convex hull was created from the brain mask. The volume conduction model was specified with a single shell using the Nolte method (Nolte, 2003). After the removal of dead channels and filtering of mains, epochs were defined based on the details of the specific study and band pass filtered based on the frequency range of interest (e.g. 14-30Hz). A source grid was then created with grid points spaced 5 mm and a leadfield matrix was calculated. Source power estimation was calculated using linear-constrained minimum-variance (LCMV) beamformer approach (Van Veen, Van Drongelen, Yuchtman, & Suzuki, 1997). Both volumetric beamformer data and MRIs were then transformed into standardized Talairach space for group-based analyses using Analysis of Functional NeuroImages (AFNI; Cox, 1996). Further methodological details of each MEG study are presented in the relevant chapters.

MEG is an ideal non-invasive tool to be used for the mapping of brain activity with high temporal resolution, and with the use of beamforming, high spatial resolution. This is important for the mapping of inhibitory activity using the stop-signal task, as the inhibitory processes elicited by this task unfold on the subsecond scale (Verbruggen & Logan, 2008b).

Chapter 4 – Induced anxiety and response inhibition

So far, the thesis has introduced the topics of anxiety, response inhibition, impulsivity, and addiction. The overall aim of the current thesis (section 1.6) is to establish an understanding of how two key features of mental disorders (anxiety and self-control) interact. This chapter operationalizes these variables into an experimental paradigm by exploring how induced anxiety influences response inhibition. As discussed in section 1.5.1, the relationship between anxiety and inhibitory control is not yet fully understood. While earlier theories suggested anxiety would impair inhibitory control due to the facilitation of the processes that must be inhibited (Eysenck et al., 2007), O. J. Robinson, Krimsky, et al. (2013), argued that induced anxiety facilitates inhibitory control due individuals engaging in more cautious responding. The latter theory was based on a study that induced anxiety using threat-of-shock and tested performance on the Go/No-go task, while the former was primarily based on differences between those with high and low trait anxiety or with differences between those with anxiety disorders and healthy controls. Shackman et al. (2006) and many other theorists argue that induced anxiety is a better way to measure the effects of anxiety because trait anxiety and anxiety disorders come with confounding factors, suggesting the study by Robinson et al. better reflects the true relationship between anxiety and response inhibition. While this is true, a study by Cornwell, Mueller, et al. (2012) also induced anxiety using threat-of-shock and found, using a mixed saccade task, that induced anxiety facilitated reflexive responding, yet impaired inhibitory control of eye movements. That is, eye movements directed away from a peripheral stimulus were impaired by anxiety. The inconsistencies between these studies could be due to the differences between eye movements and hand movements, due to the ratio of inhibitory signals to non-inhibitory signals, or due to the interpretation of what each study is measuring. One possibility is that, in this instance, the Go/No-go task was revealing differences in sustained attention rather than response inhibition. Indeed, from an evolutionary perspective, anxiety likely facilitates sustained

attention. If the mind wanders or the individual becomes tired in a threatening situation, the individual may be less likely to survive. An alternative task is needed to reveal the true relationship between induced anxiety and response inhibition. As outlined in section 1.5.1, the Stop-signal task is ideal for this.

4.1 Paper – Threat-induced anxiety weakens inhibitory control

4.1.1 Rationale for using the Stop-signal task

Although O. J. Robinson, Krimsky, et al. (2013) provided some insight as to how threat-induced anxiety influences inhibitory control, the presentation of the no-go stimulus within the Go/No-go task does not unambiguously initiate a motor response (MacLeod et al., 2003). This is because the stimulus signalling a go trial is different from the stimulus signalling a no-go trial. As the task relies on the discrimination of sensory stimuli, the improved performance during threat-induced anxiety could be attributed to the sensitization of early sensory-perceptual processes (Baas, Milstein, Donlevy, & Grillon, 2006; Fucci, Abdoun, & Lutz, 2019; Shackman, Maxwell, McMenamin, Greischar, & Davidson, 2011), in addition to the improved sustained anxiety. In contrast to the Go/No-go task, the Stop-signal task ensures that the go responses are unequivocally initiated. This is because the signal to inhibit a response does not occur until after the go-signal (Logan & Cowan, 1984). Thus, the coming paper will explore how induced anxiety influences performance on the stop-signal task as a way to determine if response inhibition is truly impaired by induced anxiety.

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Short communication

Threat-induced anxiety weakens inhibitory control

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ABSTRACT

Growing evidence indicates that anxiety impairs cognitive control processes, including inhibitory functioning. However, there are reports of anxiety state-related improvements in response inhibition performance in a go/nogo (GNG) task. Here we employed the stop-signal task (SST) to examine in complementary fashion the link between anticipatory anxiety and inhibitory control. Participants (N = 45) completed the SST under threat of unpredictable shocks and safe conditions while physiological activity (skin conductance and heart rate) was monitored. In addition to increased physiological activity, we found that stop-signal reaction time (SSRT), a robust measure of stopping efficiency, was prolonged during threat compared to safe without any difference in choice reaction times to go stimuli. This finding supports the claim of impaired inhibitory control in anxiety, and by consideration of differences between the SST and GNG tasks, can be reconciled with evidence of improved response inhibition on the latter under similar threat conditions.

1. Introduction

Anxiety often impairs cognitive functioning. Eysenck and colleagues (2007) theorize that anxiety primarily disrupts inhibition and shifting, two key components of executive functioning or cognitive control (Miyake, Friedman, Emerson, Witzki, & Howerter, 2000), which may underlie many effects observed across diverse cognitive tasks (also see Pessoa, 2009 for a more general treatment of emotion and cognition). Much of the evidence linking anxiety to impaired cognitive performance, however, comes from correlational studies involving anxiety patients and, more commonly, healthy individuals ranging in subclinical levels of trait anxiety (e.g., Derakshan, Ansari, Hansard, Shoker, & Eysenck, 2009; Forster, Nunez Elizalde, Castle, & Bishop, 2015). While these data are critical to examining the relationship between anxiety and cognition, and characterising deficits in patients, experimental studies that manipulate anxious arousal are needed to establish causation (Shackman et al., 2006).

The threat of shock paradigm holds considerable promise for its ability to separately elicit 'fear' and 'anxiety' states (Schmitz & Grillon, 2012). Inspired by rodent studies (Davis, Walker, Miles, & Grillon, 2010), the distinction between fear and anxiety is achieved by varying the predictability and duration of threat. Phasic fear is elicited by short-duration cues (e.g., 10-sec) signalling imminent shock and sustained anxiety is elicited by long-duration contexts (e.g., > 60-sec) in which shocks are unpredictable. Clinical and pharmacological studies involving startle reflex modulation have substantiated the dissociation of these two defensive states and support the validity of using threat of unpredictable shocks, in particular, to elevate anxious arousal (Grillon, 2008). In addition, neurophysiological data suggests that threat of unpredictable shocks sensitizes sensory-perceptual systems and boosts stimulus-driven attention (Balderston et al., 2017; Cornwell, Garrido, Overstreet, Pine, & Grillon, 2017; Cornwell et al., 2007). This effect could have important downstream negative consequences on executive functioning and the ability to flexibly control behavior.

While various cognitive deficits have been observed during unpredictable threat (Robinson, Vytal, Cornwell, & Grillon, 2013), Robinson, Krimsky, and Grillon, (2013) reported that threat-induced anxiety, surprisingly, improved response inhibition performance on a go/nogo task (GNG). Participants, under threat, were better able to withhold responses to the infrequently-presented nogo stimulus (.10 probability) than when safe. This finding has been replicated multiple times (Grillon et al., 2017; Mkrtchian, Roiser, & Robinson, 2017; Torrisi et al., 2016), running counter to theoretical predictions (Eysenck, Derakshan, Santos, & Calvo, 2007) and empirical evidence from other inhibitory tasks (mixed-saccade task, Cornwell, Mueller, Kaplan, Grillon, & Ernst, 2012; Stroop task, Pallak, Pittman, Heller, & Munson, 1975). Recent analyses of these GNG data suggest that those with the highest state anxiety and clinically anxious patients also have a heightened tendency to withhold responses erroneously to the go stimulus under unpredictable threat (Grillon et al., 2017). This raises some ambiguity whether the GNG task is optimized to recruit inhibitory control mechanisms.

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Here we tested the hypothesis that anxiety impairs inhibitory control in the stop-signal task (SST). With the stop-signal presented after the go stimuli, the SST has the advantage over the GNG task that actions are explicitly cued and initiated centrally *before* the countermanding signal is presented; hence the SST unambiguously operationalizes inhibition (MacLeod, Dodd, Sheard, Wilson, & Bibi, 2003). Moreover, by adaptively modifying the delay between go- and stop-signals based on performance, stopping efficiency can be estimated (stop-signal reaction time, SSRT) using well-established methods (Logan & Cowan, 1984). This allows for more precise quantification of inhibitory control in high versus low anxiety states. We predicted that participants under threat of shock would show slower SSRTs compared to safe conditions.

2. Methods

2.1. Participants

In total, fifty healthy adults volunteered for university course credit. Two participants failed to complete the study, and three others were removed from analyses for poor performance (p(inhibition) < .25). The final sample was 45 participants (30 women; mean age ± SD, 22 ± 5 years), exceeding the minimum sample ($N = 34$) that we calculated was necessary to maintain 80% power (alpha = .05, two-tailed) assuming a medium effect size ($dz = .05$, Faul, Erdfelder, Lang, & Buchner, 2007). The study was approved by the local ethics committee and informed consent was obtained from each participant.

2.2. Design

Participants completed the SST with concurrent physiological monitoring of skin conductance level (SCL) and heart rate (HR) under threat of unpredictable shocks and safe conditions. For threat, participants were told that they could "receive electric shocks at any time." For safe, participants were instructed that they were "safe from shock." Order was counterbalanced across participants and the stimulation electrodes were removed and re-attached between blocks. Participants rated their anxiety on a scale from 0 ('no anxiety') to 10 ('extreme anxiety') after each block. Shocks (10 total) were delivered pseudo-randomly during threat (0, 1 or 2 shocks/block), early, middle or late in a block, and timed to occur at least 2 s before a stop-signal trial.

2.3. Task procedure

Before performing the SST, participants completed the Spielberger State-Trait Anxiety Inventory (Spielberger, Gorsuch, & Lushene, 1970) and the UPPS-P Impulsive Behavioural Scale (Lynam, Smith, Cyders, Fischer, & Whiteside, 2007) to measure trait impulsivity. No other measures, tasks or conditions were administered. Participants then completed one practice block. Physiological and behavioural data were acquired in 20 task blocks (10 threat/safe) lasting ~72 s/block. Each block contained 34 trials (ITI, 1.7–4.1 s) with a stop-signal probability of .29 (10/34), presented in pseudo-random order (Hughes, Fulham, & Michie, 2016). Trials began with a fixation cross (500-ms) followed by a go stimulus (1000-ms), left or right pointing arrow. Participants pressed the corresponding arrow key as quickly and accurately as possible.

The stop-signal was an auditory tone (900 Hz; 500-ms) presented through headphones. Stop-signal delays (SSD) were set using both ascending and descending staircase algorithms starting at 50 and 250 ms. Separate staircases were used for each go stimulus and for threat and safe. SSD adjusted by 50 ms, with an increase following successful inhibition and a decrease following failed inhibition, to achieve an approximately .50 p(inhibition) in each condition. To allow for reasonable convergence, data from the first threat and safe block were discarded from analysis. Participants were instructed not to delay their go response in anticipation of a stop-signal.

Stop-signal reaction time (SSRT) was calculated using the preferred integration method, which accounts for deviations from a .50 p(inhibition) by computing the integral of the cumulative goRT distribution defined by the p(response) for a given SSD (Logan & Cowan, 1984; Verbruggen & Logan, 2009; Verbruggen, Chambers, & Logan, 2013).

2.4. Physiological measures

Physiological data were continuously recorded (50 Hz lowpass filter) and analysed using LabChart 8 (ADInstruments, NZ). Electrocardiographic electrodes were attached to each forearm with a ground placed on the left ankle to measure HR. SCL electrodes were strapped to the proximal phalanges of the non-dominant index and ring fingers. A bar electrode was used to deliver a 25-ms electrical shock to the non-dominant wrist (PowerLab 26 T). Shock intensity (3–20 mA) was calibrated individually using a work-up procedure to determine a moderately uncomfortable level. Threat and safe blocks 4 and 8, during which no shocks were administered, were used for calculating average HR and SCL.

3. Results

3.1. Subjective and physiological differences

Participants, on average, reported higher anxiety during threat (mean ± SEM, 4.4 ± 0.2) relative to safe conditions (1.4 ± 0.2), $t_{44} = 14.00$, $p < .001$. In addition, SCL and HR were significantly higher during threat (9.61 ± 1.12 μS, 75.5 ± 1.6 bpm) compared to safe (8.01 ± 1.07 μS, 74.5 ± 1.4 bpm), $t_{44} = 4.75$, $p < .001$ and $t_{44} = 2.11$, $p = .04$, respectively.

3.2. Stop-signal task performance effects

Table 1 presents SST performance data across threat and safe conditions. While accuracy and reaction time on go trials were not different across conditions, SSRT was significantly delayed under threat relative to safe conditions. Mean stop signal delays were significantly shorter during threat relative to safe. To rule out the possibility that shocks interfered with inhibitory control, SSRT was also estimated from the two threat blocks (4th and 8th) with no shocks (and two adjacent safe blocks). SSRT was significantly longer during threat (296 ± 7 ms) compared to safe (268 ± 5 ms), $t_{44} = 4.44$, $p < .001$. Finally, no correlations were observed between questionnaire scores and SST data.

Table 1
Mean (± SEM) stop-signal task performance ($N = 45$) across threat and safe conditions.

		Threat	Safe	Student *t*	Cohen's *dz*
Go trials					
	Missed Go (%)	1.9 ± 0.4	1.5 ± 0.4	0.80	
	Incorrect Go (%)	1.0 ± 0.2	1.1 ± 0.2	−0.49	
	Median Go RT (ms)	533 ± 16	538 ± 18	−1.07	.17
Stop trials					
	p(inhibition)	.49 ± .02	.52 ± .01	−2.70	.40
	SSRT(ms)	289 ± 7	266 ± 5	3.72*	.51
	Mean SSD (ms)	244 ± 15	259 ± 15	−4.62*	.67
	Median Failed RT (ms)	499 ± 14	505 ± 16	−1.02	.16

Note. Summary statistics are calculated over 9 threat and 9 safe blocks. Median Go RT is calculated over accurate go trials only. SSRT = stop signal reaction time; SSD = stop signal delay.

* Significant t's evaluated at alpha < .05 adjusted for multiple comparisons using a modified Bonferroni step-down procedure (Rom, 1990).

^ Statistically equivalent means based on a two one-sided test of equivalence using 5% bounds, $t(44) = 4.32$, $p < 0.001$ (Lakens, 2017).

4. Discussion

We compared SST performance in healthy individuals during threat of unpredictable shocks and during safe conditions. The main finding of slower SSRT estimates during threat of shock indicates that anxiety weakens inhibitory control, supporting theory (Eysenck et al., 2007) and converging with other evidence of a negative impact of anxiety (Cornwell et al., 2012; Pallak et al., 1975). Although this is the first report of experimentally-induced sustained anxiety effects on SST performance, previous studies have reported similar effects on SSRT with emotional stimuli embedded in the SST (Pessoa, Padmala, Kenzer, & Bauer, 2012; Verbruggen & De Houwer, 2007). Nevertheless, our result runs counter to studies reporting that threat of shock improves withholding responses to no-go stimuli in a GNG task (Grillon et al., 2017; Mkrtchian et al., 2017; Robinson, Krimsky et al., 2013; Torrisi et al., 2016).

Verbruggen and Logan (2008) argue that the two tasks place differential demands on automatic versus controlled inhibition. The GNG task, with consistent mapping between the go stimulus (or nogo stimulus) and response (or no response), allows for the development of stimulus-driven (automatic) inhibitory processes through associative learning. The beneficial effect of anxiety seen in the GNG task could then be due to general heightening of sensory-perceptual processing and facilitation of stimulus-driven attention (2017, Cornwell et al., 2007; Shackman, Maxwell, McMenamin, Greischar, & Davidson, 2011), which could promote associatively-linked responding and withholding in an aversive context (Mkrtchian et al., 2017). The SST does not have consistent stimulus-response mapping insofar as go and stop signals are independently presented in sequence, which triggers controlled inhibitory processes more reliably than the GNG task (Verbruggen & Logan, 2008). Thus the detrimental effect seen in the SST may directly reflect weakened cognitive control under threat.

Slower SSRT under threat was not directly linked to shock administration, insofar as we showed a similar effect when only blocks without shocks were analysed. It remains possible that the anticipation of aversive shocks creates attentional competition between sensory modalities and thus interfered with processing the auditory stop-signal. We contend that this is unlikely based on previous observations of an attention-to-prepulse effect[1] on startle responses without explicit attentional instructions during long-duration unpredictable threat (Cornwell, Echiverri, Covington, & Grillon, 2008; Grillon & Davis, 1997). In those studies, an auditory prepulse inhibited startle more – or a greater attention-to-prepulse effect was observed – during threat than safe. This suggests that anticipating unpredictable shocks does not reduce stimulus-driven processing in other sensory modalities, pointing more to the possibility that slower SSRT under threat results from weakened inhibitory processes downstream from early perceptual-attentional processing.

To conclude, impaired inhibitory control might have important implications for clinical anxiety that are worth future examination. Together with improved GNG performance, these complementary data could pinpoint more exactly the neurocognitive mechanisms that are disrupted in anxiety patients. In addition, the anxiety-related effects on SST may be relevant to other psychopathologies with impulse control and/or substance abuse problems (Bari & Robbins, 2013), which could be exacerbated during periods of elevated stress and anxiety.

Declaration of interest

None.

[1] Attention-to-prepulse refers to the effect of greater inhibition of the startle reflex when a low-intensity prepulse stimulus, which briefly precedes the startle-eliciting probe, is task-relevant and thus attended to versus task-irrelevant (e.g., Filion, Dawson, & Schell, 1993)

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4.2 Additional results and discussion

Performance based on outcome of the previous trial

Additional analysis were performed, which relate to the overall theme of the thesis. Chapter 8 will explore Stop-signal task performance in a group with addiction. Evidence suggests that those with addiction not only have slower SSRT (J. L. Smith et al., 2014), but also have less adaptive responding; where unlike healthy controls, those with addiction do not slow their responses after stop-signal errors (Lawrence, Luty, Bogdan, Sahakian, & Clark, 2009; C. R. Li, Huang, Constable, & Sinha, 2006; C. R. Li, Luo, Yan, Bergquist, & Sinha, 2009). Due to this, post error slowing was explored in the current sample to provide a baseline before exploring those with addiction problems in chapter 8. Further, the impact of anxiety will be explored on post error slowing.

Performance was compared across the outcome of previous trials to determine how participants updated their strategy based on continued feedback. The results are shown in Figure 4. Means and SDs are also shown in Table 1.

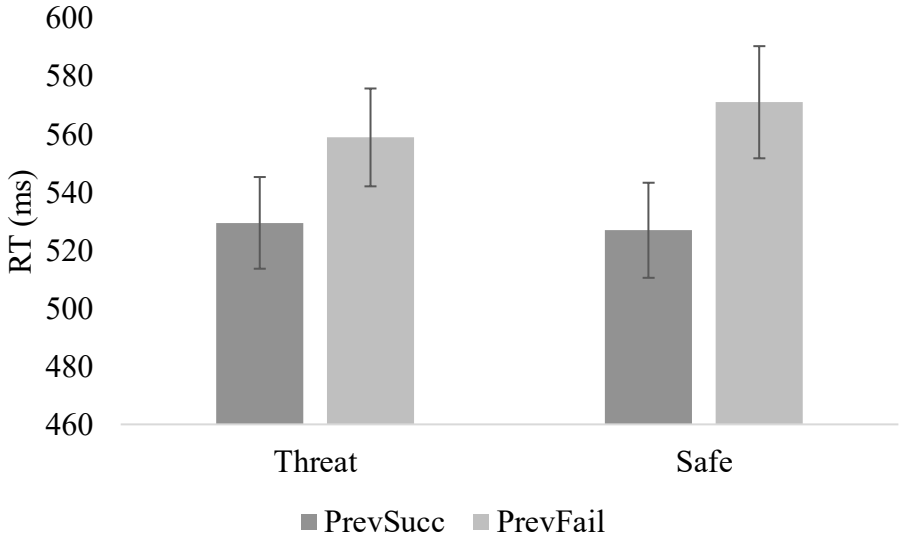

Figure 4: Mean RT in milliseconds to trials with correct responses separated by the outcome of the previous trial. PrevSucc = previous trial was a successfully inhibited stop-signal trial. PrevFail = previous trial was stop-signal trial that was responded to. Error bars represent standard error.

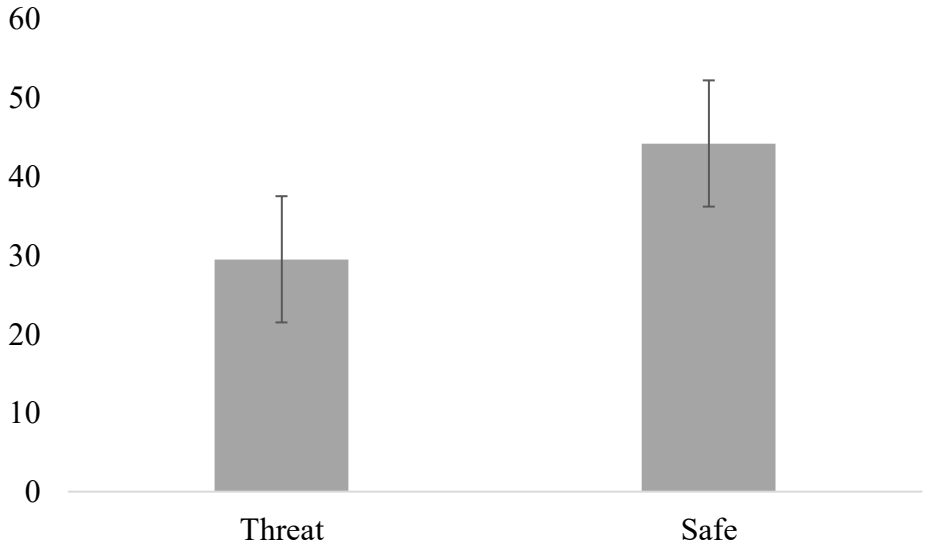

Figure 5: Difference in mean RT between trials with a previous failed outcome minus trials with a previous successful outcome. Error bars represent standard error.

Table 1. *Mean reaction times and SD for trials with correct responses separated by the outcome of the previous trial*

		Mean	SD	M_{diff}	*t*	*p*
Threat	Successful	529.5	108.32	29.39	3.65	= .001
	Failed	558.89	115.61			
Safe	Successful	526.88	112.33	44.20	4.49	< .001
	Failed	571.07	132.51			

Note: Successful = previous trial was a successfully inhibited stop-signal trial. Failed = previous trial was stop-signal trial that was responded to. M_{diff} = Mean difference.

Figure 4 shows that reaction times (RT) to trials that followed a failed stop signal were slower than RTs to trials that followed an inhibited stop-signal. This difference appears to be smaller in THREAT compared to SAFE (Figure 5). A 2(condition; THREAT and SAFE) by 2(previous trial; successful stop and unsuccessful stop) ANOVA was conducted on go trials with a correct response (i.e., press left when arrow indicates left). There was no main effect of condition, there was a main effect of previous task ($F(46) = 19.37$, $p < .001$) where previous trial predicted RT – specifically participants slowed their responses after failed stop trials. There was also significant interaction ($F(46) = 4.98$, $p = .031$). This suggests that under THREAT participants were less adaptive in their responding.

The finding that RT are slower for trials following a failed stop signal under safe conditions is consistent with previous literature (Bissett & Logan, 2011, 2012; Verbruggen & Logan, 2008a). However, the finding that this relationship is diminished during anxious arousal is novel and supports the theory that anxiety disrupts the ability to update working memory and

task strategy (Eysenck et al., 2007; Miyake et al., 2000). Combined with the main findings from this study, the results suggest that anxious arousal impairs inhibitory control and adaptive responding.

4.3 Chapter Summary

The data presented indicates that inhibitory mechanisms are disrupted by threat-induced anxiety. This is shown through the slower SSRT (Roxburgh, Hughes, & Cornwell, 2019), as well as the rigid responding shown in the additional results (Figure 4). In contrast to the findings of the Go/No-go task (O. J. Robinson, Krimsky, et al., 2013), the impaired inhibition found during anxiety in the Stop-signal task are consistent with the 'attentional control theory', which suggests that anxiety facilitates early stimulus driven attention and that goal-directed attention is attenuated as a result (Eysenck et al., 2007). The findings are also consistent with results from the mixed saccade task, which showed that eye saccades towards a cue are facilitated by threat-induced anxiety, but inhibition of these saccades (away from the cue) is impaired (Cornwell, Mueller, et al., 2012). The findings are inconsistent with results from the Go/No-go task, which shows that errors of commission are reduced during threat induced anxiety (Grillon et al., 2017; Mkrtchian, Roiser, & Robinson, 2017; O. J. Robinson, Krimsky, et al., 2013; Torrisi et al., 2016). Given the many replications of the Go/No-go result, and the repetition of impaired performance on the SST shown in chapter 5 of the current thesis, differing results between the Stop-signal task and the Go/No-go task are likely due to the differences between the two task types rather than a statistical anomaly. In their first study of the Go/No-go task, Robinson et al., (2013) noted that there were no differences in RT to go signals between threat and safe conditions, which they argued indicates improved task performance was not due to sensitization

of early sensory-perceptual processes. However, it is the detection of rarer no-go stimuli that is more likely to be facilitated by anxiety. Evidence for the processing preference for novel stimuli during anxious arousal can be seen in the early facilitation of rare deviant tones during threat-induced anxiety in the mismatch negativity task (Cornwell et al., 2007; Cornwell et al., 2017). Therefore, this chapter argues that anxiety impairs response inhibition and that the reduction in errors of commission during the Go/No-go task is due to the anxiety-induced facilitation of novel stimuli processing. Despite these findings, questions remain about the influence of anxiety on attention. While Eysenck (2007) argue that anxiety facilitates stimulus-driven attention and impairs goal-directed attention, and the current results offer some support for this assertion; it is possible that induced anxiety facilitates sustained attention more generally. Indeed, the improved Go/No-go task performance during induced anxiety could be explained through the hypothesis that anxiety facilitates sustained attentional control. The Go/No-go task is a long and repetitive task. Errors of commission could occur due to lapses in attention. It is possible that the induction of anxiety counteracts lapses of attention. In support of this hypothesis, a recent study showed that anxiety decreased alpha oscillatory power in the intraparietal sulcus, which the authors interpreted as increased excitability of a key attentional control region (Balderston, Hale, et al., 2017). Through this lens, it could be argued that the impaired inhibition seen in the current stop-signal study is not due to improved stimulus-driven attention at the expense of goal-directed attention. Instead, induced anxiety, might impair inhibition more directly. Possibly by hijacking resources typically used for inhibitory control, which was proposed by Shackman et al. (2006). Shackman et al. argued that the monitoring of threat takes up resources in key regions including the right frontal areas, which are typically thought to be important in response inhibition. This leaves fewer cognitive resources available for inhibition. The exact mechanism behind anxiety-induced impaired inhibitory control remains elusive. Further, the neural mechanisms behind this relationship are not well understood. Chapter 5 will measure MEG data from participants engaging in the stop-signal task during threatening and non-threatening conditions to reveal the

oscillatory correlates underpinning the relationship between anxiety and response inhibition. Further, chapter 6 will look at the neural oscillatory changes associated with sustained anxiety more generally, which will further reveal the mechanisms underpinning anxiety.

Chapter 5 – Anxiety and response inhibition: Neural underpinnings

Chapter 4 revealed that induced anxiety impairs performance on the stop signal task so that participants have a slower SSRT. This was interpreted to mean that response inhibition is impaired during states of anxiety. Further, it was argued this impaired inhibition is likely the result of anxiety facilitating or prioritising an aspect of processing, due to the adaptive nature of anxiety, at the expense of another. One possibility is that anxiety facilitated early sensory attention at the expense of inhibitory control. Another possibility was that anxiety took up key cognitive resources for processes such as threat monitoring, which meant inhibitory control was impaired. The answers to these questions remain elusive and the neural mechanisms underpinning the improved inhibitory control are not well understood. This chapter will explore performance on the stop-signal task during threatening and non-threatening conditions while taking simultaneous MEG recordings in an attempt to answer these questions. Further, this proposed experimental paradigm will address the overall aims of the thesis – to establish an understanding of how two key features of mental disorders (anxiety and self-control) interact (section 1.6). To our knowledge few studies have explored this intersection. While the network involved in stopping has been extensively studied (Aron et al., 2004; Zhang, Geng, & Lee, 2017), as has the network underpinning anxiety (Grupe & Nitschke, 2013), though with some gaps (see chapter 6), only Torrisi et al. (2016) has explored this intersection and found that regions involved in sustained attention (e.g. IPL) and in inhibitory control (right IFG) were more activated during go trials in the Go/No-go task during threat compared to safe. However, these regions did not differ during comparisons of successful no-go trials. This might mean that during threatening conditions, participants generally had greater sustained attention and subsequent inhibitory preparation. However, when comparing successful inhibition, there was no difference due to participants in both conditions having paid attention and successfully inhibiting the task.

Put simply, the lapses in attention were not detected when only comparing successful trials. These findings suggest the Go/No-go task is revealing differences in sustained attention between threatening and non-threatening conditions, which leaves the relationship between anxiety and inhibitory control not well understood. This chapter will explore the neural underpinnings of the relationship between anxiety and inhibitory control using the Stop-signal task.

The brain network associated with response inhibition has been extensively studied with several brain regions being implicated, but most consistently implicated is the right IFG and the pre SMA (Aron et al., 2014; Nachev, Kennard, & Husain, 2008). Particularly, the right IFG has been implicated in lesion studies, TMS, fMRI, and other neuroimaging studies (Aron et al., 2004; Jana, Hannah, Muralidharan, & Aron, 2020; Lee et al., 2016). Chapter 4 revealed that anxiety impairs response inhibition, but it is not clear how or if this relationship is reflected in right IFG dysfunction. Indeed, how anxiety influences the functioning of the right IFG is not fully elucidated, though evidence from an oddball paradigm provides some answers.

Cornwell et al. (2017) looked at the neural correlates of the oddball paradigm during threatening and non-threatening conditions using dynamic causal modelling. They found that feedforward projections in response to deviant tones from the auditory cortex to the IFG were facilitated by anxiety. This was taken to mean that anxiety facilitated the detection and processing of novel sensory stimuli. However, feedback projections from the IFG were attenuated, suggesting the facilitation of early stimuli came at the expense of later processing. Put simply, anxiety means faster acting, but slower counteracting. In the case of the stop signal task, this later processing would be operationalised as response inhibition. If the proposed study confirms that later processing in the right IFG is impaired in favour of early stimulus detection, it is expected that changes in right IFG activity underpin the impaired inhibitory control seen during induced anxiety.

5.1 Paper – Threat-induced anxiety weakens inhibitory control

5.1.1 Rationale for the variables used

As outlined in section 4.1.1, the stop signal task allows researchers to be more certain that, during a stop-signal trial, go signals are unambiguously initiated and must then be inhibited. This helps ensure the anxiety induction is influencing response inhibition rather that early stimulus detection (see section 4.1.1). Further, as outlined in section 3.1, the threat-of-shock procedure ensure anxiety is reliably induced (also see, Shackman et al., 2006). Chapter 4 established these two procedures can be used together. Chapter 5 includes the addition of MEG.

As outlined in section 3.4.1, The MEG has several advantages over other imaging techniques such as fMRI when exploring induced anxiety. First, MEG is a primary measure of brain activity as opposed to fMRI, which measures blood flow (E. L. Hall et al., 2014). Second, blood flow related changes (as measured with fMRI) can be confounded by the changes induced by anxious arousal (Giardino et al., 2007). Third, MEG has a higher temporal resolution than fMRI, allowing differentiation of brain activity on a millisecond scale (Baillet, 2017), which as shown in chapter 4, is where stop-signal activity is likely situated (average SSRT in chapter 4 was less than 300ms). Finally, unlike EEG, MEG is able to resolve activity across brain regions with high spatial resolution and without the signal distortion caused by head tissue (Baillet, 2017).

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Anxious arousal alters prefrontal cortical control of stopping

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Abstract

Anxiety heightens vigilance and stimulus-driven attention to the environment, which may in turn disrupt cognitive control processes such as response inhibition. How this unfolds at the neural level is unclear. Previous evidence implicates the right inferior frontal gyrus (IFG) as an important cortical node in both stimulus-driven attention and inhibitory control. Here we used magnetoencephalography (MEG) to investigate the neural mechanisms involved in the relationship between threat-induced anxiety and stopping during a stop-signal task, where a visual go signal was occasionally followed by an auditory stop signal. Healthy individuals ($N = 18$) performed the task during the threat of unpredictable shocks and safety to modulate anxious arousal. Behaviorally, we observed that stopping was impaired during threat (i.e. slower estimated stop-signal reaction times), indicating that anxious arousal weakens inhibitory control. MEG source analyses revealed that bilateral IFG and right dorsal prefrontal cortex showed increased beta-band activity (14–30 Hz) to the stop signal that varied as a function of successful stopping during nonanxious (safe) conditions only. Moreover, peak beta-band responses from right IFG were inversely correlated with stopping efficiency during nonanxious conditions. These findings support theoretical claims that beta oscillations function to maintain the current sensorimotor state, and that the lack of differential beta-band activity in prefrontal cortices underlies anxiety-related deficits in inhibitory control. We specifically argue that altered right IFG functioning might directly link impaired cognitive control to heightened stimulus-driven responding in anxiety states.

KEYWORDS

anxiety, beta oscillation, magnetoencephalography, right inferior frontal gyrus, stop signal

1 | INTRODUCTION

In situations of distal or uncertain threat, anxiety is an adaptive defensive state marked by heightened vigilance to the environment (Grillon et al., 2019; Okon-Singer et al., 2015; Robinson, Vytal, Cornwell, & Grillon, 2013). Evidence from experimental manipulations of anxious arousal points to sensitization of early sensory-perceptual processes (Baas et al., 2006; Fucci et al., 2019; Shackman et al., 2011), which may, in turn, facilitate stimulus-driven orienting to perturbations in the environment (Cornwell

Abbreviations: BOLD, blood-oxygen-level-dependent; EEG, electroencephalography; FDR, false discovery rate; IFG, inferior frontal gyrus; LCMV, linear-constrained minimum-variance; MEG, magnetoencephalography; MRI, magnetic resonance imaging; PFC, prefrontal cortex; RT, reaction time; SMA, supplementary motor area; SSD, stop-signal delay; SSRT, stop-signal reaction times; SST, stop-signal task.

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et al., 2007, 2012; Eysenck et al., 2007). This likely hinders goal-directed attention and controlled cognitive processes (Eysenck et al., 2007; Robinson, Vytal, et al., 2013), but how this unfolds at the neural level is not well understood. In a study employing a passive auditory oddball sequence, we used dynamic causal modeling to determine how a temporo-frontal cortical network was modulated by threat-induced anxiety (Cornwell et al., 2017). There we showed with magnetoencephalography (MEG) that anxious arousal induces a shift toward biased feedforward signaling in response to deviant stimuli, which could be attributed in part to weakened feedback coupling between right inferior frontal gyrus (IFG) and auditory cortices. Put simply, the incoming sensory signals from the auditory cortex to the IFG are facilitated by anxious arousal but the outgoing signal from the IFG is diminished. This raises the possibility that altered right IFG functioning could underlie anxiety-related deficits in cognitive control given its role in motor inhibition (Aron et al., 2014) and potential position at the intersection of stimulus-driven and goal-directed attention systems (Corbetta & Shulman, 2002; Fox et al., 2006).

To test this hypothesis, we turned to the stop-signal task (SST) that demands repeated responses to stimuli with occasional alerts (i.e. stop signals) to quickly abort the response. Functional MRI studies of the SST strongly implicate right IFG, along with the pre-supplementary motor area (pre-SMA) and left IFG, as a key components of a prefrontal cortical network activated following the presentation of the relatively rare stop-signal stimulus (Aron et al., 2014; Rae et al., 2014; Zhang et al., 2017), which in this behavioral context is often linked to the triggering of the stopping process. We recently found that increased anxious arousal elicited by unpredictable threat impairs inhibitory control on an auditory SST (Roxburgh et al., 2019). Individuals exposed to extended threat periods of unpredictable shock delivery were slower to abort their actions, as estimated by their stop-signal reaction times (SSRTs), than when they performed the task during safe periods. We suggest this finding indirectly supports the hypothesis that heightened stimulus-driven attention and impaired cognitive control in an anxious state can both be explained by altered functioning of the right IFG. The current study sought more direct evidence with MEG measurements during which participants performed an auditory SST under anxious and nonanxious conditions.

In the SST, the stop signal follows the go signal by a few hundred milliseconds at most, and the inhibitory process triggered by the stop signal takes another few hundred milliseconds to successfully run its course (Verbruggen et al., 2019), making direct measurements of neuronal population activity (e.g., intracranial EEG, MEG) more attractive than blood-oxygen-level-dependent (BOLD) measurements. Accordingly, we used MEG to specifically capture cortical activity elicited by an auditory stop signal in the brief interval in which stopping is instantiated. While there are many ways to analyze electrophysiological data, examining changes in beta oscillatory power (14–30 Hz) has a strong theoretical basis. Engel and Fries (2010) argue that beta-band activity reflects maintenance of the current cognitive or sensorimotor state. Their "status quo" theory predicts that new motor movements are associated with a reduction in beta oscillations, while the inhibition of movement results in increased beta oscillations. Intracranial EEG data support these claims, showing that beta power increases in the right IFG during successful compared to unsuccessful stopping during a SST (Swann et al., 2009; Wessel et al., 2013). Spitzer and Haegens (2017) extend the function of beta oscillations to "waking up" or endogenously reactivating, in addition to maintaining, cognitive sets. This theoretical claim incorporates evidence that beta oscillations can occur in brief bursts and carry specific content in working memory. Collectively, it is argued that beta oscillations are an important neurophysiological component of prefrontal cortex (PFC) functioning, including right IFG where spontaneous beta oscillatory events can be observed (Sherman et al., 2016). More recently, prefrontal beta activity has been linked to motor inhibition (Jana et al., 2020; Wessel, 2020). Thus, we placed our primary focus on beta-band activity in examining anxiety-related modulation of stop signal-elicited cortical responses.

In addition to replicating at the behavioral-level weakened inhibitory control (i.e. slower SSRT Roxburgh et al., 2019), we aim to provide direct evidence that threat-induced anxiety modulates stop signal-elicited beta-band activity in prefrontal cortical regions. Based on the contention that right IFG lies at the intersection of stimulus-driven and goal-directed attention systems (Corbetta & Shulman, 2002) and that feedback coupling is weakened in this region during anxious arousal (Cornwell et al., 2017), we predicted that (a) anxiety will specifically impede the translation of rapid orientation and stimulus detection to triggering a controlled stop in the right IFG. We also hypothesized that (b) other key prefrontal cortical regions, specifically left IFG and pre-SMA, will be associated with inhibitory control, but we make no predictions about how anxiety might influence inhibitory processing in these regions.

2 | METHODS

2.1 | Participants

Twenty-five healthy adults, recruited through flyers at a Melbourne university, volunteered for the study and received compensation for their time. Sample size was determined a priori, based on Roxburgh et al. (2019), which reported a medium effect size ($d = 0.51$) of threat-induced anxiety

on inhibitory performance. A sample of 25 participants was sought in order to obtain ~80% power to detect such an effect (paired *t*-test; one-tailed, power = 0.7974). One participant was removed from analyses for poor performance on the SST (p(inhibition) <30%). Six more participants were removed for excessive head movement during MEG scanning (exceeding 5 mm). The final sample was 18 participants (4 women and 14 men; mean age ±*SD*, 27 ± 6.5 years; right-handed). The study was undertaken with the understanding and written consent of each participant. The study was approved by the Swinburne Human Research Ethics Committee and conducted in accordance with the World Medical Association Declaration of Helsinki.

2.2 | Design

Magnetoencephalography recordings were made in two runs during which participants completed an auditory SST. In the third and final run, participants were exposed to similar trial conditions but were asked to execute a response irrespective of whether an auditory stimulus was presented (ignore-tone task). In all runs, threat of unpredictable shocks and safe contexts was alternated to modulate anxious arousal, with the starting context counterbalanced across participants. For the unpredictable threat context (THREAT), participants were informed before completing the trial block that they could "receive electric shocks at any time." For the safe context (SAFE), participants were told that they were "safe from shock." Shocks (10 total across the three runs) were delivered pseudo-randomly during THREAT (0, 1, or 2 shocks/block) to the wrist of the nondominant hand. For the two runs of the SST, only seven shocks (among 100 stop and 230 go trials) were delivered during THREAT. Shocks were presented during intertrial intervals and did not occur during the immediate intervals before stop trials, giving 3–10 s between shock delivery and the next stop trial. Shock intensity was set beforehand to a moderately uncomfortable level (see below). Participants retrospectively rated their anxiety after each run for THREAT and SAFE on a scale from 0 ("no anxiety") to 10 ("extreme anxiety").

2.3 | Task procedure

Before performing the SST, participants provided informed consent and completed the Spielberger State-Trait Anxiety Inventory (Spielberger, 1983) and the UPPS-P Impulsive Behavioral Scale (Lynam et al., 2007). They then completed one practice run of the SST before moving to a magnetically shield room where a shock workup procedure was completed, which began with the presentation of an initial weak shock and, after participant feedback, was followed by shocks of increasing amplitude until a level that participants rated as "moderately aversive" was reached. MEG and behavioral data were then acquired in two runs containing 10 task blocks (5 THREAT and SAFE) lasting approximately 72 s/block. Each block contained 33 trials (intertrial interval, 1.7–4.1 s) with a stop-signal probability of 0.30 (10/33), presented in pseudo-random order (Hughes et al., 2016). Participants completed an additional third run during MEG recordings where they were instructed to "ignore the tones," giving a total of four runs—two runs of the SST, one additional run for the ignore-tone task, as well as a practice SST run prior to task commencement. Trials began with a fixation cross (500 ms) followed by a go stimulus (1,000 ms), either a left or right pointing arrow, to which they responded with left or right button press on a button box with their dominant (right) hand.

The auditory stop-signal was a pure tone (900 Hz; 50 ms) presented binaurally through tubal-insert earphones. Stop-signal delays (SSDs) were set using both descending and ascending staircase algorithms (50-ms steps, starting with 250 ms and 0 ms, respectively) following the same protocol used by Roxburgh et al. (2019) to achieve an approximately 0.50 p(inhibition) in each context. For the final ignore-tone task, we used the observed SSDs from run 2 to schedule timing of tone presentation. Participants were instructed to respond by button press as quickly as possible in both the SST and ignore-tone task, and not to delay their response in anticipation of a stop-signal in the SST.

2.4 | MEG and MRI acquisition

Magnetoencephalography recordings were made with a 306-channel Elekta Neuromag® TRIUX magnetometer system (Helsinki, Finland). Magnetic flux density was digitized at a sampling rate of 1,000 Hz in a magnetically shielded room with internal active shielding disengaged. Head position in relation to sensors was tracked using five continuous head positioning indicator coils (one on each mastoid and three across the forehead). The head positioning indicator coils and three fiducial positions (nasion and preauricular points) were digitized with a Polhemus FASTRAK head digitizing system (Polhemus Inc.). Participants that exceeded 5 mm in total head displacement from the start of the scan were removed from analysis. A T1-weighted MRI was subsequently obtained from each participant with a 3-T Siemens Trio system using the following parameters: TR = 1.9s, TE = 2.5 ms, sagittal slice thickness = 1 mm, matrix = 256 × 256. Vitamin E capsules were attached to the three fiducial points during the MRI scan to facilitate spatial coregistration.

2.5 | MEG analysis

Magnetoencephalography data were analyzed using a linear-constrained minimum-variance (LCMV) beamformer approach implemented in Fieldtrip (Oostenveld et al., 2011). While noisy and flat channels were removed from the analysis, no other data/noise statistical reduction techniques were used prior to source analysis. A single data covariance matrix (without regularization) was calculated across all remaining sensors from data bandpass-filtered between 14 and 30 Hz over epochs time-locked to stop-signal presentation (−250 to 500 ms), for all trials of the SST across THREAT and SAFE contexts (50 × 2 contexts × 2 runs = 200 epochs). For lead-field calculation, single-shell head models were generated using the Nolte method (Nolte, 2003) from the spatially coregistered T1-weighted MRIs. Power in the post stop-signal period was integrated over sliding 100-ms windows from 0 to 300 ms in 50-ms steps (−50 to 50 ms, 0–100 ms, 50–150 ms, …; see Figure 1), separately for successful and unsuccessful stop trials (Outcome) and THREAT and SAFE (Context). Because SSDs vary from trial to trial, and significantly differ between successful and unsuccessful stop trials, we normalized post stop-signal power to an average 100-ms baseline window before stop-signal presentation, pooled across conditions (−150 to −50 ms). Event-related power changes were expressed as log10-transformed power ratios (post/pre). In order to study the specificity of any observed beta-band effects, a similar approach was carried out to examine alpha and gamma-band activity after bandpass-filtering between 8–13 Hz and 30–80 Hz, respectively.

Group-based analyses were carried out using the Analysis of Functional NeuroImages (Cox, 1996). Whole-brain beamformer images with 5-mm grid spacing for each time window were first interrogated to identify stop signal-elicited changes in beta-band power. For this, we averaged beamformer images for successful and unsuccessful stop trials and THREAT and SAFE contexts and performed a one-sample t test (per time window) to test for voxels showing significant deviations from zero (reflecting no change in beta-band power from pre to post stop-signal). A voxel-wise FDR correction ($q < 0.05$), calculated over the entire distribution of p values obtained from each beamformer image across all time windows, controlled the false-positive rate. Next, we performed 2 × 2 ANOVAs to determine effects related to Context (THREAT vs. SAFE) and Outcome (successful vs. unsuccessful stop trial), and their interaction. We applied a similar FDR correction ($q < 0.05$) for reporting significant main or interactional effects.

We performed two region-of-interest (ROI) analyses to directly probe our hypotheses, one for the right IFG and one for the pre-SMA. For the former, two 5-mm spherical ROIs were defined based on parcellation analyses of right IFG (Hartwigsen et al., 2019). We specifically used clusters 2 and 4 (center-of-gravity: 53, 15, 5 mm and 50, 19, 1 mm in MNI space), located in right ventro-posterior IFG, which are most clearly associated with action execution and inhibition. Given that they overlapped, we averaged them to create a composite ROI. For the pre-SMA, we also used a 5-mm spherical ROI centered at coordinates reported by Nachev et al. (2007). MANOVAs were carried out to compare beta power modulation as a function of Context, Outcome, and Time. Spearman rank-order correlations (which are more robust for studies correlating behavior and imaging data Rousselet & Pernet, 2012) were then calculated to determine whether a monotonic relationship was observed between beta power, averaged across successful and unsuccessful stops, and SSRT. For this, we restricted the analysis to the time window with peak beta power.

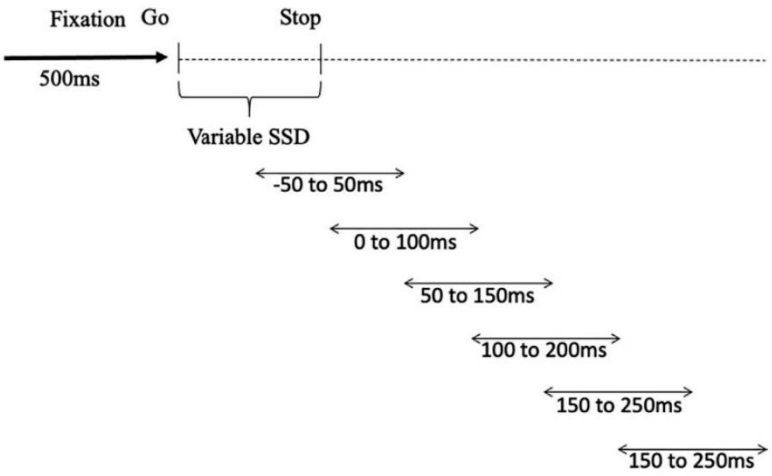

FIGURE 1 Trial structure of the stop-signal task showing the timing of the six epoch windows relative to the trial events. Stop-signal delay (SSD) represents stop-signal delay. Average SSD was 218 ms during THREAT and 233 ms during SAFE

TABLE 1 Stop-signal task performance across THREAT and SAFE contexts

	THREAT	SAFE	Student *t*	*p*	Cohen's *dz*
Go trials					
Median Go RT (ms)	444	444	0.11	.917	
Incorrect Go (%)	0.99	1.30	−1.32	.204	
Missed Go (%)	0.07	0.22	−1.07	.302	
Stop trials					
SSRT (ms)	221	202	2.35	.031*	0.55
P(inhibition)	0.51	0.53	−2.27	.036	0.55
Mean SSD (ms)	218	233	−2.16	.046	0.51
Median failed RT (ms)	417	407	2.50	.023	0.59

Note: $N = 18$. Median RTs are calculated on correct trials only. SSRT = stop-signal reaction time; SSD = stop-signal delay. Measures other than SSRT are not a priori and have had Bonferroni corrections applied.

2.6 | Stop-signal analysis

Stop-signal data were analyzed using R Studio (RStudio, 2015). The integration method was used to calculate SSRT. This method accounts for deviations from a 0.50 p(inhibition) by integrating the RT into a cumulative distribution and using the p(response) to determine the integral (i.e., distribution cut off); the mean SSD is then subtracted from this value (Verbruggen et al., 2019). Missed go trials were replaced with maximum go RT according to recent recommendations (Verbruggen et al., 2019).

3 | RESULTS

3.1 | Behavioral results

As a manipulation check, we compared subjective anxiety between THREAT and SAFE conditions. On average participants reported higher anxiety during THREAT than SAFE in run 1 of the SST ($M_{diff} = 3.25$, $t(17) = 9.21$, $p < .001$), and run 2 of the SST ($M_{diff} = 3.81$, $t(17) = 8.55$, $p < .001$), suggesting anxiety was successfully induced. Table 1 reports performance on the SST. Consistent with our previous study (Roxburgh et al., 2019), we found significantly slower mean estimated SSRT in response to the stop signal during THREAT relative to SAFE. Mean SSD also tended to be shorter in THREAT than SAFE, but the difference was not significant after correction for multiple pairwise tests. We performed the same analysis with those excluded from the MEG analysis because of excessive head movements, and found a robust difference in mean estimated SSRT between contexts ($M_{threat} = 224$ ms, $M_{safe} = 197$ ms, $t(23) = 3.80$, $p = .001$, $dz = 0.78$). This replicated finding supports the claim that threat-induced anxiety weakens reactive inhibitory control. With the larger sample, median go RT between THREAT ($M_{threat} = 475$ ms) and SAFE contexts ($M_{safe} = 471$ ms) remained not significantly different, $t(23) = 1.31$, $p = .21$. However, to determine whether task performance is generally impaired during THREAT, we analyzed RT performance on the ignore-tone task. A 2 × 2 ANOVA on median go RT with Context (THREAT, SAFE) and Tone (present, absent) as repeated factors revealed only a main effect of Context, $F(1,23) = 5.41$, $p = .029$, with faster responding during THREAT ($M_{threat} = 381$ ms) relative to SAFE ($M_{safe} = 388$ ms). Thus, with no demand to occasionally stop a response, threat-induced anxiety facilitated choice responding. Because task order was not counterbalanced, we were unable to validly analyze RT performance between the SST and ignore-tone tasks.

3.2 | MEG results

3.2.1 | Threat-induced anxiety alters inhibition-related beta-band activity in two key prefrontal cortical nodes

Exploratory whole-brain adaptive beamformer analyses were carried out to identify regions showing significant modulation of beta-band activity (14–30 Hz) triggered by the stop signal. Figure 2 shows stop signal-elicited beta power averaged across all conditions (FDR < 5%). As can be observed, substantial increases in beta power span bilateral temporal and prefrontal cortices, including ventrolateral and dorsomedial regions. These early increases in beta-band activity are followed by robust decreases in beta power in sensorimotor and parietal cortices.

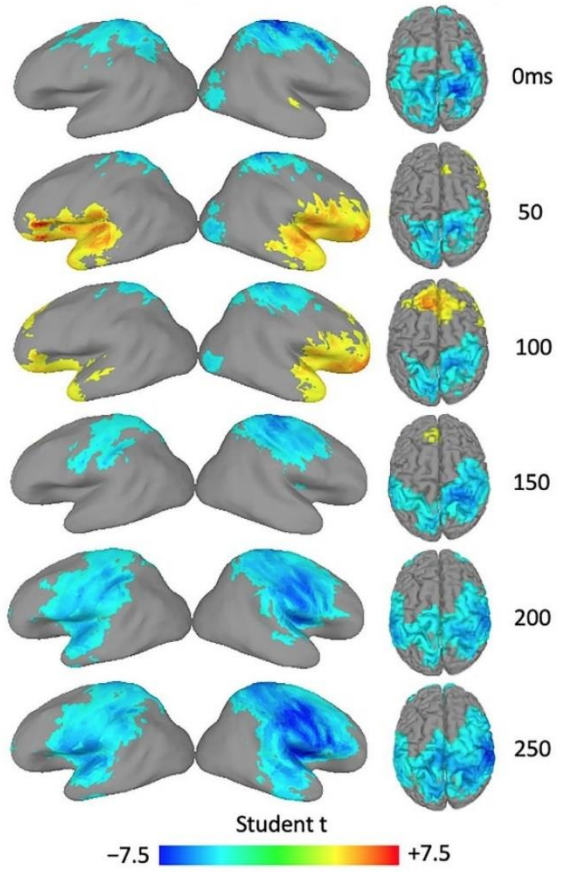

FIGURE 2 Beta-band activity in response to the auditory stop signal shows early increased responding in bilateral temporal cortices and ventrolateral and dorsomedial prefrontal cortices. This is followed by widespread decreases in beta-band-activity in sensorimotor and parietal cortices. Inflated and pial surface reconstructions of a standardized brain are overlayed with t statistic maps comparing mean beta power ratios (post/pre, log10-transformed) for all stop trials against zero. Surface maps are thresholded at an FDR < 5%. Time windows are labeled according to their midpoints (0 ms = −50 to 50 ms, 50 ms = 0 to 100 ms, etc.)

Continuing with the whole-brain exploration, we next tested with voxel-wise 2 × 2 ANOVAs for regions showing a main effect of Context and/or Context-by-Outcome interactions. Although no regions showed beta power differences between Contexts, two clusters in prefrontal cortices exhibited a significant Context-by-Outcome interaction (FDR < 5%): left IFG/anterior insula (aIns) and right dorsal prefrontal cortex (dPFC, Figure 3a,b). A third cluster was also observed in the right cerebellum (peak = 8, −73, −26 mm in MNI space). Mean time courses averaged across voxels surviving correction show that these prefrontal cortical interactions were driven by significantly greater and more protracted beta-band activity on successful stop trials compared to unsuccessful stop trials in SAFE but not THREAT.

3.2.2 | Right IFG indiscriminately responds to the stop signal during THREAT context

Given substantial evidence of right IFG and pre-SMA (Nachev et al., 2007; Swick et al., 2011) involvement in the SST, we probed these structures further with an a priori ROI analysis to address hypotheses 1 and 2 and possible false negative results in the foregoing whole-brain analysis, especially in light of the robust response in right ventrolateral PFC to the stop signal (see Figure 2). As can be observed in the time courses, the stop signal elicited robust increases in beta-band power in right IFG and, to a lesser extent, pre-SMA in both THREAT and SAFE (Figure 4). Separate MANOVAs revealed significant modulation across time in right IFG (Wilk's $\lambda = 0.19$, $F(5,13) = 10.8$, $p < .001$) and pre-SMA (Wilk's $\lambda = 0.18$, $F(5,13) = 11.5$, $p < .001$). While no other effects were significant for the pre-SMA, a Context-by-Outcome interaction was observed in the right IFG (Wilk's $\lambda = 0.75$, $F(1,17) = 5.6$, $p = .03$). Like the other two prefrontal clusters identified in the whole-brain analysis (Figure 3), right IFG showed greater stop signal-elicited beta-band activity on successful versus unsuccessful stop trials in SAFE only.

For descriptive purposes, we also measured beta power elicited by the tone in the ignore-tone task and present the time courses for THREAT and SAFE together with those obtained in the SST (Figure S1). Visual inspection of these time courses are consistent with the interpretation that, during THREAT, indiscriminate responding to the stop signal reflects amplified beta power when stopping and failing to stop. Again, however, because the ignore-tone task always followed the SST, we did not directly analyze data between tasks.

3.2.3 | Threat disrupts relationship between right IFG beta and SSRT

To further test hypothesis 1, we correlated beta power with estimated SSRTs between participants in both conditions. We averaged beta power across successful and unsuccessful stop trials to account for variable numbers of successful stop trials between participants that could confound beta power estimates. Consistent with a role in stopping, we found a negative monotonic relationship between peak beta power (50–150 ms) and estimated SSRT, suggesting that those with stronger right IFG beta responses on stop trials showed faster stopping than those with weaker ones (Figure 5). However,

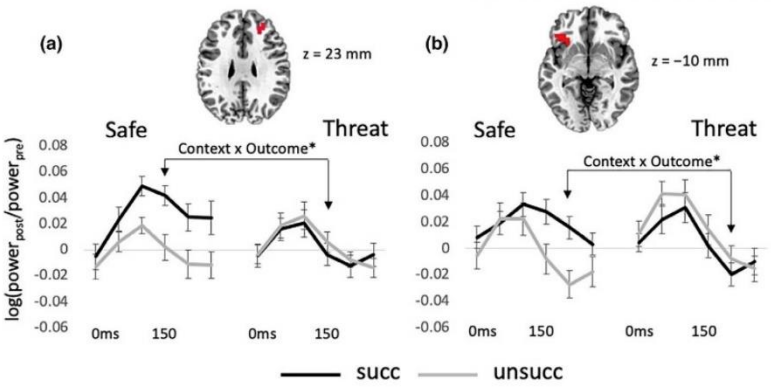

FIGURE 3 Right dPFC (a) and Left IFG/aIns (b) show beta-band activity associated with successful stopping during nonanxious (SAFE) conditions only. Mean beta power across voxels comprising these two clusters was calculated to show time courses of stop signal-elicited responses in these two regions. The time windows showing significant interactions from the whole-brain analyses are indicated by arrows. succ represents successful stop trials and unsucc represents unsuccessful stop trials

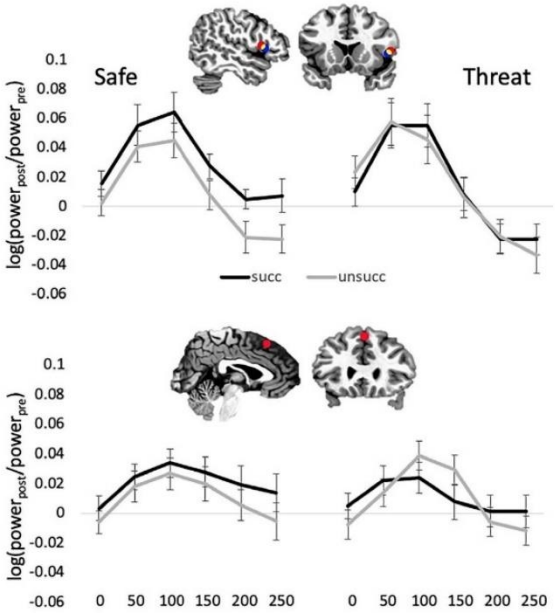

FIGURE 4 Right IFG (top) and pre-SMA (bottom) show beta-band activity associated with successful stopping during nonanxious (SAFE) conditions only. Mean beta power across voxels contained within spherical ROI masks were extracted to show time courses of stop signal-elicited responses in these two regions. Two 5-mm spherical masks were originally specified (red, blue) for the right ventro-posterior IFG, but because of their overlap (yellow), they were combined. succ represents successful stop trials and unsucc represents unsuccessful stop trials

this was only true in SAFE, with a significantly stronger correlation observed there compared to THREAT ($z = -1.65$, $p < .05$, one-tailed). No time windows in THREAT showed a similar negative rank-order correlation (ranging from $r_s = 0.03$ to 0.23).

3.2.4 | Right IFG does not exhibit stop signal-elicited gamma-band activity

We considered the possibility that threat-induced anxiety might shift the oscillatory response of the right IFG upward and carried out a parallel set of exploratory analyses in the gamma-band (30–80 Hz). In this case, a MANOVA of the ROI-extracted data failed to reveal Context, Inhibition, interactional effects, or evidence of a temporal change in stop signal-elicited gamma-band activity (all $ps > .20$). Unlike that observed for beta-band activity, very little signal in the gamma range could be detected from the right IFG.

3.2.5 | Right IFG alpha activity relates to inhibition in the SAFE context only

We also explored the opposite possibility and estimated alpha (8–13 Hz) power from right IFG. With alpha, we integrated power over a single 200-ms window (0–200 ms relative to stop-signal onset normalized to a common pre-stop-signal baseline window, −250 to −50 ms) to ensure a time period long enough to contain slower oscillations. Analysis revealed a main effect of inhibition, $F(1,17) = 6.20$, $p = .023$, qualified by a trending Context-by-Outcome interaction, $F(1,17) = 3.55$, $p = .077$, which resulted from a difference in alpha power on successful versus unsuccessful stop trials in SAFE ($t(17) = 2.72$, $p = .015$), but not in THREAT ($t(17) = 0.58$, *ns*, Figure S2). Like beta-band activity, the link between alpha power in right IFG and inhibition was disrupted under anxious conditions.

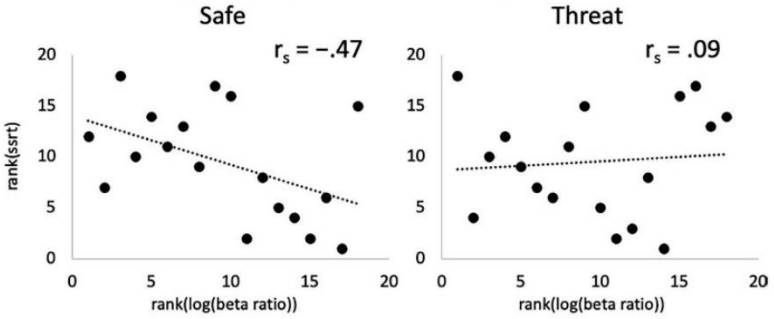

FIGURE 5 Right IFG beta-band activity inversely correlates with estimated SSRT during nonanxious (SAFE) conditions only. Scatterplots, with least square lines, show the rank-order monotonic relationship between log-transformed beta power ratios (post/pre) at the peak response window (see Figure 3) and estimated SSRTs for the 18 participants

3.2.6 | Response inhibition is marked by opposite changes in sensorimotor and visual cortical beta

Returning to the exploratory whole-brain analyses, Figure S3 displays regional differences in beta-band activity on successful versus unsuccessful stop trials irrespective of Context (i.e. main effect of Outcome). Two major clusters exhibited beta power that discriminated successful from unsuccessful stopping—sensorimotor and visual cortical regions—with additional clusters in bilateral parietal cortices, left prefrontal cortices, and cerebellum (Table S1). Sensorimotor cortices showed robust decreases in beta power that intensified over time, particularly on unsuccessful stop trials, indicative of motor response execution. Visual cortical regions showed the reverse pattern, with greater beta-band activity on unsuccessful stop trials relative to successful stop trials (Figure S3). Decreased beta could reflect disruption of visuomotor signaling in order to cancel the action triggered by the visual go stimulus. However, because the main aim of the study was to examine anxiety-related effects, these main effects of Outcome were not explored further.

4 | DISCUSSION

The SST demands exquisite control over behavior by having to abruptly stop a planned motor response when an occasional stop signal occurs. Anxious arousal, induced by the threat of unpredictable shock, diminishes this inhibitory control as we have previously shown (Roxburgh et al., 2019) and successfully replicated here. With MEG source analyses, we were able to isolate neural oscillatory changes time-locked to the auditory stop signal in the brief interval in which stopping is instantiated. Three key prefrontal cortical regions exhibited anxiety-related modulation of beta-band (14–30 Hz) activity: bilateral IFG and right dPFC. In these regions, greater beta-band activity was linked to successful stopping under nonanxious (SAFE) conditions only. Thus, weakened inhibitory control under threat-induced anxiety may be attributed, in part, to the lack of differential beta-band activity in these prefrontal regions. In addition, peak beta-band responses in right IFG were inversely correlated with the speed of stopping (i.e. estimated SSRT), but this was also seen only under nonanxious conditions. While these results await replication in a larger sample, these results suggest anxious arousal specifically disrupts the cortical pathway from stimulus-driven reorienting to triggering controlled mechanisms critical to inhibiting motor actions.

Using adaptive beamformers, we witnessed a robust increase in beta-band activity in right IFG (Figures 2 and 4a) elicited by the stop signal that peaked prior to mean estimated SSRTs, supporting its potential role in triggering the stopping process. ROI-extracted time courses further revealed that under nonanxious conditions beta-band activity was stronger on successful stops compared to unsuccessful stops. Greater right IFG responding on successful stops converges with similar analyses of beta-band activity from invasive electrophysiology (Swann et al., 2009; Wessel et al., 2013) and MEG recordings (Jha et al., 2015). These findings support the theoretical claim that maintenance of the current sensorimotor (or cognitive) state, in this case successfully inhibiting a planned action, is marked by increased cortical beta oscillations (Engel & Fries, 2010). Most significantly, peak beta power was inversely correlated with estimated SSRT under nonanxious conditions, which has not been reported before. Although a similar correlation has emerged in some functional MRI studies (Congdon et al., 2010; Whelan et al., 2012; White et al., 2014), our finding, based on the timing of this correlated activity, supports a more direct link between right IFG beta-band activity and stopping efficiency (Aron et al., 2014). In addition to the greater beta activity during successful compared to failed stops, alpha activity showed a similar differential response (Figure S2). This is consistent with the idea that event-related alpha synchronization reflects top-down inhibitory control (Klimesch et al., 2007) and supports the findings of Jha et al., (2015), who found that theta-alpha activity increased in the right IFG following a stop signal.

Under anxious conditions, the link between right IFG and stopping becomes less clear-cut. Beta-band activity showed just as robust of an increase following the stop signal during

unpredictable threat, but it was not associated with successful stopping nor did it correlate with estimated SSRT. The absence of positive results does not appear to be driven by a shift in frequency-specific activity, insofar as we found little evidence of stop signal-elicited gamma-band or differential alpha-band activity in right IFG in the THREAT context. Right IFG is thought to be one critical structure in which stimulus-driven and goal-directed attention processes converge (Corbetta & Shulman, 2002; Fox et al., 2006). Previously, we showed using a passive auditory oddball sequence that threat-induced anxiety produces biased feedforward processing of deviant auditory stimuli, which was partly the result of weakened feedback coupling between right IFG and auditory cortices (Cornwell et al., 2017). The current data extend these results and directly links impaired inhibitory control to heightened stimulus-driven responding in anxiety states by altering right IFG functioning.

Whole-brain analyses revealed that beta-band responses in the left IFG/aIns and right dPFC were also associated with successful stopping under nonanxious (SAFE) conditions. Functional MRI studies have also reported the activation of left IFG/aIns in SSTs (Hung et al., 2018; Li et al., 2006; McNab et al., 2008; Padmala & Pessoa, 2010; Rubia et al., 2007), and thus there is some debate about the extent to which the underlying processes are predominantly right lateralized. Indeed, invasive recordings that have taken advantage of bilateral coverage of subdural electrodes have reported left IFG activity associated with successful stopping (Fonken et al., 2016). Similarly, an MEG study found an increase in beta power on successful compared to unsuccessful stop trials in left and right IFG (Jha et al., 2015). Response inhibition has also been associated with right dPFC activity (Hughes et al., 2014; Hung et al., 2018; Zhang et al., 2017), another prefrontal cortical region in which we observed greater beta-band activity during successful compared to unsuccessful stops. Interestingly, like the right IFG, threat-induced anxiety altered activity in left IFG/aIns and dPFC, suggesting that the lack of differential beta-band activity in these regions may also contribute to inhibitory control deficits. Previous studies have reported anxiety-related modulation of these prefrontal regions (Alvarez et al., 2011; Cornwell et al., 2017; Shankman et al., 2014; Somerville et al., 2012), as well evidence implicating them in anxiety-related impairments on other tasks tapping cognitive control (Balderston et al., 2017; Choi et al., 2012).

Notably, of the three PFC regions, only the right IFG beta-band activity correlated with estimated SSRT. SSRT quantifies the speed of the covert stopping process, and is based on an influential theoretical model that assumes the go process and stop process are independent (independent horse race model; Logan & Cowan, 1984). Despite its explanatory success at the cognitive–behavioral level, it is also recognized that the assumption of independence might not hold true for the underlying neural mechanisms (Verbruggen & Logan, 2009). Our findings present a mixed picture, with left IFG/aIns and right dPFC showing successful stop-related activity but no relationship to stopping efficiency as operationalized by SSRT. Differential beta-band activity in these structures likely peaked too late to influence SSRT. In these cases, there could be control mechanisms that involve interplay between go and stop processes (e.g. reciprocal inhibition), which is not captured by the race model. The inverse correlation between right IFG beta-band activity and SSRT points, as previous MEG evidence does (Jha et al., 2015), to a special case in which go- and stop-related prefrontal cortical processes operate independently to a certain point. This could be taken to reflect a more pivotal role for right IFG, over other prefrontal cortical regions, in triggering a stop (Aron et al., 2014). At the same time, the lack of a correlation in right IFG during anxious conditions suggests that robust stop signal-elicited increases in beta-band activity do not necessarily translate to faster stopping.

Finally, we also performed an ROI analysis of pre-SMA but did not find that beta-band activity was related to successful inhibition. The pre-SMA has been proposed to be important in changing motor sequences (Nachev et al., 2008). While this may encompass motor inhibition, the tasks that are used in the studies of pre-SMA and inhibition often use a stop/change paradigm (e.g. Jha et al., 2015; Nachev et al., 2007), but see Sharp et al. (2010). Jha et al. (2015) showed that the pre-SMA is sensitive to contextual complexity using a stop/change task where correct responses required remembering previous stimuli. Similarly, other evidence suggests that pre-SMA activity can be conditional on a previous response and is important in the planning of sequential movements (Nachev et al., 2008; Shima & Tanji, 2000; Tanji & Shima, 1994). Thus, the present finding that pre-SMA activity did not reflect outright stopping outcome might relate to the fact that we used a simple SST. This is consistent with a recent meta-analysis (Zhang et al., 2017) that did not find specific evidence for pre-SMA involvement in canceling actions. A larger sample would be necessary to come to more definitive conclusions.

Our MEG analyses were able to isolate stop signal-elicited activity in the brief interval in which stopping is instantiated. This temporal precision is not possible with functional MRI with the slow rise of the BOLD response. Nevertheless, finding a proper baseline period to normalize stop signal-elicited activity, given the need to account for noise in adaptive beamformer output (e.g. depth bias), posed a challenge in the present data. Given that SSD systematically vary, on average, between successful and unsuccessful stop trials (and between contexts), we opted to use a pooled baseline across all trials. In this way, mean power in each condition was expressed relative to the same baseline power estimate and, therefore, any observed differences between conditions could be attributed

solely to the post stop-signal period. We found this preferable to the method used by Swann et al. (2009) in which data were normalized by a baseline period well before the go signal on stop trials (i.e. −1,750 to −1,250 ms relative to stop signal onset). Because our SST was divided into alternating contexts of only 33 continuously performed trials, stop trials were more likely to occur in pairs. Using a relatively distant baseline period would then have risked inhibitory-related activity leaking from the previous stop trial into the baseline power estimate. Another interesting approach, used by Jha et al. (2015) in their MEG study, is to parameterize event-related oscillatory changes using general linear modeling as done in functional MRI. It is unclear, however, whether such a statistical approach may introduce temporal smoothing in the modeled oscillatory responses and explain their finding that successful stopping was related to increased cortical beta-band activity, but only after the estimated finishing time of the stopping process (i.e. post-SSRT).

With the unpredictable threat paradigm, it is possible that shock anticipation divides attention, which in turn produces deficits in task performance. Indeed, recent theoretical modeling work indicates patient population differences in SST performance may be driven, in part, by attention lapses rather than inhibitory control deficits per se (Matzke et al., 2017). Although we were unable to explicitly test this because a within-subjects model has not been developed and tested (Matsze, personal communication, August 17 2020), this explanation cannot easily accommodate data that suggest anxious arousal improves cognitive–behavioral performance. For example, it was previously shown that threat-induced anxiety hinders the execution of controlled anti-saccades, but facilitates stimulus-driven pro-saccades (Cornwell et al., 2012). Similarly under unpredictable threat, withholding responses on no-go trials in a go/no-go task is improved (Robinson, Krimsky, & Grillon, 2013). Although the latter finding may reflect heightened attention rather than improved inhibitory control per se (Torrisi et al., 2016), it suggests that the potential delivery of shocks does not constitute an ongoing distraction that generally disrupts task performance. Finally, in the present study, we observed that while go RT tended to be (nonsignificantly) slower under anxious conditions during the SST, go RT was significantly faster in the final task in which participants ignored the tone stimulus. This finding cannot be properly substantiated by the current data, given that task order was not counterbalanced, but we can speculate that high anxious arousal may require greater (proactive) adjustment in go responding to meet the demands of having to occasionally stop. Importantly, faster go responding in the ignore-tone task, together with the prior observation of faster pro-saccade initiation in a mixed saccade task (Cornwell et al., 2012) likely rules out the possibility that unpredictable threat causes performance deficits simply by dividing attention. Together with slower SSRTs, our findings support the claim that threat-induced anxiety facilitates stimulus-driven responding while simultaneously impeding controlled actions (including inhibiting actions).

In summary, we identified altered activity in three prefrontal cortical regions—all of which have been linked to stopping—that potentially underlies anxiety-related deficits in inhibitory control. Moreover, we were able to link beta-band oscillatory responses to successful stopping, and specifically establish that right IFG beta-band responses reflect stopping efficiency under nonanxious conditions. These findings, which would benefit from replication in a larger sample, may carry implications for pathologies in which impulse control and anxiety symptoms overlap. Stop-signal task deficits have been identified across a range of disorders characterized by high impulsivity such as obsessive–compulsive disorder (Chamberlain et al., 2006), addiction (Smith et al., 2014), and attention deficit hyperactivity disorder (Oosterlaan et al., 1998). One mediating factor, highlighted by the current results, that could contribute to impaired inhibitory control in these disorders is elevated anxiety, which has been linked to increased pathology in addiction (Sinha, 2001) and OCD (Rachman, 2002). Moreover, right IFG functioning has been associated with the inhibition of drug craving (Volkow et al., 2010), and, interestingly, those with methamphetamine addiction have been shown to exhibit reduced gray matter in right IFG, poorer response inhibition, and poorer affect regulation compared to healthy controls (Tabibnia et al., 2011). Furthermore, insula (Naqvi & Bechara, 2009) and dPFC (Cisler et al., 2013) disruption is also implicated in addiction. Although it should be acknowledged that behavioral tasks may be limited in quantifying individual differences because of potentially low test–retest reliability (Enkavi et al., 2019), here we have worked out a replicable within-subject experimental manipulation that could be extended to patient populations. Our findings suggest that anxious arousal could exacerbate these deficits by disrupting prefrontal cortical mechanisms responsible for controlling behavior and may inform future interventions that could incorporate anxiety management for treating compulsive behavior and/or preventing drug relapse.

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CONFLICT OF INTEREST

The authors declare no competing interests.

AUTHORS' CONTRIBUTIONS

A.D.R. and B.R.C. conceived the experiment and analyzed the data; A.D.R., D.J.W., and B.R.C. designed the experiment and reviewed the results and wrote the paper. A.D.R. performed data collection.

DATA AVAILABILITY STATEMENT

All data used for this study are stored at Swinburne University of Technology, and are accessible upon request as far as allowed by guidelines established with the Swinburne Human Research Ethics Committee. The conditions of project ethical approval do not permit public archiving of anonymized study data. Readers seeking access to the data should contact the Corresponding author at Swinburne University. Access will be granted to named individuals in accordance with ethical procedures governing the reuse of the data. We confirm that all measures, conditions, data exclusions, and the determination of sample size have been included in this paper.

PEER REVIEW

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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Supplementary Materials for

Anxious arousal alters prefrontal cortical control of stopping

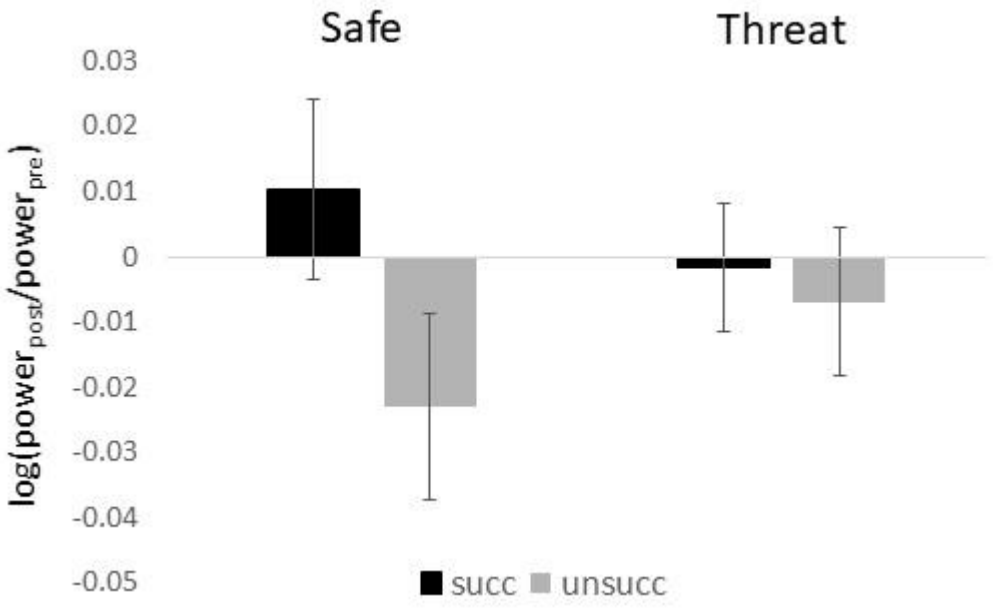
Ariel D. Roxburgh, David J. White, & Brian R. Cornwell

Contents:

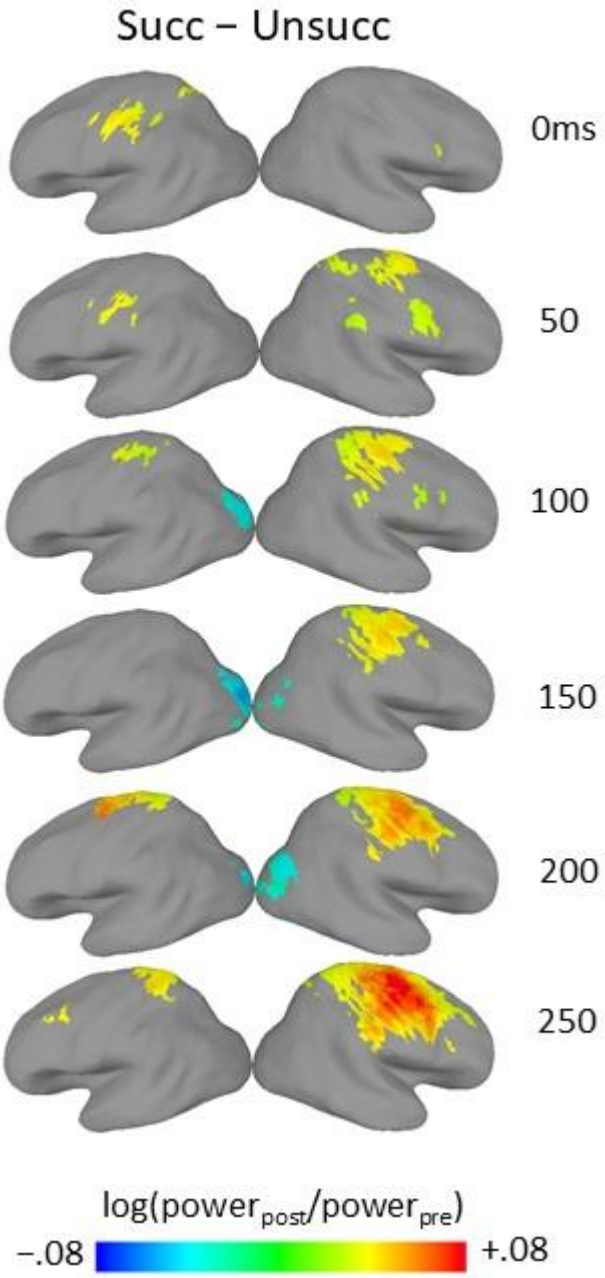
Supplementary Table 1. Brain regions showing differential beta-band activity between successful and unsuccessful stop trials irrespective of context.

	Side	BA	Size	Peak(xyz)			F statistic
-50 to 50ms							
Precuneus	L	7	55	-13	-46	53	23.9
Inferior parietal lobule	L	40/2	53	-45	-26	45	20.2
Precentral gyrus	R	6	5	61	8	26	17.3
0 to 100ms							
Precentral gyrus	R	6	108	35	-13	62	23.7
Precuneus	R	7	82	14	-51	64	21.4
Precentral gyrus	R	6/4	35	61	-3	32	20.4
Inferior parietal lobule	L	40/2	23	-45	-26	45	17.4
Supramarginal gyrus	R	40	9	46	-42	41	17.7
50 to 150ms							
Lingual gyrus	L	18	174	-2	-87	4	43.9
Precentral gyrus	R	4	158	35	-19	62	22.5
Cerebellum	R		75	24	-70	-59	17.9
Precentral gyrus	R	6	28	40	-3	27	16.5
Inferior parietal lobule	L	40	27	-34	-35	63	22.9
100 to 200ms							
Lingual gyrus	L	17/18	783	-2	-87	7	51.4
Precentral gyrus	R	6	192	35	-13	62	36.8
Cuneus/Precuneus	R	19	27	14	-84	44	18.6
Inferior occipital gyrus	L	18	16	-34	-98	-7	20.0
150 to 250ms							
Postcentral gyrus	R	3/4	554	24	-30	69	59.3
Cuneus	L	18	299	-2	-101	16	27.4
Cerebellum	R		58	46	-78	-31	29.2
Cerebellum	R		23	19	-44	-61	16.6
200 to 300 ms							
Precentral gyrus	R	4	841	40	-17	52	51.2
Medial frontal gyrus	L	10	113	-13	61	-7	26.7
Cerebellum	R		20	14	-80	-47	18.1
Middle frontal gyrus	L	6	10	-40	9	43	15.3
Middle occipital gyrus	R	19	7	30	-76	3	15.8

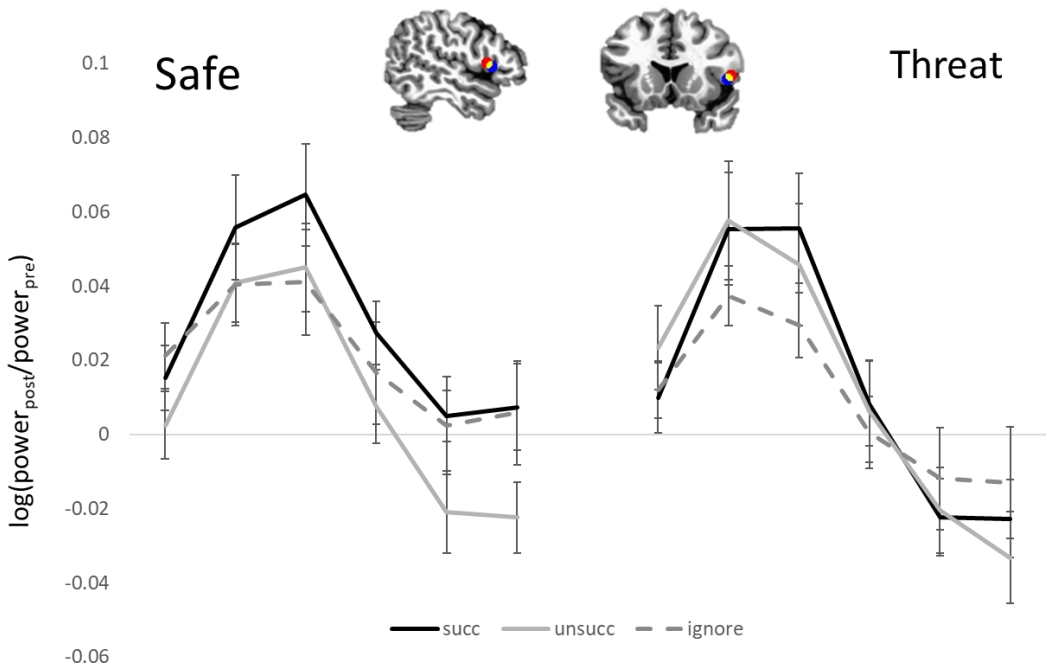
Note: BA = Brodmann Area, Size is in voxel counts. Coordinates are in MNI space.



Supplementary Figure 1. Stop signal-elicited alpha-band (8-13Hz) activity in right IFG shows differential response under nonanxious (safe) conditions only. Bar graph shows mean alpha power ratios extracted from the same ROI as done for beta-band activity (Figure 3 in main text). Power was calculated between 0 and 200 ms, time-locked to the stop signal. succ = successful stop trials, unsucc = unsuccessful stop trials.



Supplementary Figure 2. Successful inhibition is associated with stop signal-elicited increases in sensorimotor and decreases in visual cortical beta-band activity. Beta power differences between successful (Succ) and unsuccessful (Unsucc) stop trials are displayed on an inflated surface reconstruction of a standardized brain. Regional activity differences are thresholded at an FDR < 5%. See Supplementary Table 1 for a full report of clusters showing differential beta-band activity. Time windows are labelled according to their midpoints (0 ms = −50 to 50 ms, 50 ms = 0 to 100 ms, etc.)



Supplementary Figure 3. Right IFG shows beta-band activity associated with successful stopping during nonanxious (safe) conditions only. The ignore tone condition (dashed line) has been overlaid for illustrative purposes but was not counterbalanced so cannot be directly compared. Mean beta power across voxels contained within spherical ROI masks were extracted to show time courses of stop signal-elicited responses in these two regions. Two 5-mm spherical masks were originally specified (red, blue) for the right ventro-posterior IFG, but because of their overlap (yellow), they were combined. succ = successful stop trials, unsucc = unsuccessful stop trials.

5.2 Chapter summary

This chapter revealed two key findings. Firstly, it replicated the findings of chapter 4 and showed that induced anxiety impairs response inhibition. Secondly, it showed that this impairment is related to right IFG dysfunction. Chapter 5 showed that not only was the difference in right IFG activation between successful stops and failed stops stronger in safe compared to threat, but also this difference was related to stopping performance in safe conditions only. The chapter also showed that the right IFG showed a strong increase in beta power in all conditions following the stop signal. This supports the assertion that feedforward projections to the right IFG were activated by the novel auditory stop signal. However, the translation of this signal to inhibitory control (a later level of processing) was impaired during threatening conditions, which supports the findings of Cornwell et al. (2017) and supports the hypothesis that anxiety facilitates early processing at the expense of later processing (Eysenck et al., 2007; O. J. Robinson, Vytal, et al., 2013). However, the alternative hypothesis that anxiety competes for cognitive resources may still apply. Shackman et al. (2006) argued that right frontal regions are allocated to the monitoring of threat and would have fewer available resources to facilitate inhibitory control. One way to explore if right frontal regions are indeed recruited during anxious arousal more generally is to measure more sustained and non-task specific changes in these regions during threatening conditions compared to safe conditions. This will be explored in chapter 6.

Chapter 6 – Neural correlates of sustained anxiety

Chapter 5 showed that the neural mechanisms that facilitate inhibitory control are altered during anxious arousal and this leads to the impaired inhibitory control seen during induced anxiety. However, it is not clear if these neurobiological changes are due to a general anxious state or are due to an anxious state but only when inhibitory control is required (answering this question will help address the main aim of the thesis – to understand the relationship between anxiety and self-control). Further it is not clear if anxiety recruits the same resources needed for inhibitory control even when inhibitory control is not required. Indeed, the more general neuro-electrophysiological signatures of sustained anxiety remain elusive. Understanding these brain related changes in state anxiety will also help address the third aim of the thesis (section 1.6), to understand the neuroelectrophysiological changes associated with threat-induced anxiety. To our knowledge only one study has explored the sustained changes from induced anxiety using MEG (Balderston, Hale, et al., 2017). Balderston, Hale, et al. exposed participants to periods of threat and periods of safe while taking simultaneous MEG recordings. The authors found a reduction in alpha activity in the intraparietal sulcus and suggested this reduction in alpha-power reflects adaptive attention related changes (e.g., improved sustained attention). This study was an important step forward in understanding the electrophysiological signature of sustained anxiety. However, several factors remain unclear. Firstly, Balderston, Hale, et al., simply had the participants view a screen without any variation of what was presented or what the participants did. This leaves open the possibility that the results are specific to that situation. Further, the authors only explored alpha oscillations, meaning it is still unclear how induced anxiety alters brain signatures in other frequency bands. Finally, as a first empirical investigation of this important question, these

findings require replication. Before presenting the study on sustained anxiety, a brief outline of the existing literature concerning the neural signatures of anxiety will be explored.

Our understanding of how anxiety manifests in the brain is based on several research methodologies. For example, the UAMA defines anxiety as anticipatory, cognitive, affective, and behavioural changes in response to uncertainty around future potential threat (Group & Nitschke, 2013). In their model, the authors explain the changes that occur during uncertainty and the neurobiological underpinnings of these changes. They reveal several key regions thought to be involved in anxiety such as the amygdala and the dorsal medial PFC. However, many of the studies used to create the UAMA model look at pathological anxiety rather than induced anxiety in a healthy group. This means the model does not always reflect the adaptive nature of anxious states nor is it free from other variables associated with anxiety disorders. One aspect of the UAMA that is relevant to understanding adaptive anxiety states is their explanation of uncertainty and how this manifests in the brain. When threat is uncertain, humans show a larger startle response (Grillon et al., 2004). A key region involved in responding to uncertainty is thought to be the anterior insula, which has been revealed using several studies that induced anxiety (Kuhnen & Knutson, 2005; Preuschoff, Quartz, & Bossaerts, 2008; Sarinopoulos et al., 2009). However, most of the studies looked at differences in brain responses locked to a cue or behaviour; meaning, the responses may not reflect more general sustained anxiety. For example, Sarinopoulos et al. (2009) looked at responses to negative pictures following certain or uncertain cues. Similarly, Kuhnen and Knutson (2005) looked at neural responses preceding particular decisions, showing anterior insula preceded risk aversive decisions. These studies both show anxiety related changes that are time locked to decisions, actions, or stimuli presentations. The studies were also conducted using fMRI. This leaves a large gap in the literature, which can be filled by

attempting to elucidate an understanding of the more general brain changes in response to sustained anxiety, particularly in the understanding of electrophysiological changes.

Many of these studies have looked at specific aspects of anxiety, (e.g. predictability; Somerville et al., 2012). However, a recent study has explored sustained brain activity during anxious and non-anxious conditions. Vytal, Overstreet, Charney, Robinson, and Grillon (2014) explored sustained state anxiety in fMRI during threat of shock and safe conditions. They found increased coupling between amygdala and dmPFC during sustained anxiety and described this amygdala/dmPFC complex as a seed that maintains an anxious state. Coupling to this seed complex was explored to see what other regions might be involved in sustained anxiety. Correlations between these seed regions and other brain regions were explored and whole brain corrected for threat compared to safe. There were several connections. For example, a positive correlation between seed regions and the thalamus, basal ganglia, insula, medial frontal gyrus, cingulate gyrus, and orbital frontal cortex. Other studies have explored sustained anxiety related changes between uncertain threat and safe conditions. There is a general prolonged insula activation during unpredictable compared to predicable threat for aversive pictures (Shankman et al., 2014; Somerville et al., 2012), and electric shocks (Alvarez, Chen, Bodurka, Kaplan, & Grillon, 2011). Sustained anxiety from unpredictable shocks is also associated with BOLD activation in the bed nucleus of the striata terminalus (BNST), insula, parietal, and frontal regions such as the right inferior frontal and right superior frontal areas (Alvarez et al., 2011). However, neural processing is an electrophysiological phenomenon and blood flow is only a secondary measure of neural activity (E. L. Hall et al., 2014). Further, anxious arousal alters cerebrovascular function and is often accompanied by respiratory changes that alter arterial CO2 tensions and create changes in cerebral blood flow (Giardino et al., 2007). Thus, changes in cerebral activity

measured using fMRI between anxious and non-anxious conditions may be confounded by anxiety-induced changes in cardiovascular function.

While there have been studies exploring the electrophysiological components of sustained unpredictable threat, they often have poor spatial resolution and have focused primarily on timing rather than region or frequency (MacNamara & Barley, 2018) or have only focused on alpha frequency (Balderston, Hale, et al., 2017).

6.1 Paper - Common sustained anxiety related changes in beta oscillations across three different tasks

6.1.1 Rationale

Despite the large number of studies exploring the neurobiological underpinnings of anxiety, there is a gap in the literature. To our knowledge no study has explored the electrophysiological activity associated with sustained anxiety, independent of task requirements with a focus on beta oscillations. While this has been explored using fMRI (Vytal et al., 2014), MEG provides additional rich data that is often missed in fMRI. Further, anxiety may cause cerebrovascular changes that underlie BOLD measurement confounding fMRI findings (Giardino et al., 2007). The proposed study will explore sustained anxiety using MEG across one passive and two active tasks, which should ensure that results are truly task independent.

Article "submitted"

A neural oscillatory signature of sustained anxiety

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Abstract

Background

Anxiety is a sustained response to uncertain threats, yet few studies have explored sustained neurobiological activities underlying anxious states, particularly spontaneous neural oscillations. To address this gap, we reanalysed magnetoencephalographic (MEG) data recorded during induced anxiety to identify differences in sustained oscillatory activity between high and low anxiety states.

Methods

We combined data from three previous MEG studies in which healthy adults (total *N*=51) were exposed to alternating periods of threat of unpredictable shock and safety while performing a range of cognitive tasks (passive oddball, mixed‐saccade or stop-signal tasks). Spontaneous band-limited oscillatory activity was extracted from middle and late intervals of the threat and safe periods, and regional power distributions were reconstructed with adaptive beamforming. Conjunction analyses were used to identify regions showing overlapping spectral power differences between threat and safe periods across the three task paradigms.

Results

MEG source analyses revealed a robust and widespread reduction in beta (14-30Hz) power during threat periods in bilateral sensorimotor cortices extending into right prefrontal regions. Alpha (8-13Hz) power reductions during threat were more circumscribed, with notable peaks in left intraparietal sulcus and thalamus.

Conclusions

Threat-induced anxiety is underpinned by a sustained reduction in spontaneous beta- and alpha-band activity in sensorimotor and parietal cortical regions. This general oscillatory pattern

likely reflects a state of heightened action readiness and vigilance to cope with uncertain threats. Our findings provide a critical reference for which to identify abnormalities in cortical oscillatory activities in clinically-anxious patients as well as evaluating the efficacy of anxiolytic treatments.

Anxiety symptoms commonly present across psychopathological diagnostic boundaries (American Psychiatric Association, 2013; Lanius et al., 2006; Nitschke & Heller, 2005), although those specifically diagnosed with anxiety disorders tend to experience more frequent and severe states of anxious arousal (American Psychiatric Association, 2013). In contrast to fear, which can be defined as a short-lived response to a perceived immediate threat, anxious arousal describes a more sustained response to threats that are uncertain and more psychologically and physically distal (Davis et al., 2010). Under these circumstances, the organism becomes cautious and hypervigilant toward the environment (Grillon, 2002; Grupe & Nitschke, 2013). While anxious arousal can serve an adaptive function when real threats materialize, it can lead to distress and impaired functioning when the state is persistent or extreme (American Psychiatric Association, 2013). Persistent hypervigilance is a hallmark of posttraumatic stress disorder (PTSD) and is associated with early exaggerated sensory-perceptual responding in patients with the disorder (Ge, Wu, Sun, & Zhang, 2011; Morgan & Grillon, 1999). Similarly, heightened sensory-perceptual responding can be seen in healthy participants during induced anxiety (Cornwell et al., 2007; Cornwell et al., 2017), indicating that experimentally-induced anxiety can model aspects of clinical anxiety. However, human studies have predominantly focused on task- or stimulus-related activity and how anxiety - measured as a state or trait variable – modulates these activities (e.g. Cornwell, Mueller, et al., 2012). Few studies have looked at sustained state-related changes related to the induction of anxiety by a well-established anxiety induction paradigm.

The threat-of-shock procedure, wherein participants are exposed to periods of threat (i.e., unpredictable shock) and safety, is a reliable way to induce anxiety that has been validated in preclinical, clinical, and pharmacological studies as an anxiety manipulation (Cornwell et al., 2017; Davis et al., 2010; Grillon, 2008; O. J. Robinson, Vytal, et al., 2013). Threat-of-shock has been used in conjunction with non-invasive neuroimaging to localize sustained changes

during anxiety states (Alvarez et al., 2011; Balderston, Hale, et al., 2017; Hasler et al., 2007; MacNamara & Barley, 2018; Vytal et al., 2014). For example, Andreatta et al. (2015), exposed participants to virtual reality settings associated with threat-of-shock or safe conditions and found threatening contexts were associated with changes in sustained fMRI-BOLD activity in emotional, navigational, and motor areas. Also using fMRI, Vytal et al. (2014) found increased coupling between the amygdala and dorsal medial prefrontal cortex (dmPFC) during sustained threat periods, which has been reported in other studies (Bijsterbosch et al., 2015; O. J. Robinson et al., 2016). Using these regions as "seeds", Vytal et al. (2014) further showed increased coupling between this seed network and areas involved in defensive responding (e.g. insula, OFC, dACC, basal ganglia, and thalamus) and decreased coupling with structures involved in emotional control (e.g. ITG). Using fMRI during periods of induced anxiety, several regions have shown increased activity such as the insula, amygdala, basal ganglia, cingulate gyrus, orbital frontal cortex, bed nucleus of the stria terminalis (BNST), and right inferior frontal gyrus (Alvarez et al., 2011; Andreatta et al., 2015; McMenamin & Pessoa, 2015; Vytal et al., 2014). Although a preliminary picture of an extended brain network underlying sustained anxiety is emerging, the exclusive reliance on hemodynamic (i.e., fMRI) and metabolic (i.e., PET, SPECT) measurements presents problems. First, anxious arousal alters cerebrovascular function and is often accompanied by respiratory changes that alter arterial CO2 tensions and create changes in cerebral blood flow (Giardino et al., 2007). Thus, changes in cerebral activity measured using fMRI between anxious and non-anxious conditions may be confounded by anxiety-induced changes in cardiovascular function. Second, fMRI scanning has been shown to be anxiogenic with its partly-enclosed, acoustically-stressful environment (Tessner, Walker, Hochman, & Hamann, 2006), which could obscure any relative differences between threatening and safe contexts.

Electrophysiological studies of anxiety have also focused predominantly on brain data in relation to task events or participant responses (e.g. Cornwell, Mueller, et al., 2012). However, there has been some research into sustained anxiety using electrophysiological measurements such as MEG and EEG. Frost, Burish, and Holmes (1978) showed no changes in EEG alpha activity between participants in threatening and non-threatening conditions. Most recent research reports asymmetry of EEG oscillatory power between hemispheres, which is thought to relate to emotion regulation (Goodman, Rietschel, Lo, Costanzo, & Hatfield, 2013; Reznik & Allen, 2018; Verona, Sadeh, & Curtin, 2009). While informative, EEG provides low spatial resolution and may not be optimally sensitive to subtle region-specific changes to consolidate with fMRI findings. Few have looked at the electrophysiological activity associated with sustained anxiety with MEG, which offers higher spatial resolution than EEG. A notable exception is Balderston, Hale, et al. (2017) who used threat-of-shock to induce anxiety while collecting both MEG and fMRI data. The authors specifically targeted alpha (8-13Hz) activity, finding threat-related reductions in the left intraparietal sulcus (IPS). Due to the IPS's role in attention (Goltz et al., 2015; Molenberghs, Mesulam, Peeters, & Vandenberghe, 2007; Thakral & Slotnick, 2009), the authors suggested anxiety facilitates attentional processing.

It has been shown that conditioned fear is associated with increased theta-band (4-8Hz) coupling between the midline frontal and amygdala regions, which is thought to reflect adjustments to uncertainty (Cavanagh & Shackman, 2015). However, it is not clear if these theta-band changes would also be shown during states of sustained anxious arousal. There is also evidence beta oscillations (i.e., 14-30 Hz) might be modulated by induced anxiety. Beta has been extensively studied (Schmidt et al., 2019) and is thought to be important in action/thought stopping in the right IFG and basal ganglia (Castiglione et al., 2019; Nicole Swann et al., 2011; N. Swann et al., 2009; Wagner et al., 2017; Zavala et al., 2015) and readiness for action over sensorimotor areas (Kilavik et al., 2013). Further, inhibitory deficits

found in induced anxiety are associated with differences in beta oscillations (Cornwell, Mueller, et al., 2012; Roxburgh, White, & Cornwell, 2020). Kilavik et al. (2013) suggest that sensorimotor beta increases are associated with motor stability, while decreases are associated with motor action and action readiness. Action readiness is likely what an adaptive anxious state would require, enabling an organism to quickly escape danger. Thus, anxiety might reduce sensorimotor beta activity to facilitate readiness for action.

Here we present a new analysis of spontaneous neural oscillatory activity from three different MEG studies employing threat of unpredictable shocks to induce sustained anxiety states. With the same method of anxiety induction, we sought to identify common oscillatory correlates of anxious arousal across three different cognitive contexts: a passive listening auditory oddball task (Oddball study; Cornwell et al., 2007), a mixed saccadic eye movement task (Mixed-saccade study; Cornwell, Mueller, et al., 2012), and a stop-signal task (Stop-signal study; Roxburgh et al., 2020). Importantly, we specifically focused our analyses on intervals during threatening and non-threatening periods in which an initial phasic fear response to the onset of threat has given way to a sustained state of anxious arousal. We hypothesize that these intervals during threatening periods are marked by decreased beta and alpha oscillatory activity in sensorimotor and parietal cortices, reflecting a state in which the individual is primed to rapidly respond to imminent danger. Whole-brain MEG analyses allowed us to examine whether other structures involved in affective processing (e.g., amygdala, hippocampus, medial prefrontal cortices) also show spontaneous oscillations that might underpin sustained anxiety.

Methods and Materials

Participants

We selected three participant samples from previous studies that used similar threat of unpredictable shock procedures. The Oddball (Cornwell et al., 2007) and Mixed-saccade

studies (Cornwell, Mueller, et al., 2012) were conducted at the National Institutes of Health (Bethesda, MD, USA), and the Stop-signal study (Roxburgh et al., 2020) was completed at Swinburne University of Technology (Hawthorn, VIC, Australia). In the Oddball and Mixed-Saccade studies, we obtained MEG recordings and MR images from 20 and 17 healthy adult volunteers, respectively. Because the present analysis was specifically aimed at identifying neural oscillatory correlates of anxious arousal, four participants from the Oddball study were excluded for not reporting increased anxiety during threat of shock periods. In the Stop-signal study, we obtained MEG recordings and MR images from 18 healthy adult volunteers. All studies were approved by local ethics boards (Combined Neuroscience Institutional Review Board of the National Institutes of Health or Swinburne University Human Research Ethics Committee) and all participants provided written informed consent prior to participation. Exclusion criteria were the same in all three studies (no past or current DSM-IV/V diagnosis, or current use of psychoactive or illicit drugs), except that the Stop-signal study relied on self-report while the other two used Structured Clinical Interviews for DSM-IV (First, Spitzer, Williams, & Gibbon, 1995) and urine analysis to determine eligibility.

Design and Procedure

MEG data were recorded in two runs containing threatening (THREAT) and non-threatening (SAFE) conditions. THREAT and SAFE conditions alternated with counterbalancing of the starting condition. During THREAT participants were informed they could receive electric shocks at any time; while participants were told they would not receive a shock during SAFE. An initial shock work-up procedure was used to determine an appropriate level of shock for each participant. Shock work-up involved the delivery of an initial weak shock followed by shocks of increasing amplitude until a level that participants rated as “moderately aversive” was achieved. Participants received 8 shocks across the 2 runs combined, which were delivered on a fixed pseudorandom schedule (the Oddball study used a single shock delivered at the end

of the first run). The start of each context was signaled by a voice recording (Oddball study) or a text message on the screen (Mixed-saccade and Stop-signal studies), indicating whether they were at risk of receiving shocks or safe for the following period. At the end of each run, participants rated their anxiety on a scale from 0 ("no anxiety") to 10 ("extreme anxiety") for each condition.

During THREAT and SAFE periods, participants engaged in one of three tasks; a passive oddball task (listening but not responding to simple auditory tones) (Cornwell et al., 2007), stop-signal task (SST; responding to visual stimuli by pressing a button and occasionally withholding responses after an auditory cue) (Roxburgh et al., 2020), or a mixed-saccade task (performing pro or anti saccades with respect to a peripheral visual cue) (Cornwell, Mueller, et al., 2012). For the mixed-saccade and stop-signal tasks each run had five THREAT and five SAFE periods, with each block lasting approximately 70 seconds. For the Oddball study each run had ten THREAT and ten SAFE periods each lasting approximately 35 seconds. In all studies, participants were instructed that the stimuli and task were unrelated to shock administration.

MEG acquisition

Data for the Oddball and Mixed-saccade studies were obtained with a CTF 275-channel whole head MEG system (VSM MedTech, Ltd., Canada) in a magnetically-shielded room (Vacuumschmelze, Germany) using synthetic third gradient balancing for active noise cancellation. Data for the Stop-signal study was obtained using a 306-channel Elekta Neuromag® TRIUX magnetometer MEG system (Helsinki, Finland) in a magnetically shielded room with internal active shielding disengaged. Magnetic flux density was digitized at a sampling rate of 600 Hz (Oddball), 1200Hz (Mixed-saccade), or 1000Hz (Stop-signal). In all studies radiological markers was placed on each fiducial position for later co-registration

with individual anatomical MRIs. In all three studies, participants that exceeded 5mm in total head displacement from the start of the scan were removed from analysis.

MEG analysis

For the Mixed-saccade and Stop-signal studies, there was a total of 10 periods for THREAT and 10 for SAFE (2 runs x 5 alternations), each lasting approximately 70 sec. Two separate 10-sec epochs were extracted from each THREAT and SAFE period. Epoch timing was chosen to ensure shocks were not delivered during the window: for the middle epoch, timing was 29-39 sec for the SST and 27-37 sec for the mixed-saccade task; for the late epoch, timing was 55-65 sec for the SST and 48-58 for the mixed-saccade task. For the Oddball study, there was a total of 20 periods for THREAT and 20 for SAFE (2 runs x 10 alternations), each lasting approximately 35 sec. Because of the shorter period, 5-sec epochs were extracted from these data (10-15 sec for the middle interval and 25-30 sec for the late interval).

Epochs were extracted and bandpass filtered using standard frequency windows: 4-8 Hz for theta, 8-13 Hz for alpha, 14-30 Hz for beta and 30-50 Hz for gamma. Noisy and flat channels were removed from the analysis; no other data/noise statistical reduction techniques were used prior to source analysis. A single data covariance matrix was calculated (without regularization) across all remaining sensors from bandpass-filtered data. For lead-field calculation, the Nolte method (Nolte, 2003) was used to generate single-shell head models from the spatially coregistered MRIs for the SST. For the Mixed-saccade and Oddball studies a multiple-spheres model was used to compute the forward solution. SST MEG data were analyzed with a linear-constrained minimum-variance (LCMV) beamformer method in Fieldtrip software (Oostenveld et al., 2011), while oddball and mixed-saccade data were analysed with synthetic aperture magnetometry (or SAM beamformer) using CTF software along with freely-available software tools developed by the NIMH MEG Core facility

(http://kurage.nimh.nih.gov). Contrasts were made directly between spectral power during THREAT and spectral power during SAFE, resulting in estimates of relative power (pseudo-F power ratio for the Oddball and Mixed-saccade studies and $\log_{10}$-transformed power ratios for the Stop-signal study). Each individual source image consisted of a volume of power ratios with a spatial sampling of 5 mm. Positive power ratios represent greater power during THREAT than SAFE, and vice versa.

Group analyses were conducted using AFNI (Cox, 1996) after transforming individual volumetric data into a common Talairach space, and normalizing voxel statistics. Differences in band power between conditions were then calculated for each window in each study. One-sample Student *t* tests were performed on a voxel-wise basis with a test case of zero, reflecting the null hypothesis of equal oscillatory signal power between THREAT and SAFE periods for a given region. To establish spatial overlap in differential regional activity across studies, joint probability values were obtained from voxel-wise *t* statistics across the three studies and a single false discovery rate (FDR) calculation was performed for all frequency bands and middle and late time intervals. Joint probability values below .0019 corresponded to an overall FDR below 1%. Thus, we settled on using a nominal $p < .05$ per study to identify convergence in regional differences across studies (joint probability value < .000125 = .05 x .05 x .05).

Results

Decreased beta-band activity during sustained THREAT across three independent samples

Whole brain adaptive beamformer analyses were carried out to examine spatial convergence of differential beta-band activity (14-30Hz) between THREAT and SAFE conditions across the three studies. Figure 1 displays common regions of differential beta during the middle interval separately for each study. As can be observed, threat-related decreases in beta power span bilateral sensorimotor cortices and right ventrolateral prefrontal cortex.

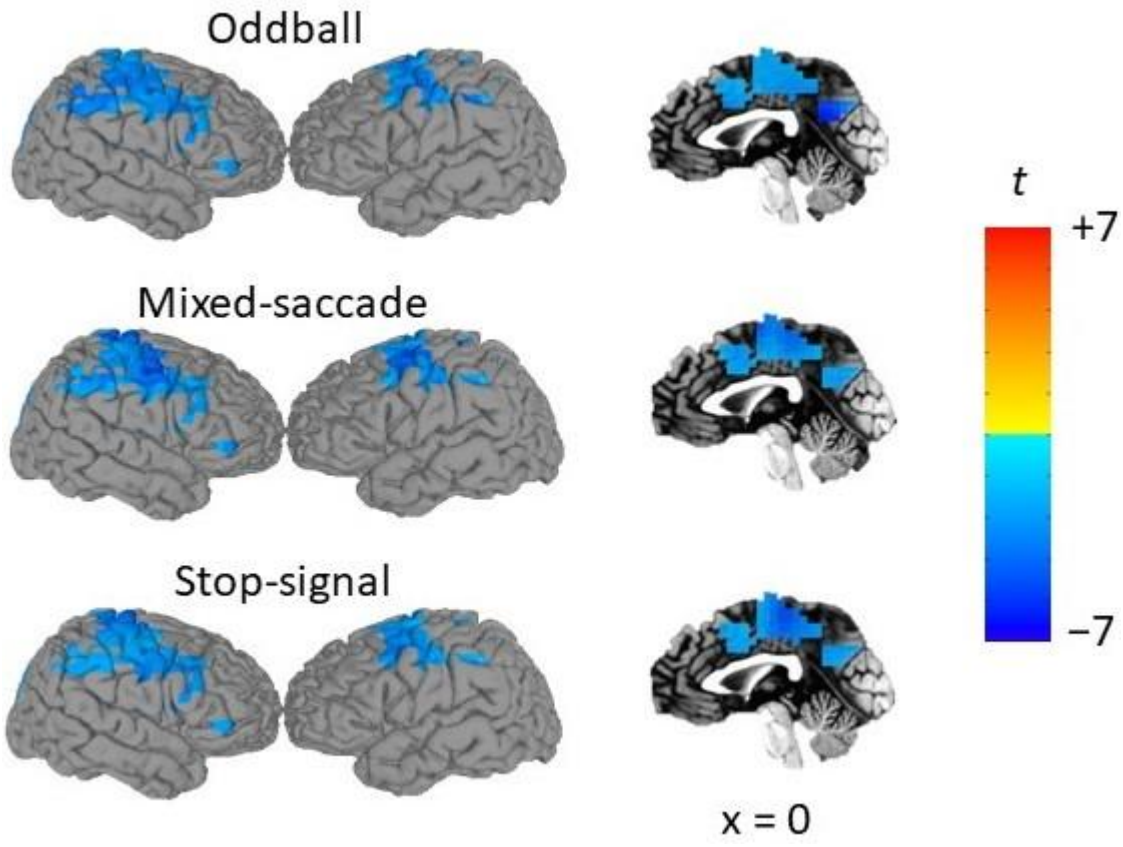

Figure 1. Decreased beta-band activity over sensorimotor and right prefrontal areas during sustained threat of unpredictable shock across three independent samples. Pial surface reconstructions and sagittal slices of a standardized brain are overlayed with t statistic maps mean beta power ratios (THREAT/SAFE, log10-transformed) over regions where mean beta power differences between conditions (THREAT – SAFE) survive a threshold of .05 for all three studies.

A reduction in beta power during THREAT compared to SAFE was found across all three studies in five regional clusters. The first large cluster spanned the bilateral sensorimotor areas and part of the superior and medial parietal lobe. The second cluster was in the right mid orbital gyrus. The third was localized to the right inferior frontal gyrus. Two more small clusters were

in the anterior cingulate cortex. Details of clusters for middle and late windows can be found in Supplementary Material (Table S1 and Table S2).

Decreased alpha-band activity during sustained THREAT across three independent samples

The same procedure used to explore beta-power related changes was used to explore alpha-power changes. Figure 2 shows the common regions of differential alpha during the middle interval separately for each study. Threat-related decreases in alpha-power can be seen in the left intraparietal sulcus (IPS), thalamus, intraparietal junction, and sensorimotor areas. Cluster details for middle and late windows are shown in Supplementary Table S3 and S4.

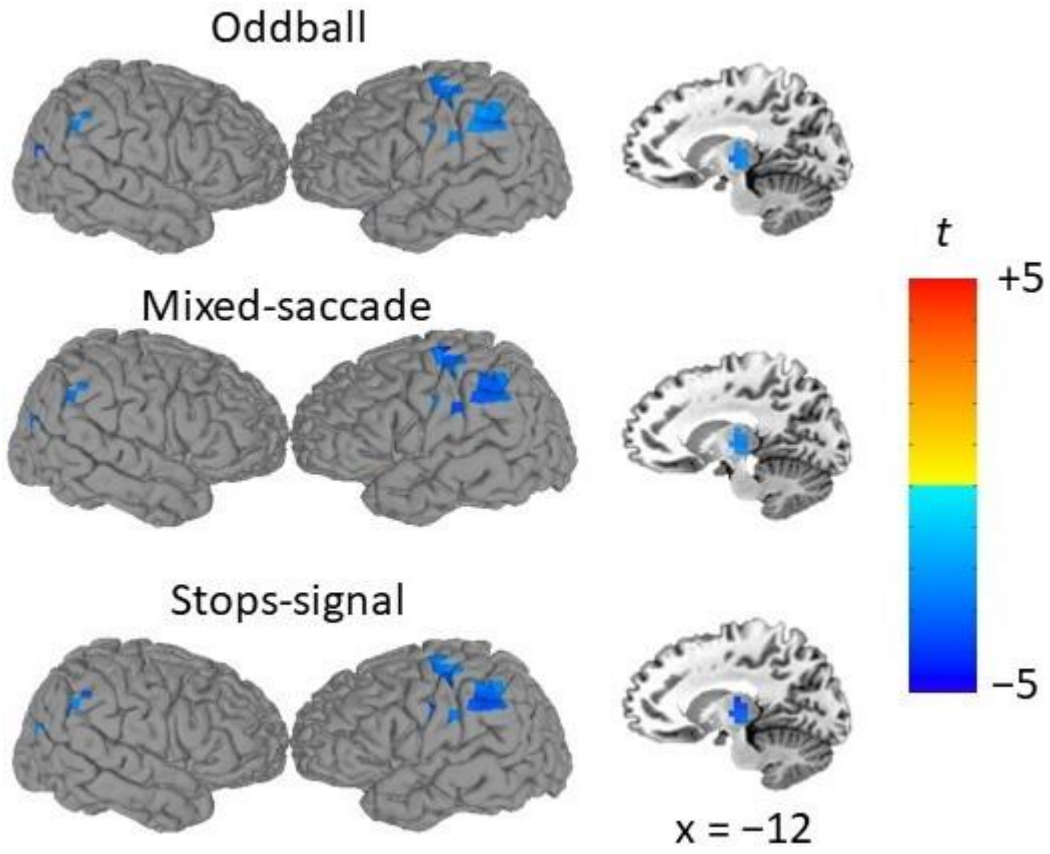

Figure 2. Decreased alpha-band activity during sustained threat of unpredictable shock across three independent samples. Pial surface reconstructions and sagittal slices of a standardized brain are overlayed with t statistic maps mean beta power ratios (THREAT/SAFE, log10-transformed) over regions where mean alpha power differences between conditions (THREAT – SAFE) survive a threshold of .05 for all three studies.

No significant differences found in theta-band or gamma-band activity during the middle windows, but a decrease in sensorimotor gamma in the late window

There were no significant clusters of differential theta power between THREAT and SAFE across all three studies. The same was true for gamma power in the middle interval. However,

there was a threat-related reduction in gamma power in the late window over sensorimotor cortices. Cluster details are shown in Supplementary Table S5.

Discussion

Across three independent studies, anxiety induction was associated with a reduction in beta band power, most prominently in bilateral sensorimotor cortices. Importantly, this reduction occurred in three different task contexts, including a passive oddball task with no motor response requirements. This suggests the reduction in beta-band power is task-independent and reflects a more general anxiety state triggered by unpredictable threat. Based on the 'status quo' theory (Engel & Fries, 2010) and related claims (Kilavik et al., 2013; Schmidt et al., 2019), threat-related reductions in sensorimotor cortical beta power likely reflect heightened action readiness even without overt motor actions (e.g., passive oddball listening), as a protective mechanism to cope with potential threat (Ekman & Davidson, 1994; O. J. Robinson, Vytal, et al., 2013). Notably, a resting state MEG study comparing patients with PTSD to healthy controls found that patients showed decreased beta oscillatory power in a number of regions including right superior frontal gyrus, mid-line supplementary motor areas (SMA), and bilateral sensorimotor cortices (M.-X. Huang et al., 2014). Thus, while the current study arguably shows adaptive cortical changes in healthy individuals exposed to the threat of unpredictable shocks, similar changes may underlie anxiety pathologies as they become persistent and situationally-inappropriate.

Reductions in beta power were also found over the right prefrontal areas including the right IFG and right mid orbital gyrus. A reduction in beta power over right prefrontal regions, particularly the right IFG, may reflect priming of stimulus-driven attention processes. Cornwell et al. (2017) found that feedforward projections to the right IFG in response to infrequent stimuli were facilitated by induced anxiety, while feedback projections were impaired;

supporting the notion that the right IFG plays a role in the detection of deviant early sensory input (Doeller et al., 2003), which is facilitated by induced anxiety at the potential cost of later processing. A likely cost of this preference for stimulus-driven processing, is impaired goal-directed processing. Increased beta power in the right IFG is generally associated with improved motor inhibition (Castiglione et al., 2019; N. Swann et al., 2009; Wagner et al., 2017; Wessel, Conner, Aron, & Tandon, 2013). However, we recently showed that inhibitory increases in right prefrontal beta are lessened during induced anxiety (Roxburgh et al., 2020). Our current data together with these previous findings suggest that anxiety induces a reduction in right prefrontal and sensorimotor beta power that likely facilitates action readiness at the expense of action inhibition. Indeed, increases in right prefrontal beta facilitate motor inhibition; while decreases in sensorimotor beta facilitate motor movements (Engel & Fries, 2010). Importantly, our study shows how anxiety-related changes could lead to cognitive deficits seen in anxiety disorders. For example, those with PTSD tend to have poorer inhibitory control (Swick, Honzel, Larsen, Ashley, & Justus, 2012; van Rooij et al., 2014), which may be due to heightened stimulus-driven responding.

The results also showed a decrease in alpha power over the left intraparietal sulcus (IPS) and thalamus. The reduced alpha-power in the IPS is consistent with the findings of Balderston, Hale, et al. (2017), who also showed with MEG a threat-induced decrease in alpha in the left intraparietal sulcus. Balderston, Hale, et al. (2017) argue this reduction in alpha reflects changes in attention due to the role of the IPS in attentional control. Our findings support this assertion. However, we show this reduction occurs regardless of task demands, it occurs even during the passive oddball task where goal-directed attention is not required. Like the findings of a reduction in sensorimotor beta, this finding shows that there are sustained anxiety related changes in the brain that are independent of task type. This suggests the induced anxiety

facilitates general changes in the preparation of possible future motor or attentional demands rather than (or in addition to) changes made in response to motor and attentional demands.

The decreased alpha found in the thalamus could reflect a node in an anxiety related network. Indeed, Balderston, Hale, et al. (2017) found an increase in connectivity between the thalamus and IPS during induced anxiety compared to safe conditions. Further, the thalamus has been implicated as a key node in the canonical fear network and in fear conditioning (Fullana et al., 2016). Finally, when exploring the functional connectivity of two key fear and anxiety related structures (bed nucleus of the stria terminalis and central amygdala) during sustained threat-induced anxiety, Torrisi et al. (2018) showed the central amygdala becomes more strongly coupled to the thalamus under threat. They argue the thalamus plays a role in sensory and attentional adaptations during sustained anxiety. Further, Hermans, Henckens, Joëls, and Fernández (2014) argue the thalamus is part of a network that responds to acute stress by facilitating attention. Our results support the contention that the thalamus plays a role in the brain's response to prolonged uncertain threat and further suggest these changes exist as a threat induced reduction in the alpha-band power. This facilitation of attention, particularly to threat, is another aspect of the hypervigilance seen in anxiety related disorders (American Psychiatric Association, 2013; Bangel, van Buschbach, Smit, Mazaheri, & Olff, 2017; Cisler & Koster, 2010).

It should be noted that the pattern of differential oscillatory power varies to a moderate degree between the middle and late interval windows. While the decrease in sensorimotor cortical beta remained in both windows, the right ventrolateral prefrontal cortical beta did not. Similarly, there were fewer regions showing reduced activity in alpha during the late window compared to the middle window. It is possible this general reduction over time (from middle to late windows) in oscillatory power differences between threat and safe could reflect a partial waning of anxious arousal over the threat period. Indeed, even the robust bilateral sensorimotor

cortical beta difference partially wanes from the middle to the late window. The general reduction in changes suggests a general reduction in the effect of the experimental manipulation. Another limitation in the data is the lack of findings in areas that show fear related changes. For example, fear is associated with changes in theta-band power in the amygdala, hippocampus, and medial PFC (Lesting et al., 2011; Maratos, Mogg, Bradley, Rippon, & Senior, 2009; Pape, Narayanan, Smid, Stork, & Seidenbecher, 2005). Further, fMRI studies implicate these structures in anxiety (Grupe & Nitschke, 2013). However, we did not find anxiety-induced changes in theta power or in these structures in any other frequency range. This may be due to the differences between anxiety and fear. The electrophysiological studies implicating these regions tended to look at short lived responses to immediate threat (i.e., fear), while the present study focused on sustained responses to unpredictable threat.

The current findings of decreased sensorimotor beta may have treatment implications. For example, it is generally accepted that benzodiazepines induce a 'beta buzz' – an increase in beta activity (Domino, French, Pohorecki, Galus, & Pandit, 1989; van Lier et al., 2004). The current findings indicate that anxiolytic effects of benzodiazepines could be to boost beta-band signalling, counteracting the suppression of beta-band activity during anxious arousal. In addition, monitoring beta oscillatory activity in real time over sensorimotor cortices may provide a useful proxy of a patient's current state of arousal. This could be used to inform exposure therapies, or it could be used to help patients reduce anxiety through neurofeedback techniques. Preliminary studies have attempted to increase beta activity in patients with anxiety without specifically target sensorimotor areas, reporting evidence of symptoms waning and cortisol levels dropping following neurofeedback training (Aliño Costa, Gadea, Hidalgo, Pérez, & Sanjuán, 2016; Moradi et al., 2011)

Overall, our data shows threat-induced anxiety is reflected in oscillatory changes in regions associated with action readiness and attention/vigilance. When prolonged or extreme, these

state-related changes may underlie the pathological hypervigilance seen in many psychiatric disorders. These findings may aid in the detection of anxious states and in the treatment of pathological anxiety and hypervigilance. However, these findings should be extended to other anxiety provoking paradigms such as speech anticipation. The authors urge future work to use additional anxiety-inducing paradigms to provide a more complete understanding of sustained anxious arousal.

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Disclosures

The authors declare no competing interests.

Supplementary material

Table S1. *Brain regions showing differential beta-band activity between THREAT and SAFE conditions during the middle window*

			Oddball				Mixed-saccade				Stop-signal			
	BA	Size	Peak(xyz)			t statistic	Peak(xyz)			t statistic	Peak(xyz)			t statistic
Sensorimotor/Precuneus	3/6/31	1873	3	-59	25	-6.80	19	-20	87	-5.77	19	-20	57	-5.71
Mid Orbital Gyrus	14	13	14	36	-5	-2.87	14	46	-11	-2.74	19	41	-5	-2.94
Right IFG	45	8	51	41	-5	-2.91	51	41	-5	-3.24	46	36	-5	-2.90
Anterior Cingulate	24	4	8	32	13	-2.29	8	27	13	-2.17	8	32	13	-2.54
Anterior Cingulate	33	4	8	23	19	-2.46	14	23	19	-2.50	14	28	19	-2.47

Note: BA = Brodmann Area, Size is in voxel counts, Coordinates are in MNI space, Sensorimotor/Precuneus is a large cluster spanning these regions, clusters required a minimum voxel number of 4 to be included in the table

Table S2. *Brain regions showing differential beta-band activity between THREAT and SAFE conditions during the late window*

			Oddball				Mixed-saccade				Stop-signal			
	BA	Size	Peak(xyz)			t statistic	Peak(xyz)			t statistic	Peak(xyz)			t statistic
Sensorimotor	3/6	1118	51	14	37	-6.19	35	-7	67	-7.20	24	-6	73	-4.77

Note: BA = Brodmann Area, Size is in voxel counts, Coordinates are in MNI space, Sensorimotor, clusters required a minimum voxel number of 4 to be included in the table

Table S3. *Brain regions showing differential alpha-band activity between THREAT and SAFE conditions during the middle window*

			Oddball				Mixed-saccade				Stop-signal			
	BA	Size	Peak(xyz)			t statistic	Peak(xyz)			t statistic	Peak(xyz)			t statistic
Middle Cingulate	23	42	19	-9	38	-2.99	19	-9	27	-4.39	14	-21	39	-3.73
Precentral Gyrus	6	35	-45	-7	61	-3.47	-40	-13	62	-3.67	-29	-15	33	-3.61
Inferior Parietal Lobule	40	28	-67	-31	40	-3.33	-61	-31	46	-3.59	-61	-31	40	-3.68
Thalamus	-	14	-13	-11	-2	-3.13	-13	-24	-1	-2.77	-13	-17	10	-4.07
Precentral Gyrus	6	9	-50	-3	27	-2.91	-50	-9	27	-2.66	-56	-3	32	-3.59
Postcentral Gyrus	2	9	40	-31	76	-2.17	35	-31	52	-3.20	30	-26	45	-2.87

Note: BA = Brodmann Area, Size is in voxel counts, Coordinates are in MNI space, Sensorimotor/Precuneus is a large cluster spanning these regions, clusters required a minimum voxel number of 4 to be included in the table

Table S4. *Brain regions showing differential alpha-band activity between THREAT and SAFE conditions during the late window*

			Oddball				Mixed-saccade				Stop-signal			
	BA	Size	Peak(xyz)			t statistic	Peak(xyz)			t statistic	Peak(xyz)			t statistic
Middle Temporal Gyrus/temporal-parietal junction	21/39	48	46	-50	7	-5.10	40	-44	18	-3.63	51	-44	12	-3.37
Middle cingulate cortex	24	17	3	-8	44	-2.76	3	-27	57	-2.62	8	-15	39	-3.45
Pre/postcentral gyrus	40	6	-29	-20	57	-2.57	-24	-30	57	-2.47	-40	-20	51	-4.13
Pre/postcentral Gyrus	4	13	-40	-9	38	-3.00	-50	-8	44	-2.79	-50	-20	45	-2.85
Postcentral Gyrus	2	6	61	-9	27	-2.46	61	-16	27	-2.37	61	-9	33	-3.89

Note: BA = Brodmann Area, Size is in voxel counts, Coordinates are in MNI space, Sensorimotor/Precuneus is a large cluster spanning these regions, clusters required a minimum voxel number of 4 to be included in the table

Table S5. *Brain regions showing differential gamma-band activity between THREAT and SAFE conditions during the late window*

			Oddball				Mixed-saccade				Stop-signal			
	BA	Size	Peak(xyz)			t statistic	Peak(xyz)			t statistic	Peak(xyz)			t statistic
Superior frontal/precentral gyrus	6	224	19	-12	79	-5.95	14	-13	62	-5.51	19	-6	79	-3.64
Superior frontal gyrus/precentral gyrus	6	8	-29	-6	73	-2.40	-34	-19	68	-3.48	-29	-7	67	-3.35

Note: BA = Brodmann Area, Size is in voxel counts, Coordinates are in MNI space, Sensorimotor/Precuneus is a large cluster spanning these regions, clusters required a minimum voxel number of 4 to be included in the table

6.2 Discussion

When put in context of the overall thesis, the results of chapter 6 help to explain the results from chapter 5. In chapter 5 it was found that during normal conditions, participants showed an increase in beta power over the right inferior frontal gyrus during inhibition, which was greater on successful inhibition. It was concluded that an increase in beta in the right IFG reflects the facilitation of motor inhibition. However, when the participants performed the same task during threatening conditions, there was no difference in beta power between successful and failed stop trials. Further, the increase in beta in the right IFG was associated with inhibitory performance during safe conditions but not during threat. In chapter 6 it was revealed that there is a sustained decrease in beta-power across the sensorimotor and right frontal regions in response to induced anxiety. This sustained decrease would not have shown up in the analysis of chapter 5, which was time locked to a window following the stop signal and then referenced against a window prior to the stop signal that was averaged across both conditions. Thus, Chapter 5 was able to show how anxiety interfered with the normal functioning of the right IFG's role in inhibitory control, but was unable to show how the electrophysiological activity in the right IFG is also altered more generally in response to anxious arousal. This anxiety-induced sustained decrease in beta activity over the right IFG likely plays a role in the alter functioning of this region during motor inhibition. Indeed, this thesis argues that sustained anxiety plays an adaptive role that facilitates "action readiness" at the expense of inhibitory control. This is reflected in decreased beta power across the sensorimotor and right frontal regions. The thesis has also balanced two possibilities: 1) that anxiety-induced impaired inhibition is due to anxiety related changes in the right IFG that reflect faster acting, but slower counteracting, supporting Cornwell et al. (2017); or 2) that anxiety-induced inhibitory impairments are due to competition for cognitive resources in key inhibitory regions such as the right IFG, which are instead used for anxiety related processes such as threat monitoring, supporting Shackman et al. (2006). Given that the anxiety-induced

reduction in beta power over the right IFG coincides with a much larger reduction in beta power over the sensorimotor areas, this chapter argues that the 'status quo' theory (Engel & Fries, 2010) applies; where these beta reductions are reflecting a readiness for action at the expense of interpreting the motor state. Put simply, this chapter argues option 1 applies; where anxiety related changes in the right IFG reflect faster acting, but slower counteracting.

One point that deserves further discussion is that the results did not reveal any anxiety related changes in oscillatory power within the amygdala. Previous anxiety research implicates the amygdala as a key node in the anxiety network. For example, the UAMA suggests the amygdala facilitates attention to threat and reinforces learning related to negative stimuli (Grupe & Nitschke, 2013). There are several possibilities that may explain why the present study did not reveal anxiety related changes in the amygdala. While it can be argued that signals from deep structures are difficult to detect with MEG due to the exponential reduction in magnetic field potential over greater distances, research has shown deep brain structures can be detected with MEG (Pizzo et al., 2019). Nevertheless, when detected by sensors beyond the scalp, the signal from the amygdala is small in power and is originating from a small region. The current study explored the whole brain with no ROI set for any locations and a familiar wise error correction was made. Family wise error is more sensitive to detecting large clusters over small clusters (G. Huang & Zhang, 2017). This may be why the current study did not detect changes in the amygdala. Indeed, sustained anxiety studies that do detect anxiety related activity in the amygdala tend to set the amygdala as an ROI (e.g. Andreatta et al., 2015; Vytal et al., 2014). The one other MEG study that did not set the amygdala as an ROI also found no anxiety induced oscillatory changes in the amygdala (Balderston et al., 2017). This leaves the possibility that the amygdala is still involved in sustained anxiety, but the current study was not designed to detect it. Alternatively, it could be hypothesized, that the amygdala need not show sustained elevated activity over a longish

unpredictable threat period to still participate in the overall defensive state; perhaps its initial response leads to downstream effects (e.g., surging noradreline release from locus coeruleus, which could excite cortical circuits) which could outlive brief amygdala activity.

Implications

The understanding of the location and frequency of anxiety related changes might aid in the assessment of anxiety and the reduction of anxiety through neurofeedback protocols. By measuring the robust reductions in sensorimotor beta, researchers may be able to identify states of anxiety in patients. Further, presenting these changes on screen may enable patients to better control their own anxiety through neurofeedback. Additioanlly, these findings may have implications for those who stutter. Recent MEG research has shown that those who stutter show greater beta desynchronization in the motor cortex (larger in right compared to left) prior to and during the execution of speech compared to controls (Mersov, Jobst, Cheyne, & De Nil, 2016). The authors argue, this greater desynchronization leads to less automaticity of speech and impairments in speech production. The current findings that induced anxiety also leads to beta desynchronization over the motor cortex may have implications in the study of stuttering when the relationship between stuttering and anxiety is considered. The co-occurrence of social anxiety and the level of trait anxiety is higher in those who stutter (Blumgart, Tran, & Craig, 2010; Craig, Hancock, Tran, & Craig, 2003; Manning & Gayle Beck, 2013). While the stuttering likely influences the development of anxiety, Van Riper (1937) showed that frequency of stuttering increased when stutterers were informed they could receive an electric shock after instances of stuttering. Further, relaxation techniques improve stuttering severity (Gilman & Yaruss, 2000). Thus, it may be that the desynchronization of sensorimotor beta during anxious states is partly responsible for the increased stuttering severity reported during times of stress in those who stutter. Thus, neurofeedback protocols may also help this population.

Chapter 7 - Trait impulsivity and response inhibition

Chapters 4 and 5 focused on response inhibition; showing that anxiety impairs this aspect of self-control. Along with chapter 6, these chapters helped to reveal that anxiety facilitates faster acting but slower counteracting and this is underlined by neuro-oscillatory changes. However, it is not clear how these laboratory measures relate to self-report measures of impulsive behaviour. As the thesis aims to understand the impact of anxiety on self-control (section 1.6), this chapter introduces an additional measure of self-control – self-reported impulsive behaviour. Exploring greater impulsive behaviour in a non-clinical population in this chapter will act as a prelude to the study of addiction (an impulsive disorder) in chapter 8. Indeed, trait impulsivity is greater in those with addiction (Mitchell & Potenza, 2014). The studies in chapters 4 and 5 included a self-report measure of trait impulsivity. However, this could not be analysed in either individual study due to insufficient sample size for such an analysis. This chapter combines the data from those two chapters to explore how trait impulsivity and response inhibition are related and how this relationship is influenced by induced anxiety.

7.1 Paper - Negative urgency is related to impaired response inhibition during threatening conditions

7.1.1 Rationale

Trait impulsivity is described as an impairment in inhibitory control and is conceptually thought to be related to inhibition (Bari & Robbins, 2013). Impulsivity is described not only as an impaired ability to inhibit impulses, but also the tendency to possess stronger impulses. Yet, some argue that response inhibition is not related to self-reported impulsivity (Cyders & Coskunpinar, 2012; Reynolds et al., 2006). Chapters 4 and 5, reveal that response inhibition performance is influenced by the environmental conditions (e.g. threat) or the individual's

current emotional state (e.g., anxiety). Given that impulsivity scales aim to measure impulsivity in real-life settings and response inhibition is measured in a laboratory, it may be these differences of external conditions are attenuating any attempt to consolidate these two aspects of self-control. Altering the laboratory conditions to more closely match the conditions that impulsivity scales aim to measure, may reveal a relationship. Further, the non-specificity of scales and behavioural tasks may be masking a relationship between trait impulsivity and response inhibition. As discussed in section 1.5.2 and section 2.3, the Barratt Impulsivity Scale does not separate impulsivity into impulsive domains (Reise, Moore, Sabb, Brown, & London, 2013). One more targeted impulsivity scale is the UPPS scale, which includes factors such as urgency – relating to impulsive action during times of negative affect (Whiteside & Lynam, 2001). Indeed, more domain specific subscales of the UPPS have shown a relationship with response inhibition, with the factor of urgency correlating with inhibitory performance in both the Go/No-go task and the stop signal task (Gay et al., 2008; Wilbertz et al., 2014). Given it was shown that anxiety impaired response inhibition in chapters 4 and 5, the relationship between induced anxiety, response inhibition, and trait impulsivity is of interest. Indeed, the lack of relationship between impulsivity and response inhibition in previous studies may be due to the conditions in which the tasks were carried out (e.g., negative urgency only describes impulsive action during times of negative affect, not during affectively-neutral conditions). The following study tries to closely match the behavioural task (relating to impulsive action) and task conditions (relating to negative affect) with the impulsivity scale of negative urgency (the tendency to act impulsively during times of negative affect).

Finally, the thesis is concerned with two key traits of psychopathology: anxiety, and self-control. Exploring how anxiety and self-control relate in individuals who tend to be more impulsive will set the stage for later research into impulsive disorders (covered in chapter 8).

Article "under review"

Negative urgency is related to impaired response inhibition during threatening conditions

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Author Contributions

A.D.R. and B.R.C. conceived the experiment; A.D.R., D.J.W. and B.R.C. designed the experiment. A.D.R. performed data collection. A.D.R. analysed the data. A.D.R., D.J.W. and B.R.C. reviewed the results and wrote the paper.

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Abstract

While it has been argued that impulsivity and inhibition are unrelated, it may instead be the case that the relationship between the two can only be seen when their characteristics are closely matched. The negative urgency subscale of the UPPS-P describes impulsive action during negative affect. This was predicted to correlate more strongly with stop-signal reaction time (SSRT) during threatening conditions than non-threatening conditions. Healthy participants (*N*=68) completed the stop-signal task in threatening (induced by threat-of-shock) and non-threatening conditions after completing the UPPS-P and Spielberg State Trait Anxiety Inventory (STAI) scales. Negative urgency correlated with the difference in SSRT (threat – safe) after controlling for other variables. Conversely, similar correlations were not observed for positive urgency, suggesting threat increases the poorer inhibition seen in those high on negative urgency but not for those high on positive urgency. Additionally, sensation seeking correlated with the difference in SSRT (threat – safe) in the opposite direction, suggesting sensation seeking was related to a reduction in the effect of threat. The findings suggest that when characteristics are closely matched, anxiety-related impulsivity is associated with inhibition and that high sensation seekers experience threatening stimuli differently.

Key words

Anxiety, Stop-signal Task, UPPS, Sensation seeking, Negative urgency

Impulsivity is a diagnostic criterion for a wide range of psychological disorders, and is described as a multidimensional construct (Rochat et al., 2018; Sperry et al., 2016; Whiteside & Lynam, 2001). Another concept related to self-control is response inhibition, which describes the cancelation, withholding, or suppression of a response (Bari & Robbins, 2013). For example, the stop-signal task, which asks participants to respond to a go-signal that is occasionally followed by a stop-signal (indicating participants should withhold their response), is a reliable measure of inhibition by action cancelation (Logan & Cowan, 1984). Impulsivity and response inhibition are both described as measures of self-control and are both related to psychological disorders such as addiction, obsessive compulsive disorder (OCD), and attention deficit hyperactivity disorder (ADHD; Lipszyc & Schachar, 2010). For example, those with addiction tend to score higher on impulsivity questionnaires (Garavan, 2011) and tend to have impaired response inhibition (J. L. Smith et al., 2014). Furthermore, impulsivity has been described as an impairment in inhibitory control (Bari & Robbins, 2013). However, some researchers have argued that trait impulsivity and response inhibition are not related based on the lack of evidence that self-report and behavioural data are statistically associated (Cyders & Coskunpinar, 2011, 2012; Dreves et al., 2020; Reynolds et al., 2006). Dreves et al. (2020) argues this lack of association is due to self-control being a formative construct. That is, the concept of self-control does not exist as a single construct independent of the tools used to measure it. However, this assertion leaves open the possibility that within specific subdomains of self-control, behavioural and self-report measures may be associated. The negative Urgency, lack of Premeditation, lack of Perseverance, and Sensation seeking (UPPS-P) scale is a multidimensional self-report measure that includes factors such as negative urgency, which relates to impulsive action, premeditation, which relates to planning, and sensation seeking, which relates to seeking out novel and thrilling experiences (Lynam et al., 2007; Whiteside & Lynam, 2001). Unlike the

Barret Impulsivity Scale (Reise et al., 2013), the more specific subscales of the UPPS-P have shown a relationship with response inhibition, with the factor of negative urgency correlating with impaired inhibition in both the Go/No-go task and the stop signal task (Gay et al., 2008; Wilbertz et al., 2014). Urgency, later named "negative urgency" (Lynam et al., 2007), is the tendency to perform impulsive actions when experiencing strong negative affect (Whiteside & Lynam, 2001). Additionally, the subscale of positive urgency describes impulsive action when experiencing strong positive affect (Lynam et al., 2007). After inducing a positive mood in participants, Johnson, Tharp, Peckham, Sanchez, and Carver (2016) found that positive urgency was related to prepotent inhibition, measured using an antisaccade task. The underlying attributes of negative and positive urgency would suggest that an induction of negative affect might strengthen the relationship between negative urgency and response inhibition but have no influence on the relationship with positive urgency.

One form of "negative affect" that is also strongly related to psychological disorders is anxiety. Anxiety (e.g. high self-reported anxiety or comorbid anxiety disorder), like impulsivity is common in those with addiction (Grant et al., 2004) and other disorders characterized by poor impulse control (Bartz & Hollander, 2006). Thus, understanding how anxiety relates to impulsivity is important. Indeed, stress is a known factor in addiction relapse (Sinha, 2007). The threat-of-shock procedure is a reliable way to induce anxiety and involves participants engaging in threatening (may receive a shock at any time) and non-threatening (safe from shock) conditions. The threat-of-shock procedure has been shown to reliably produce psychological and physiological characteristics of anxious arousal; increasing heart rate, Galvanic skin response, startle response, subjective anxiety, as well as a number of cognitive and behavioural changes consistent with models of anxiety (O. J. Robinson, Vytal, et al., 2013). Furthermore, the procedure has a number of benefits over other anxiety manipulations (for a summary see Shackman et al., 2006). Most importantly,

the threat-of-shock procedure has recently been used to show that response inhibition is impaired by anxiety (Roxburgh et al., 2019; Roxburgh et al., 2020).

Given that anxiety has been shown to impair response inhibition (Roxburgh et al., 2019; Roxburgh et al., 2020) and is related to disorders of impulsivity (Grant et al., 2004), the relationship between induced anxiety, response inhibition, and impulsivity is of interest. The current study uses data from Roxburgh et al. (2019) and Roxburgh et al. (2020) and aims to explore whether trait impulsivity (using the UPPS-P) is related to response inhibition (measured with the stop-signal task), and if this relationship is influenced by the induction of anxiety. In line with Wilbertz et al. (2014) it is hypothesised the negative urgency will be negatively correlated with response inhibition under non-threatening conditions. Furthermore, it is hypothesised that negative urgency will be correlated with response inhibition during threatening conditions. The main hypothesis relates to the influence of induced anxiety and it is expected that the relationship between negative urgency and response inhibition will be stronger during threatening conditions than non-threatening conditions, but the same difference will not be shown for positive urgency. The other subscales of the UPPS-P will be explored to further address the research aims and determine if impulsivity is related to response inhibition or threat induced changes in response inhibition. Finally, trait anxiety will also be explored to determine how individual differences in baseline anxiety influence the effect of threat on impulse control.

Method

Participants

Participant data consisted of adult university students and was taken from two response inhibition studies (Roxburgh et al., 2019; Roxburgh et al., 2020). Twenty-four were taken

from the participants in Roxburgh et al., (2020). Unlike the procedure in Roxburgh et al., (2020), no participants were removed for head movements as the current study did not explore neuroimaging data. Forty-five participants were taken from Roxburgh et al., (2019). One additional outlier was removed once all the data were combined, who had a Stop-signal Reaction Time (SSRT) that was 3.87 standard deviations above the mean. The final sample was 68 participants (38 women, 30 men; mean age ± SD, 24 ± 6 years). A sample of 63 participants is required to find an effect size .29 (as found by Wilbertz et al., 2014), at a power of 90, alpha of .05, and with 5 predictor variables. The current sample, which was established based on the available sample from Roxburgh et al., (2019) and (2020), was determined to be adequate before analyses.

Procedure

Participants first competed the UPPS-P Impulsive Behavioural Scale (UPPS-P) and Spielberger State-Trait Anxiety Inventory (STAI) questionnaires followed by a practice run of the stop-signal task. Electrodes were then attached to the wrist, and the participants underwent the shock-workup procedure to determine the appropriate level of shock. Participants then completed the stop signal task in either a MEG (Roxburgh et al., 2020) or behavioural lab (Roxburgh et al., 2019). The THREAT condition, where participants were told they could receive an aversive electric shock at any time, and the SAFE condition, where participants were told they are safe, were alternated with counterbalancing of the starting condition. Participants completed 10 blocks of either 33 or 34 trials (ITI 1.7 to 4.1 s) in each condition with a stop-signal probability of .3. There was a total of 100 stop trials for each condition. No more than 10 shocks were delivered during the task.

Trials began with a fixation cross (500-ms) followed by a go stimulus (1000-ms), left or right pointing arrow, which participants were instructed to respond to as quickly and accurately as

possible using the corresponding button. The stop-signal was a pure auditory tone (900 Hz; 500-ms) presented through headphones or through tubal-insert earphones. Stop-signal delays (SSD) were set using both ascending (starting at 50ms) and descending (starting at 250ms) staircase algorithms. Separate staircases were used for each go stimulus (left/right) and for THREAT and SAFE conditions. SSD increased by 50 ms, following successful inhibition and decreased following failed inhibition, to achieve an approximately .50 p(inhibition). Stop-signal reaction time (SSRT) was calculated using the integration method. For more detail of procedure and analysis see Roxburgh et al., (2019) and Roxburgh et al., (2020).

Measures

UPPS-P Impulsive Behavioural Scale. The UPPS-P (Lynam et al., 2007) comprises 59 Likert-type items and is designed to measure five areas of impulsivity: negative urgency (e.g. "I have trouble resisting my cravings (for food, cigarettes, etc.)"), (lack of) premeditation (e.g. "My thinking is usually careful and purposeful"), (lack of) perseverance (e.g. "I generally like to see things through to the end"), sensation seeking (e.g. "I generally seek new and exciting experiences and sensations"), and positive urgency (e.g. "When I am very happy, I can't seem to stop myself from doing things that can have bad consequences"). Higher scores indicate greater impulsivity.

Spielberger State-Trait Anxiety Inventory (STAI). The STAI (Spielberger, 1983) comprises 40 Likert-type items intended to assess state and trait anxiety. However, the state portion of the STAI was not analysed as it only provides the state of participants prior to the study, which would change after the threat-of-shock procedure. Trait anxiety assessed how participants feel "in general" using items such as "I feel nervous and restless". Higher scores indicate greater anxiety.

Data analysis

Data were analysed in Statistical Package for the Social Sciences (SPSS). Six responses (out of 4002) were missing from items in the UPPS-P questionnaires and an MCAR test revealed they were missing completely at random (MCAR $p = 1.00$). Expectation maximisation (EM) was used to replace missing data (Schafer & Olsen, 1998). One critical outlier ($z \pm 3.29$) was removed, who had a z-score for SSRT in THREAT of 3.87. No multivariate outliers were identified. Skewness and kurtosis fell within the acceptable range of ±1.5 for each variable, supporting assumptions of normality. One participant failed to complete the trait portion of the STAI and this participant was removed from any analyses exploring trait anxiety. There were no multivariate outliers in any of the multiple regression analyses (Mahalanobis' Distance $p < .001$). The assumptions for multicollinearity and singularity were also met with no two predictor variables correlating above $r = .9$ (Supplementary Table 1). Scatterplots of residuals showed the assumptions for linearity and normality were met.

Results

Descriptive statistics

A correlation matrix including means, standard deviations, and Cronbach's alphas are shown in Table 1 for each variable.

Table 1: Correlation matrix and descriptive statistics for each variable

	Mean	SD	1	2	3	4	5	6	7	8	9
1. SSRT THREAT	263.54	49.2	_								
2. SSRT SAFE	241.38	51.7	.79**	_							
3. SSRT diff	22.16	32.99	.26*	-.39**	_						
4. Negative Urgency	2.21	.62	.27*	.23	.04	(.90)					
5. Lack of Premeditation	1.99	.47	-.04	.18	-.33**	.19	(.85)				
6. Lack of Perseverance	1.94	.45	-.01	.08	-.14	.41**	.31**	(.80)			
7. Sensation Seeking	2.96	.59	.01	.19	-.29*	.26*	.36**	.07	(.87)		
8. Positive Urgency	1.82	.63	.17	.18	-.03	.75**	.21	.28*	.34**	(.94)	
9. STAI Trait	38.18	8.61	.08	.13	-.08	.73**	.09	.32**	.1	.46**	(.90)

Note: Cronbach's alphas are shown in diagonal, SSRT = Stop-signal reaction time, diff = (THREAT – SAFE), * $p < .05$, ** $p < .01$

Table 1 shows there was no significant correlation between negative urgency and SSRT during SAFE conditions (r = .23, p = .062), though the relationship was marginally significant. As expected, there was a significant correlation between negative urgency and SSRT during the THREAT condition (r = .27, p = .029), which is shown in Figure 1. Those who had higher negative urgency (i.e., more impulsive) tended to have slower inhibitory control during threatening conditions (THREAT). There was no significant raw correlation between the difference in SSRT and negative urgency.

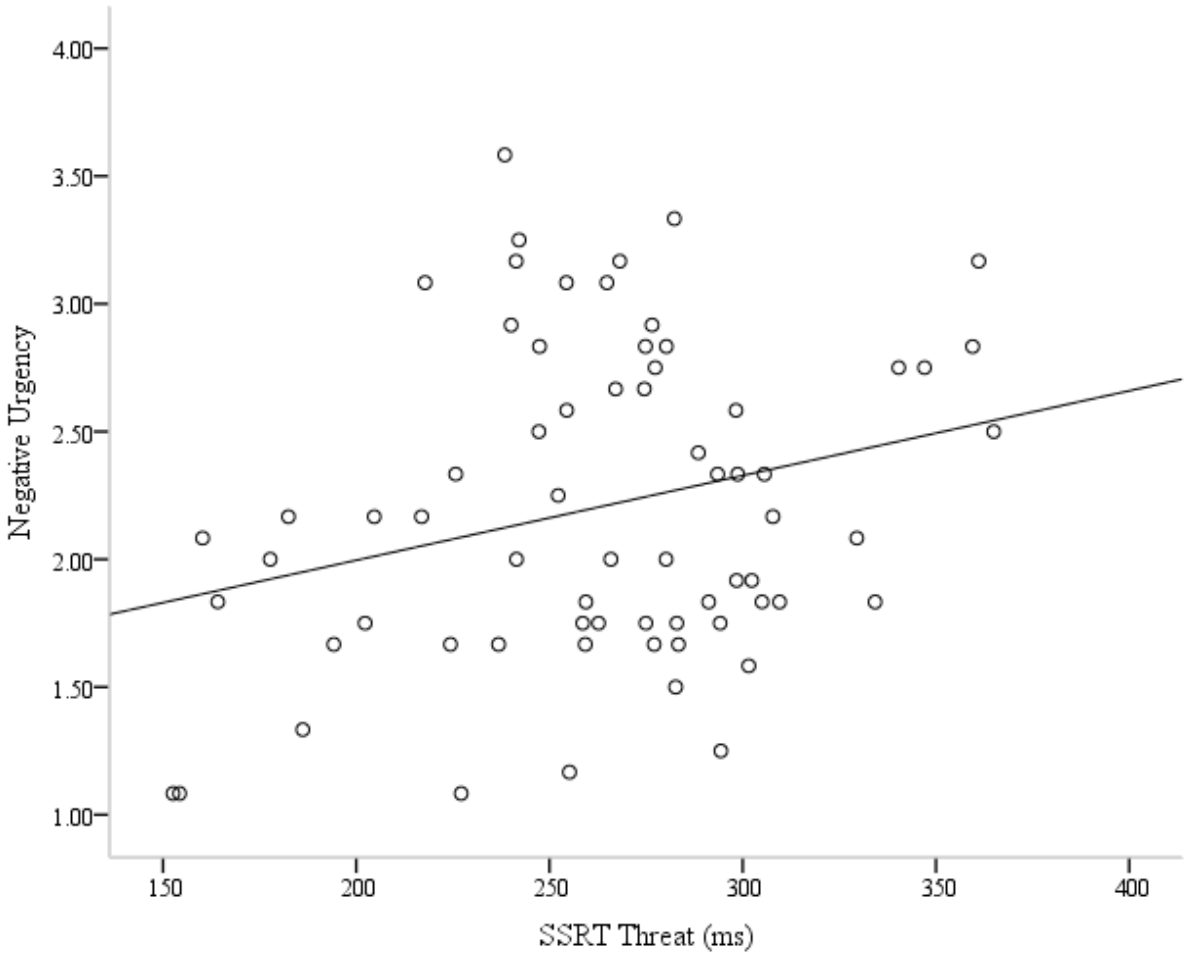

Figure 1. *Scatterplot for the correlation between SSRT during the THREAT condition and negative urgency.*

Within group comparisons results

To consolidate the main findings of the previous two studies (Roxburgh et al., 2019; Roxburgh et al., 2020), differences in SSRT were compared across SAFE and THREAT conditions. SSRT was significantly slower in THREAT compared to SAFE conditions ($t(67) = 5.54$, $p < .001$), suggesting induced anxiety impairs response inhibition.

Regression analyses

A multiple regression analysis was conducted to explore the main aim and determine how induced anxiety (THREAT – SAFE) impacts the relationship between trait impulsivity and response inhibition (see "Difference" rows in Table 2). To aid in comparison, two additional multiple regression analyses were conducted for THREAT and SAFE conditions separately and placed alongside the main analysis in Table 2 (see "THREAT" and "SAFE" rows in Table 2).

Table 2. L*inear Regression Analyses for each DV – SSRT in THREAT, SAFE, and difference (THREAT – SAFE), with the UPPS-P subscales and trait STAI as the IVs*

	B	*SE B*	β	*t*	*p*	Partial
Negative Urgency						
THREAT	**48.86**	**19.59**	**.62**	**2.49**	**.015**	**.31**
SAFE	22.97	21.03	.27	1.09	.279	.14
Difference	**25.89**	**12.46**	**.48**	**2.08**	**.042**	**.26**
Lack of Premeditation						
THREAT	-2.54	14.34	-.02	-.18	.860	-.02
SAFE	15.48	15.40	.14	1.01	.319	.13
Difference	-18.02	9.12	-.25	-1.98	.053	-.25
Lack of Perseverance						
THREAT	-14.02	15.01	-.13	-.93	.354	-.12
SAFE	-5.33	16.12	-.05	-.33	.742	-.04
Difference	-8.70	9.55	-.12	-.91	.366	-.12
Sensation Seeking						
THREAT	-5.67	11.34	-.07	-.50	.619	-.06
SAFE	8.88	12.18	.10	.73	.469	.09
Difference	**-14.55**	**7.21**	**-.26**	**-2.02**	**.048**	**-.25**
Positive Urgency						
THREAT	-8.21	14.80	-.11	-.55	.581	-.07
SAFE	-4.62	15.90	-.06	-.29	.772	-.04
Difference	-3.59	9.42	-.07	-.38	.705	-.049
Trait anxiety						
THREAT	-1.52	1.03	-.27	-1.48	.144	-.19
SAFE	-.31	1.10	-.05	-.28	.781	-.04
Difference	-1.21	.65	-.31	-1.86	.068	-.23

R^2	THREAT = .13	SAFE = .09	**Difference = .22**
F	THREAT = 1.43	SAFE = .99	**Difference = 2.85**
p	THREAT = .219	SAFE = .443	**Difference = .017**

Note: B = regression coefficient, SE B = standard error of B, β = standardized coefficient, zero-order = raw correlation between the IV and DV, Partial = correlation after all other IVs are accounted for, **bold** = significant ($p < .05$)

First addressing the main hypothesis, Table 2 shows that the difference in SSRT (THREAT-SAFE) is associated with negative urgency but not positive urgency. More generally, Table 2 shows that the combination of trait impulsivity subscales and trait anxiety are linearly related to the difference in SSRT between THREAT and SAFE conditions (Diff: $p = .017$). The pattern shows that greater trait impulsivity and anxiety is associated with a smaller difference in SSRT between THREAT and SAFE conditions. The model also shows that sensation seeking had a significant relationship with the difference in SSRT, suggesting that those high on sensation seeking were less impacted by the threat-of-shock procedure. The direction of the relationship is consistent for all subscales except negative urgency. Importantly, while the raw correlation between negative urgency and SSRT difference is not significant (Table 1), when all other variables are accounted for, the partial correlation is significant (Table 2). This suggests that when other trait variables such as sensation seeking are held constant, negative urgency is related to an anxiety-induced shift in SSRT; where those who score higher in negative urgency have a greater impairment in inhibitory control during threatening conditions. Conversely, the same relationship was not found for positive urgency, with THREAT not significantly impacting inhibitory performance for those high on positive urgency. Table 2 also shows that the partial correlation for negative urgency was significant during THREAT but not SAFE conditions.

Discussion

The current study aimed to explore the relationship between response inhibition, trait anxiety, and trait impulsivity during threatening and non-threatening conditions. The prediction that that negative urgency would be correlated with SSRT during THREAT was supported, suggesting those high on negative urgency had poorer inhibitory control during anxious arousal. This

association was significant for the raw correlations and after all other variables were accounted for. Unlike the findings of Wilbertz et al. (2014), this relationship was not significant under non-threatening conditions (though it was marginally significant). The prediction that THREAT would increase the impairment of response inhibition for those high in negative urgency but not for those high in positive urgency was supported. When all other trait variables were held constant, negative urgency was associated with a larger difference in SSRT (THREAT - SAFE), while positive urgency was not. This finding contrasted the overall regression analysis, which showed that together greater trait anxiety and impulsivity was associated with a smaller difference in inhibitory control between THREAT and SAFE conditions, and that sensation seeking was a significant driver of this relationship. This was consistent across all subscales except negative urgency, which showed a significant relationship in the opposite direction after all other variables were held constant. While the partial correlation between trait anxiety and SSRT difference was only marginally significant, this potentially unexpected finding (trait anxiety related to smaller SSRT differences) should be addressed. Intuition might suggest that higher trait anxiety should yield a larger THREAT effect. However, work by Lissek, Pine, and Grillon (2006) suggests high trait anxiety could dampen the effects of THREAT, not because they are unaffected, but because their anxiety levels do not properly wane during SAFE. However, the effect in question was not significant. This is an interesting area of research, but more investigation is required.

The finding of a relationship between negative urgency and response inhibition is consistent with other literature using the UPPS subscale of urgency (Gay et al., 2008; Wilbertz et al., 2014) but not with literature using unidimensional impulsivity scales (Reynolds et al., 2006). However, the present findings suggest that this relationship is dependent on anxiety, induced by threat-of-shock. The finding of a relationship between negative urgency and response inhibition supports the claim that impulsivity comprises multiple distinct variables, and that behavioural and self-

report measures of self-control are related when closely matched (Bari & Robbins, 2013; Reise et al., 2013; Whiteside & Lynam, 2001; Wilbertz et al., 2014). Further, the findings supports the notion that anxious impulsivity is related to response inhibition after the induction of a relevant emotional state; as was found by Johnson et al. (2016) who showed positive urgency was related to prepotent inhibition after the induction of a positive mood.

Unexpectedly, the raw relationship between difference in SSRT and negative urgency was not significant. However, negative urgency was associated with greater impulsivity and trait anxiety, which themselves were together associated with a reduction in the effect of THREAT on response inhibition. When these other variables were held constant, negative urgency was associated with a greater reduction in inhibitory control during threatening conditions, which supports the premise of the subscale – describing impulsive action during times of intense negative affect (Whiteside & Lynam, 2001). Importantly, this was not the case for positive urgency, supporting the theoretical differences between the two scales (Lynam et al., 2007).

A key driver in the regression analysis was sensation seeking, which had a significant partial correlation and was also significant in the raw correlation with SSRT difference. The finding that sensation seeking reduced the effects of induced anxiety on response inhibition suggests higher sensation seeking participants were less influenced by the threat-of-shock procedure. This finding supports other literature showing that those high on sensation seeking are less influenced by threat, with evidence of a decreased reaction to aversive stimuli (Breivik, Roth, & Jørgensen, 1998; Lissek et al., 2005; Y. Zheng et al., 2015). For example, high sensation seeking is associated with a reduced startle response to aversive stimuli (Lissek et al., 2005) and reduced threat perceptions (Quick & Stephenson, 2008). Suggesting that those high on sensation seeking respond differently to anxiety and anxious stimuli than others. Conversely, those low on "experience seeking" (which is similar to sensation seeking) reported greater state anxiety when faced with risky situations (Breivik et al., 1998). Furthermore, those high on sensation seeking

exhibit reduced ERP responses after viewing pictures associated with physical risk compared with low sensation seekers (Y. Zheng et al., 2015). Thus, the current finding supports the contention that high sensation seeking is associated with a reduction in the effects of threat. The tendency for those high in negative urgency to also be high in sensation seeking and other impulsivity traits, likely masks the impact of threating conditions; however, this masking was removed after controlling for other impulsivity and anxiety traits. Given that sensation seeking and impulsivity are correlated but are thought to have differing neural underpinning and developmental pathways (Steinberg et al., 2008), future research may wish to investigate how age factors into the relationship between anxiety-induced inhibition, sensation seeking, and negative urgency in adolescents. It may be that the relationship varies across different stages of adolescence.

While the results of the current study were derived from previous data, the authors would like to note the hypotheses were not post-hoc constructed. The UPPS-P was included in the two previous data sets for the purpose of testing the relationship between negative urgency and anxiety-induced inhibition. Although the paper was not preregistered online independently, the methodology and predictions of the current study and the two previous studies were all included in one ethics application, which was submitted and approved before data was collected for any of the three papers. The original publications were intended to test mean-level differences in performance under high vs low anxiety, which did not require large samples. Individual differences in trait impulsivity necessitated a larger sample, and thus this analysis had to wait for the two studies to be completed and consolidated.

The study has limitations on generality as the sample comprised university students from Australia. This suggests the study may not be generalizable to non-student populations, or populations from other countries.

The current study shows that when adequately separated into sub-domains, trait impulsivity is related to response inhibition and to differences in the impact of threatening conditions. Specifically, negative urgency is associated with impaired inhibition during threatening conditions. Conversely, threatening conditions does not impact inhibitory control for those high on positive urgency. Finally, sensation seeking is associated with a reduction in the impact of threating conditions.

Data Accessibility

All data used for this study are stored securely, and are accessible upon request as far as allowed by guidelines established with the governing research ethics committee. The conditions of project ethical approval do not permit public archiving of anonymised study data. Readers seeking access to the data should contact the Corresponding author. Access will be granted to named individuals in accordance with ethical procedures governing the reuse of the data.

Acknowledgement of no independent preregistration

The authors acknowledge that the research was not preregistered in an independent online registry. However, access to the original ethics application is available upon request.

Conflict of interest statement

The authors, Ariel D. Roxburgh, David J. White, & Brian R. Cornwell, declare no competing interests for the paper: Negative urgency is related to impaired response inhibition during threatening conditions.

7.2 Discussion

The study used the data from chapters 4 and 5, which originally showed induced anxiety impaired response inhibition, and explored the added variable of negative urgency. The study showed that those high on negative urgency tended to show greater anxiety-induced inhibitory impairments. These findings tie some of the themes of this thesis together. In section 2.3, it was noted that Bari and Robbins (2013) describe the failure of the inhibitory process as "impulsivity". Yet, researchers have struggled to identify any relationship between the two (behavioural measures of inhibition and self-reported measures of impulsivity). The findings of this chapter suggest that the two are related if conditions and tasks are closely matched to the aspects of self-control being measured. Further, the current findings showed that positive urgency was not related to response inhibition during threatening conditions, but negative urgency was. This provides evidence for the assertion that impulsivity is in fact a term used to describe several discreet but related factors rather than a unidimensional construct (Lynam et al., 2007; Sperry et al., 2016). Importantly, this study helps link the laboratory measures of chapters 4 and 5, with impulsive behaviour more generally over an individual's life outside the laboratory. This helps to validate some to the data presented. It is now possible to speculate that the findings of chapters 4 and 5 could related to impulsive behaviour during anxious states more generally.

The finding that sensation seeking reduced the effects of induced anxiety on response inhibition, suggests high sensation seeking participants were less influenced by the threat-of-shock procedure. This finding supports other literature showing that those high on sensation seeking are less influenced by the threat. For example, those high on sensation seeking have smaller startle responses during threatening situations (Lissek & Powers, 2003) and have reduced threat perceptions (Quick & Stephenson, 2008). More importantly, this finding separates

sensation seeking from other impulsivity constructs and further supports the notion that impulsivity is comprised of multiple factors (Rochat et al., 2018; Sperry et al., 2016; Whiteside & Lynam, 2001). It also suggests the findings of chapters 4, 5, and 6 might be attenuated in those high on sensation seeking. Future studies may wish to look at the neural correlates of induced anxiety in those high on sensation seeking. It is possible those high on sensation seeking would show a reduced neural-oscillatory response to stress, which could be emulated in those with anxiety disorders to lessen the deleterious effects of anxiety.

Finally, the findings of chapter 7 are important to consider when trying to understand the implications of the findings of this thesis in relation to psychopathology. For example, those with addiction tend to score higher on negative urgency (Mitchell & Potenza, 2014) and have impaired response inhibition (J. L. Smith et al., 2014). Further, the impulsive symptoms of addiction tend to be worse during times of stress and anxiety (S. A. Brown et al., 1995; Shaham et al., 2000; Sinha, 2001, 2007). Thus, exploring how the variables in this thesis manifest and interact in those with addiction will show the clinical relevance of what has been shown so far. If addiction includes symptoms comparable to an extreme version of impulsive behaviour, it might be expected that similar increases in anxiety-induced inhibitory impairments will be seen in those with addictions as seen in those high on negative urgency. Chapter 8 will explore this relationship in a preliminary sample of nine participants with addiction.

Chapter 8 – Anxiety and response inhibition in addiction

The mechanisms of anxiety (explored in chapter 6) and its influence on inhibitory functioning (explored in chapter 4 and 5) are important when considering disorders associated with anxiety and characterized by impaired impulse control such as addiction, ADHD, and OCD (Chamberlain & Sahakian, 2007). Exploring how these variables interact in the presentation of psychological disorders is important in translating the theories presented in this thesis so far into clinically relevant models. It is also an important aim of the thesis (section 1.6), which is to establish an understanding of how two key features of mental disorders (anxiety and self-control) interact and to explore this interaction in a disorder characterised by both features. One area that is of particular relevance to the findings of the thesis so far and to the aims of the thesis is addiction.

The thesis has presented a number of findings; 1) anxiety impairs inhibitory control, 2) this impairment is likely driven by altered functioning in key frontal regions that are associated with inhibition, 3) anxious states produce sensorimotor and right frontal changes regardless of the organism's current activity, and these changes likely lead to a "readiness for action" that undermines other processes such as response inhibition, 4) negative urgency is associated with greater anxiety-induced inhibitory impairment. Many of these findings point to some possible hypotheses relating to addiction. Each will be explored before presenting a preliminary study focused on addiction.

1) *Anxiety impairs inhibitory control*. This finding is particularly relevant to addiction, which is a disorder characterised by a loss of control (American Psychiatric Association, 2013), and is a disorder associated with greater trait anxiety (Comeau et al., 2001; Dixon et al., 2014; Wedekind et al., 2013) and comorbid anxiety disorders (Grant et al., 2004). Importantly, the loss of control that characterises addiction appears to be greater during times of stress and anxiety, often

leading to relapse (S. A. Brown et al., 1995; Koob, 2009; Shaham et al., 2000; Sinha, 2001, 2007). In fact the link between stress and addiction has been investigated in the brain, with discoveries suggesting the BNST is a critical node connecting stress regions and reward regions of the brain (Stamatakis et al., 2014). Further, altered BNST functioning is found in rodents, non-human primates, and humans with addiction (Stamatakis et al., 2014). Our finding, that anxiety impairs inhibitory control in healthy individuals, naturally leads to the question of how this relationship might present in those with addiction problems. However, in considering such a hypothesis, the other findings of the thesis should be discussed.

2) *Anxiety-induced inhibitory impairments are likely driven by altered functioning in key frontal regions that are associated with inhibition.* The most prominent pre-frontal region explored in chapter 4 was the right IFG. This is also an important region in the loss of control that characterises addiction. Response inhibition (which is impaired in addiction; J. L. Smith et al., 2014) is correlated with the regulation of emotions and inhibition of cravings in individuals with addiction problems (Tabibnia et al., 2011). Further, drug craving, emotion regulation, and response inhibition have been associated with right IFG dysfunction (Aron et al., 2014; Ersche et al., 2012; Roxburgh et al., 2020; Tabibnia et al., 2011; Volkow et al., 2010); supporting the connection between the characteristics of addiction and impaired response inhibition driven by right IFG dysfunction. Further, stimulant dependant individuals show abnormalities in connections to frontal regions (such as the right IFG), which were also associated with motor control impairment (Ersche et al., 2012). Interestingly, these right frontal abnormalities are found in the biological siblings who have no history of drug abuse, suggesting the abnormalities are not due to stimulant dependence (Ersche et al., 2012). Overall, studies suggest those with addiction problems have impaired response inhibition and this is associated with right frontal abnormalities (Ersche et al., 2012; Ersche et al., 2013; Tabibnia et al., 2011; Volkow et al., 2010); further, these patterns are found in the relatives of those with addiction problems (Ersche

et al., 2012). While no studies have directly measured how the induction of anxiety might influence the right-frontal inhibitory mechanisms in those with addiction problems, the previously shown greater loss of control during stressful events suggests, induced anxiety could magnify right frontal and inhibitory impairments in those with addiction problems.

3) *Anxious states produce sensorimotor and right frontal changes regardless of the organism's current activity, and these changes likely lead to a "readiness for action" that undermines other processes such as response inhibition*. These findings can also be related to addiction. A group of researchers were interested in the motor-related symptoms found in some case studies of addiction such as dystonia, tics, and dyskinesias; and hypothesized that movement related regions in stimulant dependant individuals might also show abnormalities (Hanlon, Wesley, Roth, Miller, & Porrino, 2010; Hanlon, Wesley, Stapleton, Laurienti, & Porrino, 2011). The authors showed sensorimotor abnormalities in cocaine abusers during a finger tapping task (Hanlon et al., 2010). Interestingly, compared to controls, cocaine abusers had significantly more activity (fMRI) in the right sensorimotor area (which was ipsilateral to the right dominant hand used for the task). The authors concluded that alterations in sensorimotor control in cocaine dependant individuals are driven by dysfunction of "laterality". However, they later concluded that cocaine dependant individuals might have a deficit in information processing that impairs more complex cognitive processing (Hanlon et al., 2011). Gremel and Lovinger (2017) describe the importance of the "sensorimotor circuit" in addiction, which comprises the sensorimotor cortex and additional subcortical regions. The authors argue that the sensorimotor circuit is important for the development of novel complex behaviours driven by operant conditioning, such as those developed in addiction. The authors argue that the transition from goal-directed to habitual actions is influenced by the sensorimotor circuit, which is important for the "habituation" stage of addiction (Gremel & Lovinger, 2017). Indeed, drugs of abuse alter the sensorimotor circuit following both acute and prolonged drug use (Everitt & Robbins, 2016).

Everitt and Robins (2016) also discuss the transition from recreational drug use to compulsive drug use. They describe habitual action and impaired top-down control of this action as central to the compulsive nature of drug taking. Together, the literature on the sensorimotor circuit and addiction suggests that this region is important in the habitual actions that underpin compulsive drug use. Given chapter 6 showed that sensorimotor activity is altered by anxiety so that it is more 'primed' for action and chapter 5 found areas involved in the inhibition of these possible actions are impaired, it might be expected that anxiety also alters sensorimotor and right frontal regions in those with addiction problems, possibly leading to a greater impairment of inhibitory control.

4) *Negative urgency is associated with greater anxiety-induced inhibitory impairment.* Those with addiction problems tend to score higher on negative urgency. This is the case for youth with addiction related behaviours (Kristine Rømer et al., 2018), adults with food addiction (VanderBroek-Stice et al., 2017), cocaine-dependant adults (Albein-Urios et al., 2012; Torres et al., 2013), adults with alcohol addiction or dependence (Coskunpinar et al., 2013; Whiteside & Lynam, 2003), and adults with other substance use disorders (Mitchell & Potenza, 2014). Further, evidence suggest the higher impulsivity traits in those with addiction problems is pre-existing (Verdejo-García et al., 2008). Similarly, though not to the same extent as negative urgency, addiction is associated with higher sensation seeking (Mitchell & Potenza, 2014). These evidence that addiction is associated with greater negative urgency, and the finding in chapter 7 that negative urgency is associated with greater anxiety-induced inhibitory impairment lead to the hypothesis that; anxiety-induced inhibitory impairments will be greater in those with addiction problems.

Understanding these mechanisms may help to improve treatments for those with addiction problems. Addiction is characterized by impaired impulse control and is associated with impaired inhibitory functioning (J. L. Smith et al., 2014). Furthermore, reduced grey matter in

right IFG in patients with this disorder is correlated with increased drug craving, poor emotion regulation, poor response inhibition, and poor inhibition of cravings (Tabibnia et al., 2011). Those with addiction problems tend to score higher on negative urgency (Mitchell & Potenza, 2014). Those with addiction problems are also more likely to relapse during times of stress and anxiety (Sinha, 2007). In the next section, the experimental paradigms introduced in chapter 5 are extended to study a cohort with addiction. Those with addiction problems are asked to complete the stop-signal task during threat and safe conditions while simultaneous MEG recordings are taken.

8.1 Paper – Anxiety and response inhibition in addiction: Preliminary findings

8.1.1 Rationale

While the evidence suggests addiction is associated with anxiety and poor inhibitory functioning, the relationship between the three is less clear. Given the evidence for a relationship between increased anxiety and impaired inhibitory functioning, it makes sense to extend this research to addiction to see how this relationship manifests in those with a disorder characterised by heightened anxiety and impaired control. Further, the study of addiction is in line with the overall aim of the thesis – to establish an understanding of how two key features of mental disorders (anxiety and self-control) interact and to explore this interaction in a disorder characterised by both features. Unfortunately, due to COVID-19, a full sample of those with addiction was unable to be collected. Further, MEG data was unable to be analysed. Thus, the findings of chapter 8 will focus on the behavioural results of the 9 participants with addiction problems that were able to be collected.

Slower and more adaptive responding during induced anxiety in a sample with addiction: Preliminary data

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Abstract

Both stress and impaired inhibitory control have been hypothesised to play a role in the development and continuation of addiction. However, the interaction of these variables has not been fully explored in this population. Previous work has shown that the induction of anxiety impairs inhibitory control. The current paper aimed to explore whether this relationship differs in those with addiction problems. Those with addiction problems ($N = 9$) and healthy controls ($N = 9$) completed the stop-signal task in threatening and non-threatening conditions. It was hypothesised that stress-induced inhibitory impairments would be greater in those with addiction problems compared to healthy controls. However, the results showed no significant interaction indicating there is not enough evidence to support the hypothesis. Interestingly, unlike healthy controls, go reaction times were slower during threatening conditions in the sample with addiction problems, suggesting this population is more cautious in threatening conditions. Furthermore, healthy controls showed adaptive responding depending on the outcome of the previous trial, while those with addiction problems only showed this adaptive responding during threatening conditions. Overall, the data suggests those with addiction problems were less adaptive in normal conditions but become more cautious and adaptive in their responses during threatening conditions. Nevertheless, this did not lead to improved inhibitory control as the population with addiction showed non-significantly slower SSRTs overall compared to healthy controls regardless of context.

Key words

Addiction, Anxiety, Stop-signal Task, Threat-of-shock, Response inhibition

A defining feature of addiction is a loss of control leading to the continuation of consumption despite negative consequences (American Psychiatric Association, 2013). One area where those with addiction problems show impaired control is response inhibition (J. L. Smith et al., 2014). Further, response inhibition is correlated with the regulation of emotions and inhibition of cravings in those with addiction problems (Tabibnia et al., 2011). Drug craving, emotion regulation, and response inhibition have been associated with right IFG dysfunction (Aron et al., 2014; Roxburgh et al., 2020; Tabibnia et al., 2011; Volkow et al., 2010); supporting the connection between the characteristics of addiction and impaired response inhibition. Further, impaired inhibition in addiction is not specific to a single substance with inhibitory deficits found in those who use cocaine, methamphetamine, MDMA, tobacco, and alcohol (J. L. Smith et al., 2014). Evidence supports the assertion that impaired response inhibition exists prior to onset of active addiction in humans (Ivanov et al., 2008; Nigg et al., 2006; Whelan et al., 2012) and rodents (Dalley et al., 2011) and remains after abstinence (C. R. Li, Milivojevic, et al., 2006; Monterosso et al., 2005; Tabibnia et al., 2011). Furthermore, impaired inhibition has been associated with poor treatment outcomes in patients with addiction problems (Brewer et al., 2008; H. C. Fox et al., 2007). Thus, understanding more about the relationship between addiction and response inhibition may help to target treatments.

Recent studies have found that anxiety impairs response inhibition (Roxburgh et al., 2019) and that the right IFG plays a role in this impairment (Roxburgh et al., 2020). Given the right IFG's role in the control of drug craving (Volkow et al., 2010) a clear picture of the role anxiety plays on response inhibition in those with addiction is needed. The link between addiction and anxiety is well formed. Those with addiction problems are more likely to have an anxiety disorder diagnosis than those without addiction (Grant et al., 2004). Further, those with addiction problems tend to score higher on self-reported anxiety scales (Comeau et al., 2001; Dixon et al., 2014; Wedekind et al., 2013). Finally, periods of stress and anxiety are often

triggers for relapse in those with addiction problems in a period of abstinence (S. A. Brown et al., 1995; Shaham et al., 2000; Sinha, 2001, 2007). Thus, the link between addiction and inhibitory control may be influenced by anxiety. Further, those with addiction have shown heightened reactivity to induced anxiety (Gorka, Lieberman, Phan, & Shankman, 2016).

The current study aims to explore the relationship between addiction, impulsivity, and response inhibition during periods of induced anxiety and periods of relative safety. Given that periods of stress increase the clinically significant loss of control found in those with addiction problems, and induced anxiety impairs response inhibition in healthy individuals, it is predicted that anxiety-induced inhibitory impairments will be greater in those with addiction problems. The paper will also explore other variables related to inhibitory control such as the adaptive changes in response time based on the outcome of previous trials, which has been shown to be impaired in those with addiction problems (Lawrence et al., 2009; C. R. Li, Milivojevic, et al., 2006). However, no hypotheses are made with respect to how induced anxiety might influence this relationship.

Method

Participants

A sample of 18 healthy control (HC) participants was taken from Roxburgh et al. (2020). An equivalent sample of abstinent participants with addiction problems (AD) was sought; however, only 9 AD participants were recruited before COVID19 restrictions interrupted recruitment. To match the number in the AD group, 9 HC participants were selected based on age from the pool of HCs to match the clinical cohort. The original HC group pool had 10 participants under 25years old and eight who were 25 or over. The AD group only had one participant under 25,

who was 21. Therefore, the eight participants from the HC pool who were 25 or over were selected, and the one participant who was 21 was also selected. Leaving both groups with 1 participant under 25 (who was 21 in both samples), and 8 participants 25 or over. This resulted in a final sample of 18 (9 in each group), who were closely matched in age (HC: $M = 31$; AD $M = 34.6$; difference in age not significant). Addiction was determined based on self-report where participants had to report either having a formal diagnosis of a substance use disorder or having received formal treatment for a substance use disorder. Most of the AD participants (8 of 9) reported using more than one substance for at least one year at least 3 or more times per week (meeting the ASI criteria for problematic consumption); with an average of 4 and a half years of consumption in this fashion. All AD participants reported using alcohol problematically and 8/9 also reported using cannabis and amphetamine problematically. AD participants had been abstinent from psychoactive drugs for at least two weeks and were not on any psychoactive medication. Similarly, the HC group were not taking any psychoactive medication. Use of medication and drugs was determined based on self-report during a phone screen. Additionally, participants in both groups were screened via self-report to ensure no other physical or mental disorders. All participants gave informed consent, and the study was approved by the Swinburne Human Research Ethics Committee.

Design

Both the HC and AD groups completed two runs of the auditory stop-signal task while simultaneous MEG recordings were taken. MEG data was not further analysed due to the excessive head movements of 3 participants. Given the already small sample size, there was insufficient data to analyse between group effects with MEG recordings. In a third and final run, participants completed a similar task; however, they were asked to ignore auditory tones and respond to all go signals. Prior to entering the MEG room, participants signed informed consent and completed the Spielberger State-Trait Anxiety Inventory (Spielberger, 1983) and the UPPS-

P Impulsive Behavioral Scale (Lynam et al., 2007) – see section 3.3 for details on these measures, before completing one practice run of the SST. Further, the AD group completed the Addiction Severity Index - Lite (ASI-Lite; Cacciola et al., 2007; McLellan et al., 1985), and answered several demographic questions including: age, education, gender, and handedness. Education is calculated by reverse coding and averaging the score given to the following categories: 1) Doctorate degree, 2) Masters degree, 3) Graduate diploma or honours degree 4) Bachelor degree 5) Advanced diploma or Diploma 6) Certificate III or IV 7) Year 12 8) Year 11 or below – lower scores indicate less education.

In all runs, anxious arousal was modulated with the threat-of-shock procedure where participants were either informed they could receive an electric shock at any time (THREAT), or they were safe from shock (SAFE). THREAT and SAFE conditions were alternated with counterbalancing of the starting condition. A total of ten shocks were delivered pseudo-randomly during THREAT to the wrist of the nondominant (left) hand. To ensure shocks did not interfere with performance, shocks were delivered during intertrial intervals (ITI; 1.7 to 4.1 seconds) and were never presented during an ITI preceding a stop-signal. Prior to the commencement of the SST, shock intensity was set individually to a level the participant judged as 'moderately aversive'. The shock workup procedure, began with the presentation of an initial weak shock and, depending on participant feedback, was followed by shocks of increasing amplitude until an appropriate level was reached. After each run, participants retrospectively rated their anxiety for THREAT and SAFE on a scale from 0 ("no anxiety") to 10 ("extreme anxiety").

SST Procedure

The two stop-signal task runs each contained 10 blocks (5 THREAT and SAFE) lasting approximately 72 seconds**.** There were 33 trials in each block with 10 of these trials containing a stop-signal (10/33 = probability of 0.30). Stop-signals were presented in pseudo-random order

(Hughes et al., 2016). The additional third run followed the same format, but participants were instructed to ignore the tones. Each trial began with a fixation cross (presented for 500 ms) followed by a go stimulus (presented for 1,000 ms), which was either a right or left pointing arrow. Participants had to respond by pressing the corresponding right or left button with their dominant (right) hand using a button box. The stop-signal was a pure auditory tone (900 Hz; 50 ms) presented in both ears through tubal-insert earphones. The delay between the go-signal and stop-signal (Stop-signal delay; SSD) was adjusted using both ascending and descending staircase algorithms. Ascending SSD began at 0ms and descending began at 250ms. Adjustments were made by increasing SSD by 50ms following a successfully inhibited trial or decreasing by the same amount following an unsuccessful trial (responded to a stop signal). This SSD adjustment was used to achieve a probability of inhibition of approximately 0.50 in each context. SSDs were pre-set for the final ignore-tone task using the schedule of timing determined in run 2 of the SST. Participants were instructed to respond to the go-signal with the correct button as quickly as possible, and not to 'wait' for the stop-signal.

Data analysis

Stop-signal data were analyzed using the integration method in R Studio (RStudio, 2015). This method accounts for deviations from a probability of inhibition of 0.50 by integrating go reaction times into a cumulative distribution and then using the probability of responding to determine the distribution cut off to give a value representing the time it takes for a stop signal to inhibit a response plus the average SSD. This SSD (mean SSD) is then subtracted from the previously determined value to ascertain the stop-signal reaction time (SSRT; Verbruggen et al., 2019). Additionally, missed go trials were replaced with maximum go RT, as this has been shown to give a more accurate result (Verbruggen et al., 2019).

Data were analysed using analysis of variance (ANOVA) and independent samples t-tests in Statistical Package for the Social Sciences (SPSS). No multivariate outliers were

identified. Skewness and kurtosis fell within the acceptable range of ±1.5 for each variable, supporting assumptions of normality.

Results

Summary results and manipulation check

Table 1 shows the means and standard deviations for each demographic and psychometric variable. The table also includes between independent samples t-test results to reveal any significant differences between groups in these variables.

Table 1. *Demographic and psychometric properties of each group*

	AD	HC	*t*	*p*
Age	34.56	31	.97	.348
Negative Urgency	**2.66**	**1.86**	**3.01**	**.008**
Premeditation (lack of)	2.12	2.02	.46	.649
Perseverance (lack of)	2.07	1.80	1.21	.243
Sensation Seeking	3.14	2.88	1.01	.329
Positive Urgency	2.29	1.65	2.09	.053
STAI State	30.78	26.67	1.16	.264
STAI Trait	40.11	32	1.73	.102
Gender	3 females/6 males	2 females/7 males	.50	.624
Education	3.89	5.44	1.72	.105

Note: STAI = state/trait anxiety inventory; HC = Healthy control group; AD = group with addiction problems; education is calculated by reverse coding and averaging the score given to the following categories: 1) Doctorate degree, 2) Masters degree, 3) Graduate diploma or honours degree 4) Bachelor degree 5) Advanced diploma or Diploma 6) Certificate III or IV 7) Year 12 8) Year 11 or below – lower scores indicate less education.

Basic statistics for the Stop-signal task are shown for each group in Table 2. These show that the probability of inhibition was close to .5 and that reaction times to failed stop trials tended to be faster than reaction times to successful go trials; thus, validating the Stop-signal task results (Verbruggen et al., 2019).

Table 2. *Stop-signal task performance across THREAT and SAFE contexts in HC and AD groups.*

	Threat	Safe	Student *t*	*p*
HC group				
Go Trials				
Median Go RT (ms)	457	458	-0.38	.711
Incorrect Go (%)	1.33	1.22	0.21	.842
Missed Go (%)	0.22	0.44	−0.43	.681
Stop Trials				
SSRT (ms)	216	194	1.59	.152
P(inhibition)	.52	.55	-1.578	.153
Mean SSD (ms)	233	254	-1.75	.119
Median Failed RT (ms)	429	419	1.71	.125
AD group				
Go Trials				
Median Go RT (ms)	503	493	1.60	.149
Incorrect Go (%)	1.89	1.78	0.18	.860
Missed Go (%)	3.00	3.11	-0.29	.782
Stop Trials				
SSRT (ms)	252	221	1.93	.089
P(inhibition)	.52	.53	-.89	.397
Mean SSD (ms)	246	260	-0.98	.354
Median Failed RT (ms)	463	431	5.33	.001

Note. N=18 (9 in each group). Median RTs are calculated on correct trials only. SSRT=stop signal reaction time; SSD=stop signal delay.

Finally, subjective anxiety is reported in Table 3 to show how well the threat manipulation worked on each group.

Table 3. Subjective anxiety for HC and AD participants in THREAT and SAFE conditions

	Group	Anxiety	Anxiety difference	SE	t	p
HC	THREAT	5.06	3.39	.64	5.26	.001
	SAFE	1.67				
AD	THREAT	3.28	1.94	.36	5.43	.001
	SAFE	1.33				

Note: SE = standard error, SSRT is in milliseconds, HC = Healthy control group, AD = group with addiction problems

A 2(condition; THREAT and SAFE) by 2(group; AD and HC) ANOVA showed a significant main effect of condition ($F(16) = 52.36$, $p < .001$), where subjective anxiety was greater during THREAT compared to SAFE, suggesting the threat manipulation worked. Additionally, there was a marginally significant main effect of group ($F(16) = 4.37$, $p = .053$), suggesting subjective anxiety was significantly lower in the AD group. The interaction was marginally significant ($F(16) = 3.84$, $p = .068$), suggesting that, while the manipulation worked in both groups, the AD group were less impacted by the threat-of-shock procedure.

General results

A 2(condition; THREAT and SAFE) by 2(group; AD and HC) ANOVA showed a significant main effect of condition ($F(16) = 6.25$, $p = .024$), where SSRT was slower during THREAT compared to SAFE but no main effect of group ($F(16) = .927$, $p = .350$), suggesting SSRT was not significantly slower in the AD group. The condition by group interaction was not significant ($F(16) = .18$, $p = .674$), suggesting that there is not enough evidence to conclude anxiety-induced inhibitory impairments were greater in those with addiction problems compared to healthy

controls. The difference in subjective anxiety was added as a covariate to see if this variable was masking a greater interaction. However, the ANCOVA showed similar results to the ANOVA: with a significant main effect of condition (p =.042), no main effect of group (p =.448), and a non-significant interaction (p =.908). Given the preliminary nature of this study, comparisons were still conducted to reveal trends.

In the AD group, the difference in SSRT between THREAT and SAFE was not significant, but close (M_{diff} = 30.61ms, $t(8) = 1.93$, $p = .089$); in the direction of AD participants showing slower SSRT during THREAT. Unlike with the larger sample (Roxburgh et al., 2020), the sample of 9 HC participants also did not have a significant difference in SSRT between THREAT and SAFE (M_{diff} = 21.65ms, $t(8) = 1.59$, $p = .152$), but trended in the same direction. A more detailed breakdown of SSRT scores in each condition is shown in Table 4.

Table 4. SSRT for HC and AD participants in THREAT and SAFE conditions

	Group	SSRT	SSRT difference	SE	t	p
SAFE	HC	193.94	-27.01	28.89	-.94	.363
	AD	221.01				
THREAT	HC	215.59	-36.03	39.15	-.92	.371
	AD	251.62				

Note: SE = standard error, SSRT is in milliseconds, HC = Healthy control group, AD = group with addiction problems

While none of these findings are statistically significant, Table 4 shows SSRT was slightly slower for AD than for HC in both THREAT and SAFE (which is consistent with

literature but is unable to be supported by such a small sample). Additionally, the difference in SSRT between the two groups was slightly higher during THREAT.

A 2(group; AD and HC) by 2(condition; THREAT and SAFE) ANOVA was conducted on go reaction times and found a significant interaction ($F(8) = 5.28$, $p = .035$). Indicating that those with addiction problems slowed their responses during THREAT but healthy controls did not. AD had slower go RT for THREAT compared to SAFE ($M_{diff} = 17.93$ms, $t(8) = 2.58$, $p = .033$). However, there was no significant difference for HC ($M_{diff} = 0.02$ms, $t(8) = .006$, $p = .995$).

Based on outcome of previous trial

To determine how participants adapted their responses based on the outcome of the previous trial, go RTs were collated in groups based on the outcome of the preceding trial. A 2(condition; THREAT and SAFE) by 2(previous trial; successful stop and unsuccessful stop) by 2(group; AD and HC) ANOVA showed a non-significant interaction ($F(16) = 3.99$, $p = .066$), indicating the overall pattern of differences in post-stop slowing between THREAT and SAFE and between AD and HC was not significant. However, there was a statistical trend that could potentially become clearer with a larger sample. Thus, comparisons will be further analysed and discussed for each group. Results for the HC participants are displayed in Table 5.

Table 5. Reaction times based on the outcome of the previous trial (HC group)

	Previous trial outcome	Mean RT	Mean RT difference	SE	t	p
SAFE	Successful	456.31	-31.56	6.19	5.1	.001

	Failed	487.87				
THREAT	Successful	454.32	-31.37	11.87	2.64	.03
	Failed	485.69				

Note: Successful = the previous trial was a stop-signal trial that was successfully inhibited, Failed = the previous trial was a stop-signal trial that the participant responded to (failed inhibition), SE = standard error, RT is in milliseconds, HC = Healthy control group.

Table 5 shows that the HC sample tended to slow responses if the previous trial was an error (failed inhibition) in both THREAT and SAFE conditions, which shows adaptive responding in different conditions. A 2(condition; anxious and non-anxious) by 2(previous trial; successful stop and unsuccessful stop) ANOVA was conducted on go trials with a correct response (i.e. press left when arrow indicates left). There was no main effect of condition, there was a main effect of previous task ($F(8) = 19.5$, $p = .002$) where previous trial outcome predicted RTs – specifically healthy participants slowed their responses after failed stop trials. Unlike with the additional results in the larger behavioural study (chapter 4), there was no significant interaction. The larger sample found that responses were still slower after failed stops compared to successful stops but this slowing was not as great as it was in threatening conditions compared to safe conditions. It is not unexpected that a sample of 9 is unable to replicate this change in magnitude of findings; however, the small sample did trend in the same direction.

Table 6. Reaction times based on the outcome of the previous trial (AD group)

	Previous trial outcome	Mean RT	Mean RT difference	SE	t	p
SAFE	Successful	515.48	14.33	10.57	1.36	.212
	Failed	501.15				

THREAT	Successful	513.31	-20.87	19.27	-1.08	.310
	Failed	534.18				

Note: Successful = the previous trial was a stop-signal trial that was successfully inhibited, Failed = the previous trial was a stop-signal trial that the participant responded to (failed inhibition), SE = standard error, RT is in milliseconds, AD = group with addiction problems

Table 6 shows that the sample with addiction problems, had no significant difference in RT for trials that followed a failed stop compared to a successful stop in either THREAT or SAFE conditions. This suggests the cohort did not show the same adaptive responding seen in the healthy sample. Interestingly, the participants with addiction problems trended in the same direction as the healthy sample during the THREAT condition but trended in the opposite direction during the SAFE condition. A 2(condition; anxious and non-anxious) by 2(previous trial; successful stop and unsuccessful stop) ANOVA was conducted on go trials with a correct response (i.e. press left when arrow indicates left). The main effect of condition was close to significant, where those with addiction problems tended to be slower to respond during threat ($F(8) = 5.18$, $p = .052$). Note that this only included trials that proceeded a stop signal (unlike the main finding that included all trials). There was no significant main effect of previous task. There was a significant interaction ($F(8) = 7.81$, $p = .023$), confirming that the trend in adaptive responding was opposite during THREAT compared to SAFE conditions in the AD group. During THREAT, the differences were more consistent with other literature where trials after a failed stops tended to be slower. However, during SAFE, AD participants tended to have faster RT after failed trials.

Discussion

The current sample of 9 participants with addiction problems and 9 healthy controls provided some preliminary data showing how anxiety-induced inhibitory impairments might differ in those with addiction problems. The primary hypothesis that anxiety-induced inhibitory impairments would be greater in an sample with addiction problems was not supported. While the data did trend in the predicted direction (SSRT difference between THREAT and SAFE: HC group = 21.65ms, AD group = 30.61ms), the interaction was not significant. These preliminary data provide little supporting evidence for any hypothesis suggesting anxiety-induced inhibitory impairments are greater in a sample with addiction problems within a stop-signal paradigm. However, such a relationship cannot yet be ruled out. Firstly, it should be noted that the subjective anxiety scores suggest the group with addiction problems were less impacted by the anxiety induction procedure. Secondly, the preliminary sample of 9 participants might not be sufficient to reveal a relationship. Additionally, it should be noted that this thesis used specific inhibitory and anxiety paradigms; a pattern might still emerge in other paradigms. Despite the lack of findings here, some interesting patterns emerged when exploring go reaction times.

The results showed that those with addiction problems slowed their responses during THREAT, but healthy controls did not. This slowing down in the AD group may suggest that participants with addiction problems respond to threatening conditions in a more cautious way than people without addiction. Indeed, heightened reactivity to threat is found in those with addiction problems (Gorka et al., 2016). One possibility is that those with addiction problems are more hypervigilant to threatening conditions. This might lead them to be more cautious during these conditions. Indeed, some argue that threat uncertainty leads to more cautious responding (O. J. Robinson, Krimsky, et al., 2013). It is also possible that this more cautious responding is compensating for a greater anxiety-induced inhibitory impairment; given that no improvements in SSRT were found after these slower and more adaptive responses. Indeed, inhibition was marginally worse during threat in the AD group. Another thing to consider is that the AD group

were “in recovery”, being at least 14 days abstinent. It is possible that those in recovery from addiction are more cautious during times of anxiety to improve behavioural control. Future work may wish to observe AD participants who are in “active addiction”. Further, future work exploring the underlying neural mechanisms may help elucidate the processes driving these observations. Finally, future studies may wish to ensure HC and AD groups are equally impacted by threat. This may involve reducing shock-intensity for participants who show a particularly strong difference in subjective anxiety between threat and safe conditions.

When looking at changes in RT based on the outcome of the previous trial, the results showed that the healthy participants tended to slow their responses after failed inhibition trials during threat and safe conditions. This was consistent with the larger sample in chapter 4. Though the current age-matched subsample was unable to reveal the significant interaction found in the larger sample (chapter 4); showing that slowing, while still present, was diminished during threat. Nevertheless, the “post error slowing” is a commonly reported finding (Bissett & Logan, 2011, 2012; Verbruggen & Logan, 2008a) and is thought to suggest a healthy adaption of responding through performance monitoring and error detection facilitated by the medial prefrontal cortex (Kerns et al., 2004). Unlike the post error slowing found in the healthy group, the participants with addiction problems did not show the same pattern of adaptive responding. In fact, during safe conditions, reaction times non-significantly sped up following failed inhibition. This is consistent with the findings of Lawrence et al. (2009), who showed that alcohol dependent participants sped up responses following failed inhibition trials; while healthy controls slowed responses. Similar deficits in post stop-signal error slowing were found in abstinent participants with a recent cocaine dependence (C. R. Li, Milivojevic, et al., 2006). Furthermore, patients with alcohol dependence showed less activation in the right dorsolateral PFC during post stop-signal-error slowing than healthy controls (C. R. Li et al., 2009). Our findings support the premise that behavioural adjustment processes in those with addiction

problems are impaired under normal conditions. This may be underlined by altered right PFC functioning, which future research may reveal. Interestingly, the changes were less pronounced in the THREAT condition. During THREAT, those with addiction problems slowed their responses after failed stops (though this slowing was not significant and was less than the healthy control group). Nevertheless, the interaction within the AD group was significant despite the small sample size, suggesting improved post-error slowing during THREAT compared to SAFE. This preliminary evidence suggests threatening conditions facilitate normal behavioural adaptations in those with addiction problems. This might be due to the general slowing of reaction times also found in this cohort during THREAT. One interpretation of these results is that, unlike healthy controls, those with addiction problems are more cautious during threatening conditions (responding more slowly). Their responses are slowed down, which likely allows for greater adaption of responses based on the outcome of the previous trial, which, unlike healthy controls, they were unable to do efficiently at normal speeds during the SAFE condition. Another possibility is that this slowed responding and improved behavioural adaption during threatening conditions is unique to those with addiction problems who are abstinent. It may be that cautious responding during times of stress is a behaviour that is utilized to reduce the chances of relapse in those recovering from addiction.

The current study reported preliminary data from a clinical sample and matched healthy controls and found evidence suggesting threatening conditions changed responses during the stop-signal task in those with addiction problems so that their responses were slower and more behaviourally adaptive. Future studies could expand on the current study with a larger sample, allowing for the analysis of MEG data and greater statistically powered analysis of outcomes. Such a study might reveal the neural mechanisms behind the more adaptive responding during threatening conditions in participants with addiction problems. Further, future studies may wish to recruit both those in recovery from addiction and those in “active addiction” to see if anxiety-

induced cautious responding is a characteristic of healthy recovery from addiction problems. Finally, future work may wish to ensure the impact of threat is controlled across samples so that both the control group and group with addiction are experiencing an equivalent anxiety induction.

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Conflict of Interest Statement

The authors declare no competing interests.

Author Contributions

A.D.R. and B.R.C. conceived the experiment; A.D.R., and B.R.C. designed the experiment. A.D.R. performed data collection. A.D.R. analysed the data. A.D.R., D.J.W. and B.R.C. reviewed the results and wrote the paper.

Data Accessibility

All data used for this study are stored at Swinburne University of Technology, and are accessible upon request as far as allowed by guidelines established with the Swinburne Human Research Ethics Committee. The conditions of project ethical approval do not permit public archiving of anonymised study data. Readers seeking access to the data should contact the Corresponding author at Swinburne University. Access will be granted to named individuals in accordance with ethical procedures governing the reuse of the data. We confirm that all measures, conditions, data exclusions and the determination of sample size has been included in this paper.

8.2 Additional results

Important to the overall thesis is how the sample with addiction problems differed in the two key impulsivity traits explored in chapter 7; sensation seeking and negative urgency.

Table 1. NU and SS means and differences across HC and AD participants

	Group	Score	Difference	SE	t	p
NU	HC	1.86	.80	.26	3.01	.008
	AD	2.66				
SS	HC	2.88	.26	.26	1.00	.329
	AD	3.14				

Note: NU = Negative Urgency, SS = Sensation Seeking, NU and SS maximum score is 4, HC = healthy control group, AD = group with addiction problems

Table 1 shows that the AD group scored significantly higher on negative urgency than the healthy group, but there was no significant difference in sensation seeking. It should be noted that the HC sample is likely to consist of individuals who are higher on sensation seeking. This is because those who respond to a flyer asking for participants to participate in a study where

they will receive electric shocks, are likely to score higher on sensation seeking. Thus, any differences in sensation seeking between AD and HC would be masked by the already high HC baseline.

8.3 Discussion and link to overall thesis

Unfortunately, the disruptions to data collection, and data loss due to excessive motion, meant there is no neuroimaging data. However, the behavioural and questionnaire findings are interesting. Firstly, it was found that the AD group scored significantly higher in negative urgency than the healthy group. This is consistent with other studies that have shown a relationship between high negative urgency and addiction (Albein-Urios et al., 2012; Coskunpinar et al., 2013; Kristine Rømer et al., 2018; Mitchell & Potenza, 2014; Torres et al., 2013; VanderBroek-Stice et al., 2017; Whiteside & Lynam, 2003). Given stress and anxiety worsen the loss of control found in addiction, and that negative urgency is also associated with greater anxiety-induced inhibitory impairment (see chapter 7), it was expected that those with addiction problems would also display greater anxiety-induced inhibitory impairments. However, the results did not support this hypothesis. While the differences in SSRT between threatening and non-threatening conditions appeared to be greater in the sample with addiction problems, this difference was not significant. Although this preliminary study was unable to support the hypothesis that anxiety-induced inhibitory impairments would be greater in those with addiction problems, the small sample size of 9 participants in each group means that this relationship might still exist, but the current sample was too small to reveal it. Further, the subjective anxiety data revealed that those with addiction problems were less impacted by the threat-of-shock procedure. This lower impact of threat would likely remove some of the impact of threat on response inhibition. Thus, if anxiety-induction was equal, the results might still reveal a greater anxiety-induced inhibitory impairment in those with addiction problems.

Despite the preliminary nature of this study, some significant findings were revealed. Most importantly, it was shown that those with addiction problems tend to slow their go reaction times during threatening conditions while healthy controls do not. Further, this more cautious responding did not result in improved response inhibition; rather, the AD group had non-significantly slightly slower SSRT in both threat and safe conditions. Also of importance is the differences in adaptive responding in each group. The healthy group tended to slow their responses after a failed stop trial; a common finding in the literature thought to indicate adaptive responding and performance/error monitoring (Bissett & Logan, 2011, 2012; Kerns et al., 2004; Verbruggen & Logan, 2008a). However, in the safe condition those in the AD group did not show this pattern. In fact, they tended to have faster responses (though non-significant) after failed trials. A finding that has been shown in other inhibition studies focused on those with addiction problems (Lawrence et al., 2009; C. R. Li, Huang, et al., 2006; C. R. Li et al., 2009). Surprisingly, this pattern of speeding up responses after an error was reversed during threatening conditions. During threat, the participants tended to slow their responses after a failed stop-signal, which was more consistent with the pattern shown in the healthy group. However, unlike the healthy group, the slowing was not significant; suggesting there was still a lack of adaptive responding. In chapter 4 it was demonstrated that healthy participants were less adaptive in their responding during threatening conditions. It was also revealed that there was no meaningful difference in reaction times between threat and safe conditions. However, the opposite seems to be true in this small sample of participants with addiction problems. These results suggest those with addiction problems might be more cautious and have greater error detection and adaptive responding when they are under threat. This seems to contradict the finding that those with addiction problems score higher on negative urgency. Higher negative urgency would suggest induced anxiety might lead to more impulsive and less cautious responding. Further, the findings in chapter 7 suggest anxiety leads to “action readiness”. However, those with addiction problems slowed their responses during threatening conditions. These preliminary findings open future

research possibilities. One important point is the AD sample in this study consisted of those who were currently abstinent. It may be that recovery from addiction is facilitated by an altered response to anxiety. This assertion is supported by the smaller difference in subjective anxiety between threat and safe conditions in the group with addiction problems. Given that anxiety increases the chance of relapse (Sinha, 2007), it is reasonable to postulate that those in recovery from addiction have learnt to be more cautious during times of anxious arousal. It should also be noted that the AD participants in the study were recruited from several places, but all indicated they had either received treatment for or been formally diagnosed with a Substance Use Disorder. It may be that the treatment received by the AD patients facilitated a reduced response to stress. Future research should also carefully note any treatment being received by participants.

Forthcoming research could attempt to replicate the findings of this chapter, while ensuring the impact of threat is equal between groups. Further, exploring the MEG data associated with these differences might help reveal what neural mechanisms are driving these changes. Including a group in current "active addiction" may also reveal if the more cautious responding is specific to those in recovery from addiction. One possibility is that greater baseline right frontal dysfunction in those with addiction problems is worsened by induced anxiety. Indeed, chapter 5 revealed that right frontal changes underpin anxiety-induced inhibitory impairment in healthy controls. It is also understood from previous literature (outlined in section 1.5.3) that those with addiction problems show right frontal dysfunction that is associated with poorer inhibitory impairment (Ersche et al., 2012; Ersche et al., 2013; Tabibnia et al., 2011; Volkow et al., 2010). Thus, it may be that the worsening of an already impaired function leads participants in recovery from addiction to compensate in other ways by slowing responses and paying more attention to their behavioural consequences. Such a finding might see changes in attentional, error detection, and inhibitory control regions. Additionally, a large enough sample

might be able to reveal how negative urgency mediates the relationship between induced anxiety and response inhibition in those with addiction problems.

Chapter 9 – Discussion

9.1 Integration of findings

Anxiety and self-control are key features of many mental disorders including addiction. This is shown in the DSM 5, which describes anxious and impulsive symptoms in a large number of disorders (American Psychiatric Association, 2013), while an alternative model, the Hierarchical Taxonomy of Psychopathology, lists "disinhibition" and "internalised distress" as two of six higher order factors of mental disorders (Kotov et al., 2017). However, studying these aspects of psychopathology has proven difficult and there is limited research looking at the relationship between the two in an experimental paradigm. Non-experimental studies make up a large portion of the literature on anxiety (Eysenck et al., 2007; Grupe & Nitschke, 2013); however experimental studies are key to ensuring findings are free from confounding factors.

Additionally, there are several barriers to understanding self-control. For instance, while there are many behavioural and self-report studies on aspects of self-control, such as impulsivity and inhibition, researchers have been unable to find a clear relationship between these two aspects of impulsive behaviour (Cyders & Coskunpinar, 2011; Dreves et al., 2020; Reynolds et al., 2006). The current thesis attempted to fill in some of the gaps in the literature by using experimental designs to induce states of anxiety and simultaneously measuring both behavioural and trait impulsivity. Finally, the thesis explored these relationships in a cohort with addiction problems (a disorder associated with both features). Overall, the aim of the present thesis was to establish an understanding of how two key features of mental disorders (anxiety and self-control) interact and extend this research to preliminarily explore this interaction in a disorder characterised by both features. It is advantageous to study aspects of disorders separately, which also helps to align neuroscience findings with clinical presentations and develop targeted treatments (Insel et al., 2010). Further, aspects of disorders such as anxiety and impulsivity are present in non-

clinical populations. Thus, research into these areas is relevant to a wider portion of the population.

In each chapter, studies were described where anxiety was experimentally induced while its effects were explored. To understand how anxious states manifest, the study from chapter 6 will first be discussed. Chapter 6 explored the neurobiological changes associated with sustained states of anxiety that were independent of task demands. This was achieved through using the threat-of-shock procedure across several passive and active tasks while taking simultaneous MEG recordings. The findings showed electrophysiological changes across several key brain regions. During anxious arousal, there was a reduction in beta power across sensorimotor and right frontal areas (most prominently, the right inferior frontal gyrus; IFG). There was also a reduction in alpha oscillatory power in the thalamus and left intraparietal sulcus (IPS) during threatening conditions. The reduction in beta power in sensorimotor areas was interpreted as a readiness for action, supporting the 'status quo' theory (Engel & Fries, 2010) and other contentions (Kilavik et al., 2013; Schmidt et al., 2019) that suggest reductions in sensorimotor beta reflect motor preparation. The findings also fit with the idea that states of anxiety serve an adaptive function preparing an organism for potential threat (Ekman & Davidson, 1994; O. J. Robinson, Vytal, et al., 2013). The 'status quo' theory also suggests increases in right frontal beta facilitate motor inhibition (Engel & Fries, 2010). Therefore, our finding of a reduction in right frontal beta suggests motor inhibition may be impaired during anxious arousal, which is precisely what was found in chapters 4 and 5. The reason for this reduction in right frontal beta during anxious arousal might be that the right frontal areas are favouring stimulus detection and motor readiness over motor inhibition. Indeed, Cornwell et al. (2017) argue that the right IFG supports the detection of deviant stimuli at the expense of feedback projections during threatening conditions, adding weight to the idea that early sensory detection is improved at the expense of later processing in the right IFG. Further, Engel and Fries (2010) suggest increases in

beta power over these right frontal areas would facilitate changes to the current motor state; thus, reductions in power in this area likely result in organisms following through with the current motor state (e.g., motor action) and come at the expense of impairments to motor inhibition.

The reductions in alpha activity in the thalamus and left IPS during threatening conditions were interpreted to reflect a facilitation of early sensory and sustained attention, which are likely important during times of anxiety from an adaptive perspective. Indeed, evidence suggests the thalamus is important in the detection of sensory stimuli and is thought to facilitate attention during distress (Hermans et al., 2014). Further, evidence shows the IPS is important in maintaining attention during prolonged tasks and shifting attention back to the main task if it drifts (Goltz et al., 2015; Molenberghs et al., 2007; Thakral & Slotnick, 2009). Taken together the findings of chapter 6 suggest that anxious states are marked by neurophysiological changes associated with a readiness for action, heightened early sensory attention, and greater sustained attention. This was the first study to explore the oscillatory changes associated with sustained anxiety across several tasks using magnetoencephalography (MEG). It is important to note that two of the tasks were active and one was passive, yet all showed a reduction in beta power over sensorimotor areas. This suggests that the 'readiness for action' associated with sustained anxiety is present regardless of motor demands. The findings of chapter 6 support the notion that anxiety plays an adaptive role (Eysenck et al., 2007); facilitating attention and action readiness. However, chapters 4 and 5 show how this change of state can lead to deleterious consequences.

Chapter 4 demonstrated that response inhibition is impaired by induced anxiety. Supporting the findings of Cornwell, Mueller, et al. (2012) but running contrary to the conclusions of O. J. Robinson, Krimsky, et al. (2013). O. J. Robinson, Krimsky, et al. (2013) provided evidence for the opposite, that anxiety improves response inhibition, using the Go/No-go task. However, Balderston, Hale, et al. (2017) and the findings from chapter 6 show that

alpha power (which usually suggests diminished activation) is reduced during anxious arousal in areas involved in sustained attention. As discussed, this suggests the network involved in sustained attention is facilitated by induced anxiety; sparking the possibility that anxiety-induced improvements in lengthy and monotonous undertakings like the Go/No-go task might be due to the facilitation of sustained attention. Further, some researchers claim that the Go/No-go task does not unambiguously initiate a go response (MacLeod, 2007), instead early discrimination between go and no-go signals can lead to no-response without the need for action withholding. Thus, the improvements found in the Go/No-go task might be due to something other than inhibition, such as early stimulus detection or improved sustained attention. Indeed, Cornwell et al. (2017) showed that the detection of deviant stimuli is facilitated by induced anxiety. In contrast to the Go/No-go task, the Stop-signal task presents a trigger for a go response before presenting the cue to inhibit the response, which ensures go responses are initiated unambiguously (Logan & Cowan, 1984). This assertion is supported by studies using lateralised readiness potentials, which is an event related potential (ERP) signal believed to reflect motor activity preparation. Studies using this measure show evidence that the motor system is often inactive during no-go trials in the Go/No-go task; however, the motor system is active during stop trials in the Stop-signal task (van Boxtel et al., 2001). Given the findings of chapter 4, that induced anxiety weakens response inhibition, and the possible alternative explanation for anxiety-induced improvements in the Go/No-go task supported by chapter 6, this thesis argues that induced anxiety indeed weakens inhibitory control. This is an important finding that directly addresses the aim of the thesis – to see how anxiety and self-control interact. The finding suggests that self-control is impaired by anxiety.

Chapter 5 replicated the findings of chapter 4 but included simultaneous MEG recordings to identify the neural mechanisms underpinning anxiety-induced impaired inhibition. The results showed that anxiety-induced impairments of response inhibition are related to right IFG

dysfunction. The chapter demonstrated that not only was the difference in right IFG activation between successful stops and failed stops stronger in safe compared to threat, but also this difference was related to stopping performance in safe conditions only. The idea that the right IFG becomes impaired or favours other processes during anxious arousal is consistent with the findings in chapter 6, that there is an anxiety-induced reduction in beta power over right frontal regions, specifically, the right IFG. As discussed, this thesis argues that these findings suggest anxious states favour action readiness at the expense of the ability to make changes to the current sensorimotor state (i.e., inhibition). The contention that reductions in beta power reflect readiness for action at the expense of impaired inhibition is an idea that has been argued previously (Engel & Fries, 2010; Kilavik et al., 2013; Schmidt et al., 2019); however, the results of chapter 4, chapter 5, and chapter 6 add robust evidence to this idea and to the idea that anxiety favours one over the other. Put simply, anxiety means enhanced acting, but impaired counteracting.

Understanding anxious states through experimental induction is also important for understanding the mechanisms underpinning this critical aspect of mental disorders. Anxious arousal can lead to impaired functioning and distress when the anxiety is persistent or extreme (American Psychiatric Association, 2013). For example, persistent hypervigilance is a key characteristic of post-traumatic stress disorder (PTSD) and is associated with early amplified sensory-perceptual responding in patients with the disorder (Ge et al., 2011; Morgan & Grillon, 1999). Interestingly, heightened sensory-perceptual responding can also be seen in healthy participants during induced anxiety (Cornwell et al., 2007; Cornwell et al., 2017), showing that experimentally induced anxiety can model aspects of mental disorders and can help understand how anxiety manifests in non-clinical populations. The other aspect of mental disorders this thesis is interested in is self-control. However, the relationship between self-reported (e.g., trait impulsivity) and laboratory (e.g. response inhibition) measures of self-control, is not well

understood. While response inhibition is impaired in many disorders characterised by poor impulse control such as addiction, attention deficit hyperactivity disorder (ADHD), and obsessive compulsive disorder (OCD; Chamberlain & Sahakian, 2007), research has failed to find a consistent relationship between trait and behavioural measures of self-control (Reynolds et al., 2006). Chapters 7 and 8 aimed to address this issue, allowing for greater interpretation of the meaning of chapters 4 and 5 in relation to disorders characterised by impulsivity and impulsive traits more generally.

Chapter 7 showed that response inhibition is most closely related to the impulsivity self-reported measure of negative urgency. Negative urgency describes impulsive action during times of negative affect. Critically, chapter 7 showed that response inhibition was only related to negative urgency during threatening conditions, which helps explain the lack of a relationship in previous studies that did not induce anxiety or that took more generalised measures of impulsivity. This addresses the aim of the thesis – to explore the interaction between anxiety and self-control. Self-control involves more than response inhibition (explored in chapters 4 and 5). The existence of the negative urgency trait suggests that some people have less self-control during times of anxiety. The findings of chapter 7 confirm this, some had greater anxiety-induced loss of self-control (measured by impaired response inhibition) than others, and this was associated with negative urgency. Chapter 7 was the first study that has used a negative state induction to mirror the aspects of a trait measure and show a relationship between self-report and behavioural aspects of self-control. Combined with the findings of Johnson et al. (2016) who induced a positive mood to find a relationship between positive urgency and prepotent inhibition, the findings of chapter 7 suggest future research attempting to consolidate behavioural and self-report measures should closely match affective states. Chapter 7 was also a strong prelude to chapter 8.

Chapter 7 showed those who describe themselves as impulsive during times of anxiety (e.g., “When I am upset I often act without thinking”), also tend to show greater anxiety-induced impaired response inhibition. This helps to link the findings of this thesis to more general behavioural traits that are found in highly impulsive people and disorders of impulse control. Those with addiction problems tend to score higher on negative urgency (Albein-Urios et al., 2012; Coskunpinar et al., 2013; Kristine Rømer et al., 2018; Mitchell & Potenza, 2014; Torres et al., 2013; VanderBroek-Stice et al., 2017; Whiteside & Lynam, 2003), and tend have impaired response inhibition (J. L. Smith et al., 2014). Further, the ‘loss of control’ that characterises addiction is heightened during times of stress, which is demonstrated by the relationship between stress and relapse (Sinha, 2007). This relationship between two critical aspects of mental disorders, impulsive behaviour and anxiety, leads to the question of how the relationship between anxiety, response inhibition, and negative urgency manifests in those with addiction problems. Chapter 8 provided a preliminary investigation into this question and opened ideas for future studies.

Chapter 8 included nine participants with addiction problems and nine age-matched controls taken from the participants in chapter 5. The experimental procedures were the same (e.g., MEG recordings were taken); however, only behavioural measures were analysed. While a clear difference in response inhibition was not found between the groups, nor was there a difference in anxiety-induced impairments in response inhibition, other behavioural findings were revealed. Those with addiction problems tended to slow their responses during threatening conditions but healthy controls did not, suggesting participants with addiction problems were more cautious during times of threat. Further, those with addiction problems did not show the typical behavioural adjustments seen in healthy controls during normal conditions. Specifically, the group with addiction problems did not slow down their responses following failed inhibition, suggesting behavioural adjustment processes in addiction are impaired under normal conditions.

This finding supports other similar findings (Lawrence et al., 2009). Interestingly, during threat, the impairments in behavioural adjustment in those with addiction problems were less pronounced. This preliminary evidence indicates that threating conditions facilitate normal behavioural adaptations in those with addiction problems. This might be due to the general slowing of responses also found in this cohort during threatening conditions. One interpretation of these results is that, unlike healthy controls, those with addiction problems are more cautious during threatening conditions. Their responses are slowed, which likely allows for greater adaption of responses based on the outcome of the previous trial, which, unlike healthy controls, they were unable to do efficiently when their responses were not slowed down.

These findings seem to run contrary to the ideas of the thesis so far – that anxiety results in impulsive behaviour. While the data was unable to show that anxiety-induced inhibitory impairments were different in those with addiction problems, it did trend in the direction of previous findings that both negative urgency and response inhibition impairments are higher in those with addiction problems. One reason greater anxiety-induced impairments were not seen might be that the participants with addiction problems were more cautious and adaptive in their responses during threat. This may be due to greater focus or more effort to carry out the task carefully. This greater focus may be a result of the heightened sustained attention underpinning anxious states found in chapter 6. Interestingly, this greater effort did not come with improved inhibition, indeed, the group with addiction problems showed non-significant slightly greater inhibitory impairments during induced anxiety compared to the non-addiction group despite greater effort. One possibility is that the group with addiction problems (who were all abstinent for at least 14 days) were utilising techniques gained in their recovery from addiction. Given that anxiety increases the chance of relapse (Sinha, 2007), those who are in recovery from addiction may need to develop techniques to lessen the impact of anxiety on impulsive behaviour. Another possible factor clouding the results is that those in the group with addiction problems were less

impacted by the threat-of-shock procedure. Given it was expected that chapter 8 would find greater threat-induced inhibitory impairments in the group with addiction problems, but the threat-induction was weaker in this group, a similar threat-induced inhibitory impairment is to be expected. Future research should ensure threat induction is equal between groups.

9.2 Limitations

While the present thesis was able to show that self-control is impaired by threat-induced anxiety; it was unable to reveal the relationship between self-control and other types of anxiety. For example, the anxiety resulting from anticipation of speech or the possible negative evaluation of others might be different from the anticipation of physical harm. Thus, it is difficult to extend the findings of this thesis to situations of social anxiety. Another possible limitation of the study is due to the necessary and valid ethical restraints placed on participant recruitment. To ensure participants have informed consent, they are made aware through advertising of the experiment's use of electric shocks. All participants in the studies of this thesis knew the study involved electric shocks before they willingly phoned or emailed the experimenter to volunteer for the study. It is possible that someone who knowingly volunteers to receive electric shocks responds differently to those shocks than others. Indeed, the existence of specific phobias (American Psychiatric Association, 2013) suggests some people are more fearful of a stimulus than others. The findings of chapter 7, that those who are higher on sensation seeking are less impacted by threat, further support this notion. Nevertheless, two points suggest this possible recruitment bias may not be a problem. First, the healthy participants in the thesis had an average sensation seeking score of 2.96, which is not above norms (Cyders, 2013). Second, unlike some specific phobias, the threat of electric shock increases autonomic arousal, startle response, and subjective anxiety in most people (Shackman et al., 2006). Another limitation is that the stop-signal task involves the presentation of a rare stop-signal, which may be facilitated by anxiety. Indeed, it is shown that anxiety facilitates the detection of novel and rare stimuli (Cornwell et al., 2017).

Indeed, the results of chapter 5 showed that threat was associated with a greater response to the stop-signal. Therefore, it is possible the stop-signal task underestimates the impact of threat on self-control as the facilitation of stop-signal detection may counteract some of the impaired control. Further, the improved sustained attention associated with anxiety (see chapter 6) may also improve Stop-signal task performance.

While the thesis was able to model the relationship between anxiety and impulsive behaviour in healthy adults, it was unable to clearly demonstrate a change in this relationship in a clinical population. This limitation was underpinned by the small sample size of chapter 8. Further, the significant difference in the impact of threat-induction between groups (measured using subjective anxiety) was a confounding factor that may have reduced any threat related impairments in the group with addiction problems. Another limitation is that trait impulsivity can only be measured retrospectively using self-reporting, making it difficult for researchers to understand how impulsive behaviour in everyday life is affected by induced anxiety. The present thesis argues that participants can reflect on their past impulsive behaviour, but this measurement may be confounded by other factors such as participants' own possible negative self-view. Another limitation is that MEG data was unable to be analysed in chapter 8. This made it impossible to reveal the hypothesised anxiety-induced inhibitory changes in right IFG in the group with addiction problems. A further limitation regarding generalizability must be acknowledged. The samples for all the studies were primarily comprised of university students, the majority of which were female. This means the results may not be generalizable to broader more diverse populations. Finally, the participants with addiction problems were all abstinent from drugs and alcohol. This meant the changes seen might be specific to those in recovery from addiction.

9.3 Implications and future directions

The understanding of the location and frequency of anxiety related changes (chapter 6) might aid in the assessment of anxiety and the reduction of anxiety through neurofeedback protocols. By measuring the strong and robust reductions in sensorimotor beta, the identification of anxious states in patients may be possible. Further, presenting these changes on screen may enable patients to better control their own anxiety through neurofeedback. Future research should test the feasibility and efficacy of neural feedback procedures that aim to increase beta power over the sensorimotor cortex to reduce anxiety. Additionally, it might be that discreet frequency bands such as alpha and beta are not independent (Canolty & Knight, 2010; Knyazev, Schutter, & van Honk, 2006). Future research should explore the cross-frequency coupling of these bands in sustained anxiety. Further, future research should explore sustained anxiety using MEG with a different anxiety induction protocol to test other types of anxiety such as speech anticipation. Additionally, other methods should be used to assess the effectiveness of the anxiety manipulation such as heart rate variability (Quintana, Alvares, & Heathers, 2016).

Chapters 4 and 5 revealed that anxiety impairs response inhibition, and this relationship can be directly measured. This has implications for the study of the interaction between emotion, and cognition. Response inhibition sits functionally (i.e. it is the competition between early and late processes; Logan & Cowan, 1984) and neurobiologically (i.e. it occurs in the right IFG – implicated in both dorsal and ventral attention systems; Corbetta & Shulman, 2002; Fox et al., 2006) between stimulus driven and goal driven processes. While early processes are thought to be facilitated by anxiety and later processes are thought to be impaired (Robinson et al., 2013), the present thesis shows that the line between the two can be moved slightly towards impairment, as response inhibition is impaired by anxiety. Future models should incorporate this knowledge into the picture of how anxiety impacts early and later cognitive processes. Additionally, other behavioural self-control tasks should be used to explore how induced anxiety

influences the various aspects of self-control such as proactive and reactive interference (Stahl et al., 2014).

Chapter 7 showed that negative urgency is related to anxiety-induced inhibitory impairments, demonstrating that behavioural and self-report aspects of self-control are related under the right conditions. This chapter provides implications for future research into the relationship between behavioural and self-report measures of conceptually related variables. While research has typically shown the two are not related or weakly related (Dreves et al., 2020), the results of chapter 7 suggest future research must consider the emotional state of participants to gain a stronger picture of these interactions.

Several questions remain unanswered that could be investigated by future researchers. It is not clear what the neural mechanisms underpinning anxiety-induced changes in cautious responding and response inhibition are in those with addiction problems. Interestingly, inhibition of drug craving has been linked to right IFG in those with addiction problems (Tabibnia et al., 2011). This opens the possibility that right IFG dysfunction during anxious arousal results in greater drug craving due to impaired inhibition. Future research might repeat the study in chapter 8 with a larger sample and with neuroimaging data included. Additionally, an inhibition of drug craving task could be added to reveal any possible anxiety-induced changes in overcoming drug craving. Moreover, a sample of those in “active addiction” should be included alongside the sample of abstinent participants to reveal the inhibitory and neuroelectrophysiological aspects of healthy recovery. Further, it is not clear how the relationship between anxiety and inhibition manifests in other impulsive disorders such as OCD and ADHD; and in anxiety disorders such as generalised anxiety disorder and social anxiety disorder. Future research may wish to include these cohorts.

9.4 Key contributions

Firstly, chapter 4 was the first study to show that induced anxiety impairs response inhibition using a robust measure of response inhibition and a robust method of anxiety induction. Chapter 5 was able to replicate this finding and show these impairments were underpinned by dysfunction in a well-established node of the inhibitory network – the right IFG. Chapter 6 was the first study to look at induced sustained anxiety related changes across several different tasks demands. It showed that states of anxious arousal are associated with neural changes reflecting increased action readiness, sustained attention, and sensory perception. Chapter 7 was the first study to model negative urgency in a laboratory by exploring impulsive action during induced anxiety – showing anxiety-induced inhibitory impairments are associated with greater negative urgency. This finding suggests impulsive behaviour in a laboratory can be related to questionnaire measure of impulsive behaviour under the correct conditions. Finally, chapter 8 provided some insight for possible future directions of research.

9.5 Conclusions

The aim of the thesis was to establish an understanding of how two key features of mental disorders (anxiety and self-control) interact and to explore this interaction in a disorder characterised by both features. Overall, the thesis showed that anxiety impairs self-control, and this impairment is greater in those with higher negative urgency (a measure of impulse control). The thesis also provided some preliminary data suggesting those in recovery from addiction are more cautious during times of stress, which likely helps them cope with the negative impacts of stress. The key findings of the thesis have shown that anxiety-induced inhibitory deficits reflect disrupted prefrontal cognitive control circuitry and has established several personality dimensions (e.g. negative urgency and sensation seeking) that contribute to inhibitory performance under anxious arousal. Further, the thesis has revealed the

neuroelectrophysiological signatures of sustained anxiety, including changes in regions associated with action readiness and sustained attention.

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Spielberger, C. D. (1966). CHAPTER 1 - Theory and Research on Anxiety11Work on this chapter was facilitated by a grant (HD 947) from the National Institute of Child Health and Human Development, United States Public Health Service. I am indebted to students and colleagues at Duke University and Vanderbilt University for their critical comments and helpful suggestions concerning a number of the ideas that are expressed herein, and particularly to Drs. L. Douglas DeNike, J. Peter Denny, Richard L. Gorsuch, Dale T. Johnson, and Edward S. Katkin, and to William F. Hodges, Kay Howard, Opal Purdue, Lou Hicks Smith, and Larry D. Southard. In C. D. Spielberger (Ed.), *Anxiety and Behavior* (pp. 3-20): Academic Press.

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Appendix

Appendix A – Authorship indication forms

SWINBURNE UNIVERSITY OF TECHNOLOGY

Swinburne Research

Authorship Indication Form

For HDR students

NOTE

This Authorship Indication form is a statement detailing the percentage of the contribution of each author in each published 'paper'. This form must be signed by each co-author and the Principal Supervisor. This form must be added to the publication of your final thesis as an appendix. Please fill out a separate form for each published paper to be included in your thesis.

DECLARATION

We hereby declare our contribution to the publication of the 'paper' entitled:

Threat-induced anxiety weakens inhibitory control

First Author

Name: Ariel Roxburgh Signature: 

Percentage of contribution: 80 % Date: 28 / 01 / 2021

Brief description of contribution to the 'paper' and your central responsibilities/role on project:
Collected data, conducted final calculation of SSRT, run data analysis, wrote paper

Second Author

Name: Matthew Hughes Signature: 

Percentage of contribution: 5 % Date: 28 / 01 / 2021

Brief description of your contribution to the 'paper':
Conducted initial calculation of SSRT, consulted on Stop-signal task

Third Author

Name: Brian Cornwell Signature: 

Percentage of contribution: 15 % Date: 25 / 01 / 2021

Brief description of your contribution to the 'paper':
Edited and co-wrote paper, helped with data analysis and experimental set-up

Fourth Author

Name:_____Signature:_____

Percentage of contribution: ____% Date: _ _ / _ _ / _ _ _ _

Brief description of your contribution to the 'paper':

Principal Supervisor:

Name: David White Signature:_____

Date: 28 / 01 / 2021

In the case of more than four authors please attach another sheet with the names, signatures and contribution of the authors.

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Swinburne Research

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DECLARATION

We hereby declare our contribution to the publication of the 'paper' entitled:

Anxious arousal alters prefrontal cortical control of stopping

First Author

Name: Ariel Roxburgh Signature: 

Percentage of contribution: 80 % Date: 02 / 02 / 2021

Brief description of contribution to the 'paper' and your central responsibilities/role on project:

Collected data, conducted all behavioural analysis, aided in initial analysis of MEG data, co-wrote paper, co-wrote grant application

Second Author

Name: David White Signature: 

Percentage of contribution: 5 % Date: 02 / 02 / 2021

Brief description of your contribution to the 'paper':

Edited paper

Third Author

Name: Brian Cornwell Signature: 

Percentage of contribution: 15 % Date: 02 / 02 / 2021

Brief description of your contribution to the 'paper':

Conducted final analysis of MEG data, co-wrote paper, co-wrote grant application.

Fourth Author

Name:_____Signature:_____

Percentage of contribution: ____% Date: _ _ / _ _ / _ _ _ _

Brief description of your contribution to the 'paper':

Principal Supervisor:

Name: David White Signature:_____

Date: 02 / 02 / 2021

In the case of more than four authors please attach another sheet with the names, signatures and contribution of the authors.

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DECLARATION

We hereby declare our contribution to the publication of the 'paper' entitled:

A neural oscillatory signature of sustained anxiety

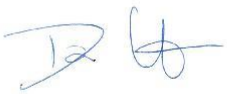
First Author

Name Ariel Roxburgh Signature: 

Percentage of contribution: 80 % Date: 20 / 01 / 2021

Brief description of contribution to the 'paper' and your central responsibilities/role on project:
Wrote paper, conducted initial analysis, edited figures

Second Author

Name: David White Signature: 

Percentage of contribution: 2.5 % Date: 02 / 02 / 2021

Brief description of your contribution to the 'paper':
Edited paper

Third Author

Name: Christian Grillon Signature: 

Percentage of contribution: 2.5 % Date: 02/ 01 / 2021

Brief description of your contribution to the 'paper':
Edited paper

Fourth Author

Name: Brian Cornwell Signature: 

Percentage of contribution: 15 % Date: 01 / 02 / 2021

Brief description of your contribution to the 'paper':
Edited paper with significant contributions. Conducted re-analysis and created figures

Principal Supervisor:

Name: David White Signature: 

Date: 02 / 02 / 2021

In the case of more than four authors please attach another sheet with the names, signatures and contribution of the authors.

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DECLARATION

We hereby declare our contribution to the publication of the 'paper' entitled:

Negative urgency is related to impaired response inhibition during threatening conditions

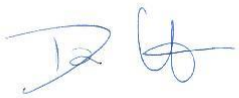
First Author

Name: Ariel Roxburgh Signature: 

Percentage of contribution: 80 % Date: 02 / 02 / 2021

Brief description of contribution to the 'paper' and your central responsibilities/role on project:
Collected data, analysed results, wrote paper

Second Author

Name: David White Signature: 

Percentage of contribution: 5 % Date: 02 / 02 / 2021

Brief description of your contribution to the 'paper':
Edited paper

Third Author

Name: Brian Cornwell Signature: 

Percentage of contribution: 15 % Date: 02 / 02 / 2021

Brief description of your contribution to the 'paper':
Edited paper, contributed to data analysis

Fourth Author

Name:_____Signature:_____

Percentage of contribution: ____% Date: _ _ / _ _ / _ _ _ _

Brief description of your contribution to the 'paper':

Principal Supervisor:

Name: David White Signature:_____

Date: 02 / 02 / 2021

In the case of more than four authors please attach another sheet with the names, signatures and contribution of the authors.

Authorship Indication Form

Swinburne Research

Authorship Indication Form

For HDR students

NOTE

This Authorship Indication form is a statement detailing the percentage of the contribution of each author in each published 'paper'. This form must be signed by each co-author and the Principal Supervisor. This form must be added to the publication of your final thesis as an appendix. Please fill out a separate form for each published paper to be included in your thesis.

DECLARATION

We hereby declare our contribution to the publication of the 'paper' entitled:

Slower and more adaptive responding during induced anxiety in a sample with addiction: Preliminary data

First Author

Name: Ariel Roxburgh Signature: 

Percentage of contribution: 80 % Date: 02 / 02 / 2021

Brief description of contribution to the 'paper' and your central responsibilities/role on project:

Collected data, analysed results, wrote paper, co-wrote grant application

Second Author

Name: David White Signature: 

Percentage of contribution: 5 % Date: 02 / 02 / 2021

Brief description of your contribution to the 'paper':

Edited paper

Third Author

Name: Brian Cornwell Signature: 

Percentage of contribution: 15 % Date: 02 / 02 / 2021

Brief description of your contribution to the 'paper':

Edited paper, contributed to data analysis, co-wrote grant application

Fourth Author

Name:_____Signature:_____

Percentage of contribution: ____% Date: _ _ / _ _ / _ _ _ _

Brief description of your contribution to the 'paper':

Principal Supervisor:

Name: David White Signature:_____

Date: 02 / 02 / 2021

In the case of more than four authors please attach another sheet with the names, signatures and contribution of the authors.

Authorship Indication Form

Appendix B – UPPS Scale

Below are a number of statements that describe ways in which people act and think. For each statement, please indicate how much you agree or disagree with the statement. If you Agree Strongly circle 1, if you Agree Somewhat circle 2, if you Disagree somewhat circle 3, and if you Disagree Strongly circle 4. Be sure to indicate your agreement or disagreement for every statement below. Also, there are questions on the following pages.

1. I have a reserved and cautious attitude toward life

2. I have trouble controlling my impulses.

3. I generally seek new and exciting experiences and sensations.

4. I generally like to see things through to the end.

5. When I am very happy, I can't seem to stop myself from doing things that can have bad consequences.

6. My thinking is usually careful and purposeful.

7. I have trouble resisting my cravings (for food, cigarettes, etc.).

8. I'll try anything once.

9. I tend to give up easily.

10. When I am in great mood, I tend to get into situations that could cause me problems.

11. I am not one of those people who blurt out things without thinking.

12. I often get involved in things I later wish I could get out of.

13. I like sports and games in which you have to choose your next move very quickly.

14. Unfinished tasks really bother me.

15. When I am very happy, I tend to do things that may cause problems in my life.

16. I like to stop and think things over before I do them.

17. When I feel bad, I will often do things I later regret in order to make myself feel better now.

18. I would enjoy water skiing.

19. Once I get going on something I hate to stop.

20. I tend to lose control when I am in a great mood.

21. I don't like to start a project until I know exactly how to proceed.

22. Sometimes when I feel bad, I can't seem to stop what I am doing even though it is making me feel worse.

23. I quite enjoy taking risks.

24. I concentrate easily.

25. When I am really ecstatic, I tend to get out of control.

26. I would enjoy parachute jumping.

27. I finish what I start.

28. I tend to value and follow a rational, "sensible" approach to things.

29. When I am upset I often act without thinking.

30. Others would say I make bad choices when I am extremely happy about something.

31. I welcome new and exciting experiences and sensations, even if they are a little frightening and unconventional.

32. I am able to pace myself so as to get things done on time.

33. I usually make up my mind through careful reasoning.

34. When I feel rejected, I will often say things that I later regret.

35. Others are shocked or worried about the things I do when I am feeling very excited.

36. I would like to learn to fly an airplane.

37. I am a person who always gets the job done.

38. I am a cautious person.

39. It is hard for me to resist acting on my feelings.

40. When I get really happy about something, I tend to do things that can have bad consequences.

41. I sometimes like doing things that are a bit frightening.

42. I almost always finish projects that I start.

43. Before I get into a new situation I like to find out what to expect from it.

44. I often make matters worse because I act without thinking when I am upset.

45. When overjoyed, I feel like I can't stop myself from going overboard.

46. I would enjoy the sensation of skiing very fast down a high mountain slope.

47. Sometimes there are so many little things to be done that I just ignore them all.

48. I usually think carefully before doing anything.

49. When I am really excited, I tend not to think of the consequences of my actions.

50. In the heat of an argument, I will often say things that I later regret.

51. I would like to go scuba diving.

52. I tend to act without thinking when I am really excited.

53. I always keep my feelings under control.

54. When I am really happy, I often find myself in situations that I normally wouldn't be comfortable with.

55. Before making up my mind, I consider all the advantages and disadvantages.

56. I would enjoy fast driving.

57. When I am very happy, I feel like it is ok to give in to cravings or overindulge.

58. Sometimes I do impulsive things that I later regret.

59. I am surprised at the things I do while in a great mood.

Scoring Instructions

This is a revised version of the UPPS Impulsive Behavior scale (Whiteside & Lynam, 2001). This version, UPPS-P (Lynam, Smith, Whiteside, & Cyders, 2006), assesses Positive Urgency (Cyders, Smith, Spillane, Fischer, Annus, & Peterson, 2007) in addition to the four pathways assessed in the original version of the scale-- Urgency (now Negative Urgency), (lack of) Premeditation, (lack of) Perseverance, and Sensation Seeking. The scale uses a 1 (agree strongly) to 4 (disagree strongly) response format. Because the items from different scales run in different directions, it is important to make sure that the correct items are reverse-scored. We suggest making all of the scales run in the direction such that higher scores indicate more impulsive behavior. Therefore, we include the scoring key for, (Negative) Urgency, (lack of) Premeditation, (lack of) Perseverance, Sensation Seeking, and Positive Urgency. For each scale, calculate the mean of the available items; this puts the scales on the same metric. We recommend requiring that a participant have at least 70% of the items before a score is calculated.

(Negative) Urgency (all items except 1 are reversed)

items 2 (R), 7(R), 12 (R), 17 (R), 22 (R), 29 (R), 34 (R), 39 (R), 44 (R), 50 (R), 53, 58 (R)

(lack of) Premeditation (no items are reversed)

items 1, 6, 11, 16, 21, 28, 33, 38, 43, 48, 55.

(lack of) Perseverance (two items are reversed)

items 4, 9 (R), 14, 19, 24, 27, 32, 37, 42, 47 (R)

Sensation Seeking (all items are reversed)

items 3 (R), 8 (R), 13 (R), 18 (R), 23 (R), 26 (R), 31 (R), 36 (R), 41 (R), 46 (R), 51 (R), 56 (R)

Positive Urgency (all items are reversed)

items 5 (R), 10 (R), 15 (R), 20 (R), 25 (R), 30 (R), 35 (R), 40 (R), 45 (R), 49 (R), 52 (R), 54 (R), 57 (R), 59 (R)

(R) indicates the item needs to be reverse scored such 1=4, 2=3, 3=2, and 4=1.

Appendix C – STAI

DIRECTIONS: A Number of statements which people have used to describe themselves are given below. Read each statement and then circle the response option to the right to indicate how you feel *right* now, that is, *at this moment*. There are no right or wrong answers. Do not spend too much time on any one statement, but give the answer which seems to describe your present feelings best.

	Not at all	Somewhat	Moderately so	Very much so
1. I feel calm	1	2	3	4
2. I feel secure	1	2	3	4
3. I am tense	1	2	3	4
4. I am regretful	1	2	3	4
5. I feel at ease	1	2	3	4
6. I feel upset	1	2	3	4
7. I am presently worrying about possible misfortunes	1	2	3	4
8. I feel rested	1	2	3	4
9. I feel anxious	1	2	3	4
10. I feel comfortable	1	2	3	4
11. I feel self-confident	1	2	3	4
12. I feel nervous	1	2	3	4
13. I am jittery	1	2	3	4
14. I feel "high strung"	1	2	3	4
15. I am relaxed	1	2	3	4
16. I feel content	1	2	3	4
17. I am worried	1	2	3	4
18. I feel over-excited and rattled	1	2	3	4
19. I feel joyful	1	2	3	4
20. I feel pleasant	1	2	3	4

DIRECTIONS: A Number of statements which people have used to describe themselves are given below. Read each statement and then circle the response option to the right to indicate how you generally feel. There are no right or wrong answers. Do not spend too much time on any one statement, but give the answer which seems to describe your present feelings best.

	Almost never	Sometimes	Often	Almost always
21. I feel pleasant	1	2	3	4
22. I feel nervous and restless	1	2	3	4
23. I feel satisfied with myself	1	2	3	4
24. I wish I could be as happy as others seem to be .	1	2	3	4
25. I feel like a failure	1	2	3	4
26. I feel rested	1	2	3	4
27. I am "calm, cool, and collected"	1	2	3	4
28. I feel that difficulties are piling up so that I cannot overcome them	1	2	3	4
29. I worry too much over something that really doesn't matter	1	2	3	4
30. I am happy	1	2	3	4
31. I have disturbing thoughts	1	2	3	4
32. I lack self-confidence	1	2	3	4
33. I feel secure	1	2	3	4
34. I make decisions easily	1	2	3	4
35. I feel inadequate	1	2	3	4
36. I am content	1	2	3	4
37. Some unimportant thought runs through my mind and bothers me	1	2	3	4
38. I take disappointments so keenly that I can't put them out of my mind	1	2	3	4
39. I am a steady person	1	2	3	4
40. I get in a state of tension or turmoil as I think over my recent concerns and interests	1	2	3	4

Appendix D – ASI (Lite)

ASI-LITE

I'm going to ask you some questions about your alcohol and other drug use and any problems you may have had in these areas. I would like to remind you that the information you give me is confidential, and will only be used for research purposes.

*[**Note:** Give Response Card to participant]*

For the following questions, the time frames will be for two different periods; for the **past 30 days prior to treatment entry** and **in your lifetime**. For lifetime use I am interested in the number of years that you used 3 or more times per week.

***[Instructions**: For drug use grid, ask for the past 30 days first, then for lifetime.*

- *In the past 30 days, how many days would you have used...(insert drug name)*
- *In you lifetime, how many years would you have used ...(insert drug name)*
- *How have you most commonly used ...(insert drug name) in the last 30 days?*

If a drug was never used (coded as "0/0"), the route of administration is coded as "9"]

		PAST 30 DAYS (Days)	LIFETIME USE (Years)	*Route of Administration
1.	Alcohol - any use at all	___/___	___/___	____
2.	Alcohol - to Intoxication	___/___	**No Answer Required**	____
3.	Heroin	___/___	___/___	____
4.	Methadone (illicit)	___/___	___/___	____
5.	Other opiates/analgesics	___/___	___/___	____
6.	Barbiturates	___/___	___/___	____
7.	Other sedatives, hypnotics, tranquillisers	___/___	___/___	____
8.	Cocaine	___/___	___/___	____
9.	Amphetamines	___/___	___/___	____
10.	Cannabis	___/___	___/___	____
11.	Hallucinogens	___/___	___/___	____
12.	Inhalants	___/___	___/___	____
13.	More than one substance per day (include alcohol)	___/___	___/___	**No Answer**

**** Route of Administration:***
1=Oral, 2=Nasal, 3=Smoking, 4=Non IV injection., 5=IV injection., 9=Never Used

Appendix E – Demographic questions

Demographic Questions

How old are you in years? _____

What is your gender (male, female, other)? _____

Do you mainly use your left or right hand? _____

What is the highest level of education you have completed? Circle your answer.

1) Doctorate degree
2) Masters degree
3) Graduate diploma or honours degree
4) Bachelor degree
5) Advanced diploma or Diploma
6) Certificate III or IV
7) Year 12
8) Year 11 or below

Appendix F – Ethics approval emails

Project 2015/112: This covers all healthy participants

From: Keith Wilkins **On Behalf Of** RES Ethics
Sent: Tuesday, 7 July 2015 4:37 PM
To: Brian Cornwell <bcornwell@swin.edu.au>
Cc: RES Ethics <resethics@swin.edu.au>
Subject: SHR Project 2015/112 Ethics Clearance

To: Dr Brian Cornwell, BPsyC/FHAD

Dear Brian

SHR Project 2015/112 Response inhibition under emotional stress: A behavioural and neuroimaging investigation
Dr Brian Cornwell, FHAD; Mr Arial Roxburgh, Dr Matthew Hughes
Approved Duration: 07-07-2015 to 31-12-2016

I refer to the above project revised protocol as emailed on 3 July 2015 with attachments. In line with the previous review by Swinburne's Human Research Ethics Committee (SUHREC), the revised protocol was given expedited review by SUHREC delegate.

I am pleased to advise that ethics clearance has been given for the above project to proceed in line with standard on-going ethics clearance conditions outlined below.

- 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 Swinburne project number. Please retain a copy of this email as part of project record-keeping.

Best wishes for the project.

Yours sincerely

Keith

Keith Wilkins
Secretary, SUHREC & Research Ethics Officer
Swinburne Research (H68)
Swinburne University of Technology
P O Box 218
HAWTHORN VIC 3122
Tel +61 3 9214 5218
Fax +61 3 9214 5267

Project 2018/419: This covers all participants with addiction problems

From: Astrid Nordmann <anordmann@swin.edu.au>
Sent: Friday, 22 February 2019 12:42 PM
To: Brian Cornwell <bcornwell@swin.edu.au>
Cc: RES Ethics <resethics@swin.edu.au>; Ariel Roxburgh <aroxburgh@swin.edu.au>; Conrad Perry <cperry@swin.edu.au>
Subject: SHR Project 2018/419 - Ethics clearance

To: Dr Brian Cornwell, FHAD

Dear Brian,

SHR Project 2018/419 – The influence of anxiety on inhibitory functioning in a clinical population

Dr Brian Cornwell, Dr Ariel Roxburgh, A/Prof. Conrad Perry - FHAD

Approved duration: 01-03-2019 to 01-01-2022

I refer to the ethical review of the above project protocol by Swinburne's Human Research Ethics Committee (SUHREC). Your response to the review, as emailed on 22 February 2019, accords with the Committee review.

I am pleased to advise that, as submitted to date, the project may proceed in line with standard on-going ethics clearance conditions outlined below.

- The approved duration is **01 March 2019** to **01 January 2022** unless an extension request is subsequently approved.

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 (2007 – updated 2018)* 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, and addition or removal of other personnel/students from the project, 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 and

variations/additions, self-audits and progress reports can be found on the Research Ethics Internet 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, citing the Swinburne project number. A copy of this email should be retained as part of project record-keeping.

Best wishes for the project.

Yours sincerely

Astrid Nordmann
Secretary, SUHREC