

Investigating Factors that Influence Cognitive Response to, and the Efficacy of,
Cognitive Remediation Therapy in People with Schizophrenia

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Abstract

Cognitive remediation therapy (CRT) has emerged as a moderately effective treatment in ameliorating the cognitive deficits found in a majority of individuals with schizophrenia. However, available evidence suggests that not everyone realises a cognitive benefit following CRT. Reasons for this are unclear. Variability in response has the potential to undermine the effectiveness of CRT in real-world settings. The goal of this thesis was therefore to arrive at a better understanding of factors that influence individual response to, and the efficacy of, CRT in people diagnosed with schizophrenia.

To address the thesis aim, Study 1 completed a systematic review of the empirical research that had examined mediators, moderators and predictors of cognitive outcome following CRT. No comprehensive synthesis of the predictor literature had previously been undertaken. Study 2 conducted a CRT intervention with a Melbourne-based schizophrenia cohort so that (a) individual patterns of cognitive response to CRT could be identified, (b) possible responder subgroups might be characterised, and (c) outcomes to emerge from the systematic review could be consolidated and extended upon by determining their predictive value of differential cognitive response to CRT. A separate, preliminary line of enquiry (Study 3) explored the relationship between the gene for encoding dysbindin-1 and cognitive performance on a neurocognitive test battery.

The systematic review identified premorbid IQ, baseline cognition, and learning potential as potential predictors of an individual's capacity to benefit from CRT. Within Study 2, 22 participants completed a minimum 24 CRT sessions. Fifty-five percent of this sample realised reliable change across at least one cognitive domain. Baseline attention/vigilance and verbal learning potential differentiated the CRT responders from non-responders while a more granular, qualitative subgroup examination yielded a possible differential association between post-intervention clinical presentation and cognitive response to CRT. In Study 3, significant diagnostic group by dysbindin-1 genotype interactions were found across a measure of working memory.

The more frequently examined purported predictors of cognitive response to CRT, such as age, years of education, and duration of illness, had little prognostic value. In contrast, potential markers of an individual's capacity to change, including baseline cognitive ability and learning potential, appear to have greater prognostic

value. There remains a critical need for large scale investigations to further investigate and characterise individual patterns of response to CRT. There is a need for novel analytic techniques to aid a better formulation to influence treatment guidelines and, in turn, clinical practice.

Declaration

In accordance with Swinburne University's Higher Degree Research Training Statement of Practice (version 5.0, effective December 2017), I hereby declare that this thesis:

- contains no material which has been accepted for the award of any other degree or diploma, except where due reference is made in the text of the examinable outcome;
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Maree P Reser

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List of Common Abbreviations

<i>AttnVig</i>	Attention/Vigilance
<i>CogComp</i>	Cognitive Composite
<i>CRT</i>	Cognitive Remediation Therapy
<i>DTNBP1</i>	Dysbindin Binding Protein-1 or Dysbindin
<i>M</i>	Mean
<i>MATRICES</i>	Measurement and Treatment Research to Improve Cognition in Schizophrenia
<i>MCCB</i>	MATRICES Consensus Cognitive Battery
<i>R-PS</i>	Reasoning and Problem Solving
<i>RCI</i>	Reliable Change Index
<i>SD</i>	Standard Deviation
<i>SocCog</i>	Social Cognition
<i>SoP</i>	Speed of Processing
<i>VerbF</i>	Verbal Fluency
<i>VerbL</i>	Verbal Learning
<i>VerbM</i>	Verbal Memory
<i>VerbL&M</i>	Verbal Learning and Memory
<i>VisL</i>	Visual Learning
<i>VisM</i>	Visual Memory
<i>VisL&M</i>	Visual Learning and Memory
<i>WM</i>	Working Memory

Note. This is an abbreviated list reflecting only the most frequently used abbreviations found across the thesis chapters. All abbreviations are defined in the first instance in text. Abbreviations are also re-defined in each of the chapters prepared for publication (4, 7, 8, and 9).

Chapter 1. Introduction and Thesis Outline

1.1 Chapter Guide

The overarching goal of this thesis was to arrive at a better understanding of factors that influence individual response to, and the efficacy of, cognitive remediation therapy in people diagnosed with schizophrenia. Given the considerable disadvantage experienced by individuals diagnosed with schizophrenia, efforts to increase the effectiveness of therapeutic interventions by providing greater transparency of factors that influence outcome, such that research outcomes can better inform clinical practice, is a worthwhile endeavour.

The purpose of this introductory chapter is to provide an overview of the broad steps taken to arrive at the finer detail that motivated and informed the chapters comprising this body of work. The purpose of the subsequent thesis outline is to provide the reader with a road map of how each chapter draws from and builds on the next, and to give place to those that do not.

1.2 Individuals with a Diagnosis of Schizophrenia

The broader context of this work was the wellbeing of individuals with a diagnosis of schizophrenia. For a majority of individuals so diagnosed, schizophrenia is a debilitating, lifelong disorder. Symptoms such as cognitive and motor deficits manifest even before the first episode of psychosis (Dickson, Laurens, Cullen, & Hodgins, 2012). And, over the course of illness, individuals with schizophrenia have significantly poorer social, vocational and everyday functioning outcomes (Bottlender, Strauss, & Möller, 2010; Harrow, Grossman, Herbener, & Davies, 2000).

1.3 Schizophrenia and Cognitive Deficits

Within this context, the scope of the thesis narrows, side stepping the characteristic delusions, hallucinations, disorganised speech, disorganised or catatonic behaviour, and negative symptoms that comprise Category A of the Diagnostic and Statistical Manual of Mental Disorders diagnostic criteria for schizophrenia (5th ed.; DSM-5; American Psychiatric Association, 2013). Attention is drawn instead to the cognitive deficits that are experienced by a majority of individuals with schizophrenia (Heinrichs, Miles, Ammari, & Muharib, 2013). In terms of wellbeing, cognitive performance has been associated with both intermediary measures of functional capacity, defined by Bowie and colleagues as “what an individual can do” in terms of everyday skills, and with more distal measures of functional outcome, or “what an individual does do” in terms of real-world performance (Bowie et al., 2008; Bowie, Reichenberg, Patterson, Heaton, & Harvey, 2006, p. 419). Overall, poorer cognitive performance has been associated with poorer quality of life across community, social, and vocational domains (Fett et al., 2011; Mohamed et al., 2008).

1.4 Cognitive Remediation Therapy (CRT)

Given the association between cognition and functional outcome, there have been increased efforts to develop interventions to improve cognitive functioning (McGurk et al., 2013). While pharmacological interventions are the primary means of ameliorating the characteristic psychotic symptoms of schizophrenia, the efficacy of antipsychotic medication in bringing about cognitive improvements is equivocal (Goldberg et al., 2007; S. K. Hill, Bishop, Palumbo, & Sweeney, 2010). In its place, CRT has emerged as a small to moderately effective intervention that brings about

improvements in both cognition and functioning (Grynszpan et al., 2011; Wykes, Huddy, Cellard, McGurk, & Czobor, 2011).

1.5 Heterogeneity of Response to CRT

At this juncture, the finer detail that motivated and informed the chapters comprising this thesis emerge. In their meta-analytic review of the efficacy of CRT, Wykes, Huddy, Cellard, and Czobor (2011) reported significant heterogeneity in effect across speed of processing (SoP), reasoning and problem solving (R-PS), and social cognition (SocCog) domains and across a global cognitive composite (CogComp). While a range of potential demographic, clinical, methodological and treatment mediators and moderators of effect were examined by Wykes et al. (2011), none were found to explain the variability in response. Closer examination of the studies that comprised the meta-analysis revealed that in some, a proportion of participants did not realise cognitive benefit following CRT. Admittedly, information regarding rates of improvement was limited to 3 of 39 studies, too small a number for generalisation but sufficient to generate interest. In a meta-analysis specific to computer-assisted cognitive remediation, Grynszpan et al. (2011) similarly reported significant heterogeneity of effect in the R-PS domain, and also across verbal learning and memory (VerbL&M) and visual learning and memory (VisL&M). As with Wykes et al., no correlates of outcome were identified.

Key points to emerge from this literature that informed this body of work included evidence that (a) not everyone realised cognitive benefit from CRT; (b) variability in response to CRT was under reported and was potentially masked by group level analysis; and (c) few, if any, factors had been identified that could explain the apparent inter-individual variability of response that in turn influenced the efficacy of CRT.

1.6 Factors That Influence the Efficacy of CRT in People Diagnosed with Schizophrenia

A wider search of the literature up to 2014 failed to identify any systematic reviews or meta-analyses of factors that influenced the efficacy of CRT in people diagnosed with schizophrenia. Rather, concluding statements in the handful of more general review articles published by some of the formative researchers in the field reiterated the need for more research into mediators and moderators of CRT efficacy (Cellard, Whaley, & Wykes, 2011; Kaneko & Keshavan, 2012; Keshavan,

Vinogradov, Rumsey, Sherrill, & Wagner, 2014; Kurtz, 2012; McGurk et al., 2013; Wykes & Spaulding, 2011). Combined with evidence of heterogeneity of response to CRT, these collective statements were the impetus for the theme that runs through the thesis chapters: to arrive at a better understanding of factors that influence individual cognitive response to, and the efficacy of, cognitive remediation therapy in people diagnosed with schizophrenia.

Given how labor intensive such approaches are, it is essential to match patients with the specific cognitive remediation therapy to which they are most likely to respond. It is therefore critical to identify clinical, neurobiological, and genetic predictors of positive response to cognitive remediation interventions. (Kaneko & Keshavan, 2012, p. 131)

1.7 Thesis Outline

The opening chapters of this thesis expand on the brief introductory sections above, providing a more detailed overview of the context in which subsequent chapters are situated.

Chapter 2 more fully describes the epidemiology, symptomatology and diagnostic criteria, and course of schizophrenia and goes on to characterise the cognitive deficits that are manifest from first episode psychosis. The prevalence and degree of cognitive deficit are reported and contrasted with healthy controls. Further evidence of their association with functional outcome is presented.

Chapter 3 serves three purposes. First, it introduces CRT, explaining several of its key underlying principles and providing a broad overview of CRT approaches. Second, it provides neurobiological, cognitive-behavioural and functional evidence of the efficacy of CRT. Finally, it presents evidence to substantiate the claim that, to the extent that it has been possible to assess, approximately 44% of individuals who participate in CRT fail to realise cognitive benefit.

Chapters 2 and 3 largely cover material that has been comprehensively addressed at multiple time points in the literature and were therefore not developed or intended for publication.

Chapter 4 presents a systematic review of the evidence base regarding factors that influence the efficacy of CRT in people diagnosed with schizophrenia. This was both a logical and essential starting point. No such synthesis existed to guide research projects or to inform clinical practitioners when discussing treatment

options with clients. Outcomes from this review helped to shape the study aims and informed selection of potential predictor variables examined in Chapters 7 and 8.

Chapter 5 draws together essential elements from Chapters 2-4 to present the general study aims and objectives for Chapters 7 and 8. Study specific hypotheses are detailed in their respective chapters.

Chapter 6 serves as the Methods section for Chapters 7 and 8, which were necessarily more succinct in detailing the study materials and methodology due to publication requirements. Information regarding the study design, ethical approvals, participant recruitment and assessment, the study intervention, and such things as data management, security and confidentiality, is provided.

Chapter 7 is the first of two empirical research papers arising from the CRT intervention facilitated by the author. With the aim of identifying factors associated with cognitive outcome following CRT, measures of intellectual status, cognitive ability and learning potential were examined as potential predictors of differential response.

Chapter 8 is the second empirical research paper, the aim of which was to more closely examine patterns and predictors of individual response to CRT so as to better inform clinical practice. In this paper, the use of heat maps was modelled as a tool to expose potential associations between cognitive domain level outcomes and variables of interest as possible predictors of response.

Chapter 9 reports the outcomes of secondary data analysis examining the relationship between DTNBP1 genotype (the gene for encoding dysbindin-1) and cognitive performance in schizophrenia and healthy controls using the MATRICS Consensus Cognitive Battery (MCCB). This standalone chapter was intended as a prelude to exploration of potential genetic correlates of cognitive response to CRT. Although sample size limitations prevented the subsequent investigation of this relationship, this is the first study to explore the association between DTNBP1 and MCCB cognitive domains.

Chapter 10 is the Discussion, where the general aim of the thesis is reviewed in light of the research outcomes. A summary of the respective study results is provided, and general limitations are considered. The implications of the research outcomes are discussed, and future directions detailed.

1.8 Scope of Research

Given evidence that functional outcomes are strengthened when CRT is delivered alongside adjunctive therapy (Wykes et al., 2011), CRT is frequently combined with other forms of psychiatric rehabilitation, such as social cognitive training and vocational training. However, the inclusion of adjunctive therapies can make it difficult to determine whether reported outcomes are directly attributable to CRT (McGurk et al., 2013). Therefore, when investigating factors that influenced response to/efficacy of CRT, studies that included adjunctive therapies were omitted.

For a similar reason, that is, to control for possible confounding factors, the thesis focus was on cognitive outcomes following CRT. While the ultimate goal of CRT is to improve functional outcomes, improvements in functioning may not be immediately evident following CRT and, if examined over longer periods, could be subject to other factors of influence (Cellard et al., 2011; Medalia & Richardson, 2005). For this reason, post-intervention rather than follow-up results were considered.

Chapter 2. Schizophrenia: Characteristics and Cognitive Deficits

2.1 Chapter Guide

While the focus of this thesis is on factors that influence the efficacy of CRT in bringing about cognitive change in individuals diagnosed with schizophrenia, understanding the context within which the subject matter sits is important. The opening sections of Chapter 2 (Section 2.2) start quite broadly, detailing how many individuals are diagnosed with schizophrenia, who is at greater risk when considering epidemiological data, what the core symptoms are, and what the typical course of illness is. While not intended to be an exhaustive examination of these factors, it is intended to impart a sense of the broader impacts of the disorder.

The closing sections of Chapter 2 (Section 2.3) shift focus to the cognitive deficits that are now considered a core feature of schizophrenia. The proportion of individuals who experience cognitive impairments is examined and the pattern of deficits presented. The role of cognition in aiding functional recovery is explored through review of the purported associations between cognition and different domains of functioning.

This chapter covers contextual material that, while important, is not the central focus of the thesis. As such, for the sake of brevity, it draws heavily on review articles and meta-analyses. It was also necessary to make some difficult decisions about what material to exclude. Given the central focus of cognitive response to CRT, a synthesis of the various aetiological theories underpinning schizophrenia was not provided. Nor were factors more generally associated with outcome, such as duration of untreated illness and age of onset, discussed. A specific review of predictors of response to CRT will be provided in Chapter 4. Also, the relationship between changes in cognition and changes in functioning is touched on, but not fully developed. It will be reviewed in more depth in Chapter 3 when CRT is introduced.

2.2 Characterising Schizophrenia

2.2.1 Epidemiology. Schizophrenia is a chronic, debilitating psychotic disorder experienced by around seven individuals per thousand (median [10, 90 quantiles] lifetime morbid risk = 7.2 [3.1, 27.1] per 1000 persons)¹, or more than 21 million people worldwide (World Health Organization, 2018). It carries a two- to three-fold increased risk of death (McGrath, Saha, Chant, & Welham, 2008). Of concern, the difference in mortality rates between individuals diagnosed with schizophrenia and the general community has increased, possibly due to health improvements realised in the community not extending to individuals with schizophrenia (McGrath et al., 2008). McGrath, Saha, Chant, and Welham (2008) argue that without intervention the gap may continue to grow as the secondary side-effects of some atypical antipsychotics result in increased health-related deaths.

In terms of risk of developing schizophrenia, males have a slightly higher incidence rate compared to females, with an estimated median male:female ratio of 1.4:1.0 (10, 90 quantiles = 0.9, 2.4; McGrath et al., 2008). However, that trend is not found in prevalence estimates (McGrath et al., 2008; Perälä et al., 2007). Perälä and colleagues (2007) suggest that the earlier age of onset and higher mortality rates found in males, coupled with the tendency for later-onset cases to be female, might explain the equivalency found in prevalence estimates.

Migrant status, economic status, and latitude have also emerged as risk factors, with migrants, individuals in developed countries and males at higher latitudes being at greater risk of developing schizophrenia (McGrath et al., 2008). There is also a higher incidence of schizophrenia in urban compared to mixed urban/rural settings (McGrath et al., 2008). While a range of underlying mechanisms have been proposed to explain the various risk factors, including genetic influences, socioeconomic status, nutritional factors, stress due to overcrowding, infections, and environmental pollutants, no definitive causal factors have been identified (McGrath et al., 2008).

2.2.2 Symptomatology and diagnostic criteria. Modern definitions of schizophrenia have evolved, influenced at different times points by Kraepelinian, Bleulerian, and Schneiderian conceptualisations of the essential features of the

¹ As data was negatively skewed, median and quantile values are reported. The mean (SD), at 11.9 (10.8), was noted by McGrath et al. (2008) as more closely approximating the commonly referred to prevalence of 1 person in 100.

disorder (Tandon, 2013). Debate continues as to whether schizophrenia is a single disorder or, in the face of its considerable heterogeneity, represents multiple aetiologically distinct subtypes (Jablensky, 2006). As noted by Jablensky (2006), such is the degree of inter-individual variability in presentation that it is possible for two individuals to be diagnosed with schizophrenia without any symptom overlap. Notwithstanding these complexities, diagnostic stability across the two major classification systems (DSM-IV and the ICD-10 [see footnote²]) is high, with high concordance between the two (Kappa = 0.891; Möller et al., 2011).

The DSM-5² (American Psychiatric Association, 2013, pp. 87–88, 99) outlines five key defining features of psychotic disorders more generally and that, more specifically, comprise Category A of the diagnostic criteria for schizophrenia:

- (1) Delusions, which represent fixed beliefs that are resistant to contrary evidence. Persecutory and referential themes are common.
- (2) Hallucinations, which take the form of perceptual experiences that occur in the absence of external stimuli; auditory hallucinations predominate.
- (3) Disorganised speech, reflective of underlying disorganised thought, examples of which include the frequent switching between topics, tangential responses and, in more extreme cases, incoherent speech.
- (4) Grossly disorganised or catatonic behaviour, which can range from childishness, to unpredictable anxiousness, to a notable decrease in reactivity to the environment.
- (5) Negative symptoms, which commonly include diminished emotional expression and a decrease in motivated self-initiated goal-directed activities but could also extend to a lack of interest in social interactions, a diminished ability to experience pleasure or to recall previous pleasurable experiences, and diminished speech output.

Diagnostic criteria, as defined in the DSM-5, is presented in Table 2.1.

² Of the other major classification system, the International Statistical Classification of Diseases and Related Health Problems (10th revision; ICD-10; World Health Organization, 1992) is currently undergoing revision, with the ICD-11 due for release 2018. In the ICD-11, the diagnostic criteria for schizophrenia more closely align with the DSM-5.

Table 2.1

DSM-5 Diagnostic Criteria for Schizophrenia

Category	Definition
A	Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated). At least one of these must be (1), (2), or (3): (1) Delusions. (2) Hallucinations. (3) Disorganized speech (e.g., frequent derailment or incoherence). (4) Grossly disorganized or catatonic behaviour. (5) Negative symptoms (i.e., diminished emotional expression or avolition).
B	For a significant portion of the time since the onset of the disturbance, level of functioning in one or more major areas, such as work, interpersonal relations or self-care, is markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, there is failure to achieve expected level of interpersonal, academic, or occupational functioning).
C	Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or by two or more symptoms listed in Criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).
D	Schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out because either 1) no major depressive or manic episodes have occurred concurrently with the active-phase symptoms, or 2) if mood episodes have occurred during active-phase symptoms, they have been present for a minority of the total duration of the active and residual periods of the illness.
E	The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.
F	If there is a history of autism spectrum disorder or a communication disorder of childhood onset, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations, in addition to the other required symptoms of schizophrenia, are also present for at least 1 month (or less if successfully treated).

Note. DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Reproduced from American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders (5th ed.)*. Washington, DC: Author. Copyright 2013 by the American Psychiatric Association.

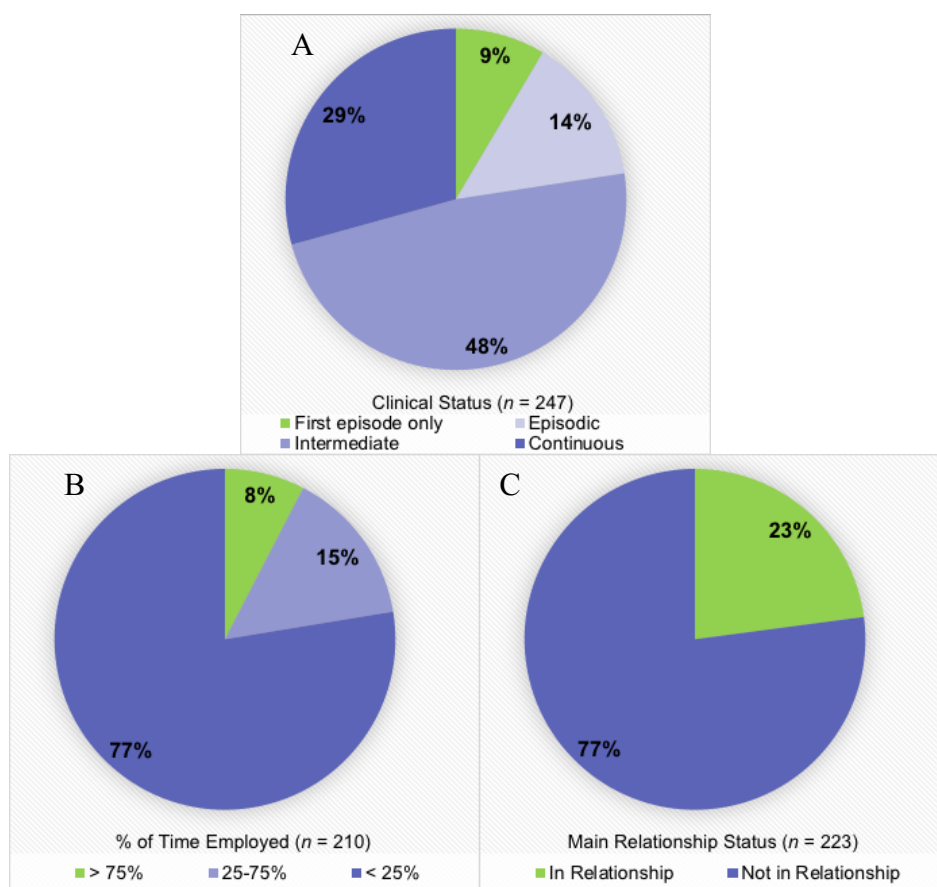
In addition to these core symptoms, a majority of individuals diagnosed with schizophrenia are likely to experience at least one psychiatric comorbidity over the course of their illness. It is estimated that approximately 50% of individuals will experience depressive symptoms, around 47% will receive a lifetime diagnosis of comorbid substance abuse, 29% will be diagnosed with post-traumatic stress disorder, 25% will experience panic attacks, and 23% will meet criteria for obsessive compulsive disorder (Buckley, Miller, Lehrer, & Castle, 2009). Individuals with such comorbidities report poorer mental health and quality of life (Tsai & Rosenheck, 2013).

Poorer outcomes have also been associated with the presence of negative symptoms at onset. For example, results from a 7-year longitudinal study following 99 individuals after a first episode of psychosis found that baseline negative, but not positive or disorganised, symptoms were associated with relationship, recreational and work impairment, and a measure of global psychosocial functioning (Milev, Ho, Arndt, & Andreasen, 2005). Similar outcomes were reported in a 10-year longitudinal study following 109 first episode cases; baseline negative symptoms were associated with poor functional outcome at follow-up (White et al., 2009).

2.2.3 Course. In keeping with the heterogeneous nature of schizophrenia, the course of illness is variable. Symptoms characteristic of schizophrenia typically emerge between late adolescence and early adulthood (Thorup, Waltoft, Pedersen, Mortensen, & Nordentoft, 2007), though cognitive and motor deficits can manifest much earlier (Dickson et al., 2012). Around 4% of cases develop before the age of 15 years (Remschmidt & Theisen, 2012). Males have a slightly earlier age of symptom onset and first admission compared to females, by 1.63 years and 1.07 years respectively (Eranti, MacCabe, Bundy, & Murray, 2013). Earlier age of onset has been associated with poorer prognosis, as measured by frequency and length of hospital care required (Rabinowitz, Levine, & Häfner, 2006). However, when analysed over longer time frames, there is some evidence that initial periods of deterioration are followed by amelioration of symptoms (Levine, Lurie, Kohn, & Levav, 2011).

A limitation of characterising course of illness through use of re-hospitalisation rates alone is the emphasis on symptomatic relapse and remission patterns. Symptomatic remission or recovery does not presuppose improvements in social, vocational, or everyday functioning, where the prognosis often appears much

poorer (Revier et al., 2015). A more granular understanding of the heterogeneous course of schizophrenia across multiple outcome domains can be gained from longitudinal studies using epidemiological cohorts (C. Morgan et al., 2014). One such study, *ÆSOP-10*, saw the successful follow-up of 387 of an initial 532 first episode psychosis cases identified across two English catchment areas (C. Morgan et al., 2014; Revier et al., 2015). As presented in Figure 2.1-A, of the subset diagnosed with non-affective psychosis, 29.3% had experienced a continuous course of symptoms across the 10-year follow-up period and nearly half experienced what was described as an intermediate course of symptoms, with at least one psychotic episode and one remission period lasting more than six months (C. Morgan et al., 2014). Figures 2.1-B and 2.1-C highlight the especially poor vocational and social outcomes experienced over the follow-up period. In *ÆSOP-10*, although 39.7% of non-affective participants had experienced symptomatic recovery at follow-up, i.e., had not experienced symptoms for a minimum two years prior, only 16% were in paid employment and 25.2% were in a relationship (C. Morgan et al., 2014).



*Figure 2.1 A-C. The AESOP-10 study: Clinical, employment and relationship status in a first episode, non-affective psychosis cohort across a 10-year follow-up period. Figure 2.1-A presents long-term clinical course. First episode only = did not experience a reoccurrence of psychosis after recovery from the first episode; episodic = at least one episode of less than 6 months duration; intermediate = at least one episode and one period of remission of greater than 6 months duration; continuous = no period of remission greater than 6 months. Figure 2.1-B presents the approximate percentage of time spent in paid employment over the 10-year period. Figure 2.1-C reflects whether participants were mainly in or not in relationships over the follow-up period. Created by MPR based on data from “Reappraising the Long-term Course and Outcome of Psychotic Disorders: The AESOP-10 Study”, by C. Morgan, J. Lappin, M. Heslin, K. Donoghue, B. Lomas, U. Reininghaus... P. Dazzan, 2014, *Psychological Medicine*, 44, p. 2719 & 2721. Copyright 2013 Cambridge University Press.*

When the course of illness in schizophrenia is considered more holistically, rates of recovery appear much lower. In a recent systematic review and meta-analysis of recovery in schizophrenia, Jääskeläinen and colleagues (Jääskeläinen et al., 2013, p. 1297) defined recovery as “[a] very good outcome that considers both clinical and social/functional dimensions and includes a duration criteria of at least 2 years for at least 1 of these measures”. Quantitative analysis of 50 samples that provided sufficient data to evaluate these criteria resulted in a median recovery estimate of 13.5% (interquartile range = 8.1% - 20.0%). That equated to an estimated median annual recovery rate of just 1.4%; for every 100 individuals with schizophrenia, only 1 to 2 each year would recover across more than one outcome domain. Jääskeläinen et al. (2013) found no evidence to suggest that recovery rates were improving. This highlights the critical need for better understanding factors that influence the effectiveness of interventions aimed at improving functional outcomes.

The relative independence of functional outcome from clinical status begs the question what else needs to be addressed to facilitate functional recovery. In a series of pivotal papers, Green and colleagues shifted the discussion from symptoms to the potentially rate-limiting role of cognition on functional outcome (M. F. Green, 1996; M. F. Green, Kern, Braff, & Mintz, 2000; M. F. Green, Kern, & Heaton, 2004; M. F. Green & Nuechterlein, 1999). Section 2.3 will quantify and characterise the pattern of cognitive deficits found in schizophrenia. Evidence of the association between cognition and social/functional recovery will be presented as a rationale for the subsequent focus on cognition in the effort to improve functional outcomes.

2.3 Schizophrenia and Cognition

It is perhaps ironic that cognitive performance, less obvious and striking than the symptoms used to define the illness and less technically impressive than brain imaging, may in the end be the signpost that leads to the source of madness. (Heinrichs, 2005, p. 239)

Subtler, but arguably more intractable than the positive symptoms that characterise schizophrenia, are impairments in cognitive functioning that are considered a core component of the disorder (Heinrichs, 2005; Keefe & Fenton, 2007).

2.3.1 Course of cognitive deficit. Impairments in general intelligence and cognitive functioning precede the first episode of psychosis, albeit at attenuated levels relative to reported deficits in schizophrenia (Dickson et al., 2012; Fusar-Poli et al., 2012; Niendam, Jalbrzikowski, & Bearden, 2009). A meta-analysis of cognitive functioning in prodromal psychosis found that, when compared to healthy controls, individuals at clinical high risk manifest deficits in general intelligence (IQ), executive functioning, verbal memory (VerbM), visual memory (VisM), verbal fluency (VerbF), and attention and working memory (WM; Fusar-Poli et al., 2012). Those who later transition to psychosis have comparatively lower IQ and poorer VerbF, VerbM, VisM, and WM than those who do not transition (Fusar-Poli et al., 2012). By first episode schizophrenia, medium-to-large impairments are evident across all cognitive domains, and approximate deficits found in chronic schizophrenia (Mesholam-Gately, Giuliano, Goff, Faraone, & Seidman, 2009; Sponheim et al., 2010). While performance across a majority of domains appears largely stable across the course of illness (Bozikas & Andreou, 2011), there is some evidence of continued domain specific deterioration. For example, in their systematic review of longitudinal studies examining cognition from first episode psychosis, Bozikas and Andreou (2011) reported evidence of potential further deterioration in VerbM. More recently, initial findings from the Suffolk County mental health 18-year longitudinal study indicated that, relative to healthy controls, there was continued deterioration with age of general verbal ability, VerbF, and executive functioning across the psychotic disorders (Fett et al., 2018). It is therefore likely that interventions aimed at limiting continued deterioration and strengthening cognitive functioning would be of benefit across the lifespan.

2.3.2 How common are cognitive deficits? Impaired cognitive functioning manifests in an estimated 70-75% of individuals diagnosed with schizophrenia (Heinrichs et al., 2013). This estimate has been derived from studies investigating so called “neuropsychologically normal” individuals diagnosed with schizophrenia (e.g., D. N. Allen, Goldstein, & Warnick, 2003; Holthausen et al., 2002; Kremen, Seidman, Faraone, Toomey, & Tsuang, 2000; Palmer et al., 1997) and from meta-analyses quantifying the breadth and strength of deficit when compared to healthy controls (e.g., Dickinson, Ramsey, & Gold, 2007; Heinrichs & Zakzanis, 1998; Schaefer, Giangrande, Weinberger, & Dickinson, 2013).

In one of the earlier studies to explore whether it was possible to be neuropsychologically normal with a diagnosis of schizophrenia, Palmer and colleagues (Palmer et al., 1997) categorised 27.5% of a clinically stable outpatient cohort as neuropsychologically normal. When compared at a cognitive domain level to a healthy control, there was equivalency in deficit scores across seven of eight domains, with the exception of the learning domain, where 23.4% of the patient group were rated as impaired. Further exploring this dichotomy, Kremen and colleagues (Kremen et al., 2000) classified 23% of a schizophrenia patient group as falling within normal cognitive limits. However, in contrast to Palmer et al. (1997), they performed significantly more poorly on measures of executive functioning and perceptual-motor speed compared to healthy controls. This pattern emerged again in a study by Allen, Goldstein, and Warnick (2003), with 19% of a schizophrenia inpatient group classified as neuropsychologically normal, but with evidence of impairments in executive functioning and psychomotor skills when compared to a patient control group. While these patient groups represented individuals with chronic schizophrenia, the same pattern of intact versus deficit performance is evident closer to the first episode of psychosis. Holthausen et al. (2002), for example, reported that 19% of a first episode schizophrenia spectrum cohort met criteria as cognitively intact. Despite having used a more stringent threshold for impairment, neuropsychologically intact participants performed significantly more poorly on measures of perceptual and psychomotor speed and on verbal learning compared to healthy controls. Based on these reports, it would seem that individuals categorised as neuropsychologically (near) normal still manifest areas of cognitive deficit.

Further corroboration of the estimate reported by Heinrichs, Miles, Ammari, and Muharib (2013) can be found in cluster analytic studies examining cognitive profiles in schizophrenia, where approximately 28% of participants are classified as cognitively (near) normal. As shown in Figure 2.2, collective results further delineate a severely impaired group who perform significantly worse than those who present with either moderate levels of deficit or specific areas of deficit (Gilbert et al., 2014; Goldstein, 1990; Goldstein, Allen, & Seaton, 1998; Goldstein & Shemansky, 1995; Heinrichs & Awad, 1993; S. K. Hill, Ragland, Gur, & Raquel, 2002; Hoti et al., 2004; Lewandowski, Sperry, Cohen, & Ongür, 2014).

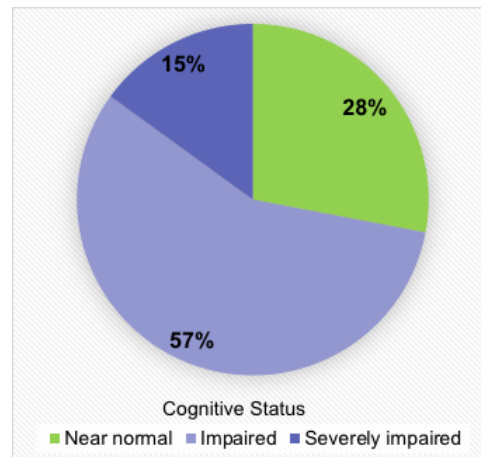


Figure 2.2. Estimated proportion of individuals diagnosed with schizophrenia who experience near normal, impaired, or severely impaired cognitive functioning. Values compiled by MPR from eight cognitive cluster analysis studies: Goldstein (1990), Goldstein, Allen, & Seaton (1998), Goldstein & Shemansky (1995), Heinrichs & Awad (1993), Hill, Ragland, R C Gur, & R E Gur (2002), Hoti, Tuulio-Henriksson, Haukka, Partonen, Holmström, & Lönnqvist (2004), Gilbert, Mérette, Jomphe, Emond, Rouleau, Bouchard... Maziade (2014), Lewandowski, Sperry, Cohen, Öngür (2014). In each study, clusters described as ‘near normal’ or ‘cognitively intact’ ($n = 315$) and clusters described as ‘severely impaired’ or ‘impaired’ ($n = 171$) relative to intermediate group(s) were identified. The number of participants by category was summed then divided by the cumulative sample size ($N = 1,109$).

In summary, there is consistent evidence that a considerable proportion of individuals diagnosed with schizophrenia experience a degree of cognitive impairment. Moreover, even within subgroups classified as neuropsychologically normal or within normal limits, there remains evidence of specific areas of deficit when compared to control groups. When considered in terms of unmet cognitive potential, it is possible that almost all individuals diagnosed with schizophrenia experience a deficit in cognitive functioning (Keefe, Eesley, & Poe, 2005).

2.3.3 Patterns of cognitive deficit. While studies examining neuropsychologically (near) normal subgroups provide a useful dichotomy for quantifying how many individuals diagnosed with schizophrenia manifest cognitive deficits, they reveal little about the pattern of deficit that commonly manifest. Consecutive meta-analyses have reported deficits of varying degree across all

cognitive domains examined, with reported effect sizes³ remaining largely consistent over time (Dickinson et al., 2007; Heinrichs & Zakzanis, 1998; Schaefer et al., 2013). Drawing on data published in the most recent of these, Figure 2.3 presents the pattern of cognitive deficit derived from 100 studies published between 2006 to 2012 (Schaefer et al., 2013). In addition to general intelligence, SoP, Verbl&M and VisL&M (episodic memory), VerbF and attention domains are consistently found to be the most impaired, though effect sizes do vary by measure (Schaefer et al., 2013).

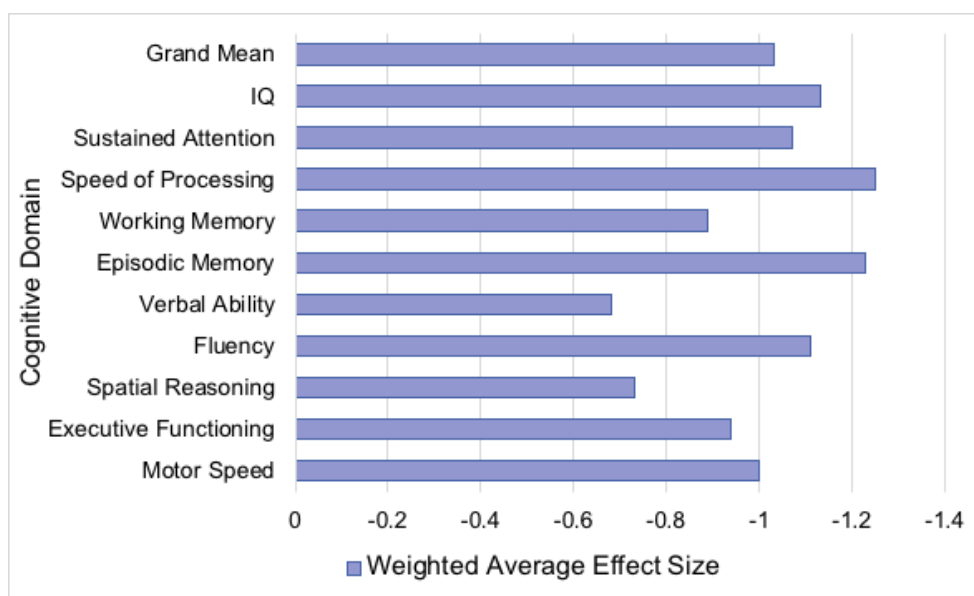


Figure 2.3. Domain level pattern of cognitive deficit in schizophrenia when compared to healthy controls, as represented by the weighted average effect size. IQ = intelligence quotient. Effect size reflects the standardised mean differences between schizophrenia and healthy control performance divided by the pooled standard deviation and adjusted for small sample size bias. Created by MPR based on data from “The Global Cognitive Impairment in Schizophrenia: Consistent Over Decades and Around the World”, by J. Schaefer, E. Giangrande, D. R. Weinberger, and D. Dickinson, 2013, *Schizophrenia Research*, 150, pp. 42-50. Copyright 2013 Elsevier B.V.

Another way of visualising the pattern of cognitive deficits is to examine performance on a standardised cognitive test battery, such as the Measurement and

³ Standardised mean differences between schizophrenia and healthy control performance divided by the pooled standard deviation and adjusted for small sample size bias (Schaefer et al. 2013).

Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB; Kern et al., 2008; Nuechterlein et al., 2008). Developed specifically for use in clinical trials evaluating the efficacy of cognitive enhancing treatments in schizophrenia patient groups (Nuechterlein et al., 2008), the MCCB has been found to be sensitive to the type of cognitive deficits found in schizophrenia and to aspects of functional outcome (August, Kiwanuka, McMahon, & Gold, 2012).

Drawing on data from a recent study that evaluated the psychometric properties of the MCCB across a pooled cohort of 2,616 stable schizophrenia patients, Figure 2.4 presents mean *T*-scores from the initial test session. The patient group's domain level performance averaged 1.5 standard deviations below that of the normative mean, with especially poor performances evident on SoP and the CogComp. The profile mirrors that published by Kern et al. (2011), in which SoP was the most impaired and R-PS the least impaired domain.

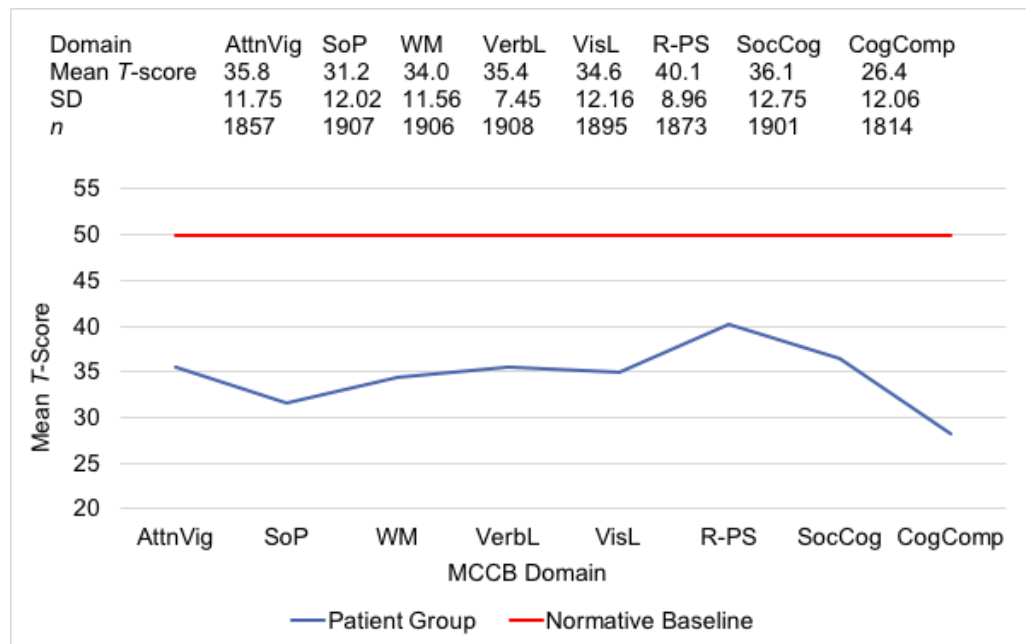


Figure 2.4. MCCB domain level mean *T*-scores from a representative pooled cohort of stable schizophrenia patients. Mean, standard deviation (SD), and the number (*n*) sampled by domain are presented in the top portion of the figure. AttnVig = attention/vigilance; SoP = speed of processing; WM = working memory; VerbL = verbal learning; VisL = visual learning; R-PS = reasoning and problem solving; SocCog = social cognition; CogComp = cognitive composite; MCCB = MATRICS Consensus Cognitive Battery. Created by MPR based on data from “Psychometric characteristics of the MATRICS Consensus Cognitive Battery in a large pooled cohort of stable schizophrenia patients”, by A. Georgiades, V. Davis, A. S. Atkins, A. Khan, T. W. Walker, A. Loebel... and R. S. E. Keefe, 2017, *Schizophrenia Research*, 190, pp. 172.179. Copyright 2017 Elsevier B.V.

2.3.4 Association between cognition and functional outcome. If

cognition is to be targeted with the aim of improving functional outcomes, several things must be true: (1) that there is an association between cognition and functional outcome and (2) that improvements in functioning are associated with improvements in cognition. Additionally, it is important to understand the nature of the relationship between cognition and functional outcome; whether it is direct or indirect, whether it is broadly based or specific to particular cognitive domains, whether it varies by outcome domain.

The association between cognition and functional outcome was made manifest over 20 years ago when, drawing on an emergent body of evidence, Green (1996) reviewed the functional consequences of neurocognitive deficits in schizophrenia. In the review of 16 studies, Green concluded that VerbM and attention/vigilance (AttnVig) in particular appeared essential for adequate functional outcome, i.e. community functioning, social problem solving and skills acquisition. Specific associations are summarised in Table 2.2. Green and colleagues (M. F. Green et al., 2000) later confirmed and extended the initial findings through a systematic and meta-analytic review of 37 studies. Significant associations were reported between functional outcome and VerbM (pooled estimated r [standard error] = 0.29 [0.04] – 0.40 [0.08], $p < .001$, secondary and immediate VerbM respectively), executive functioning (0.23 [0.03], $p < .001$), and AttnVig (0.20 [0.04], $p < .001$) domains. Green et al. (2000) observed that when neurocognitive composites were used, cognition explained between 20% to 60% of the variance in functional outcome. A final review by Green and colleagues (M. F. Green, Kern, et al., 2004) examined 18 longitudinal studies not included in the earlier meta-analysis. Results demonstrated that baseline cognition influenced functional outcome over time, from 6 months to up to 20 years later. A more recent meta-analysis, inclusive of 48 studies published between 1977 and 2009, found further support for the relationship between cognition and functioning (Fett et al., 2011). Adopting the same outcome domains as those used by Green and colleagues, estimated average correlations by cognitive domain ranged from small to medium (Fett et al., 2011); values are presented in Table 2.2.

While these reviews and meta-analyses provide strong evidence of a relationship between cognition and functional outcome, they have several limitations. In each analysis, community functioning was comprised a mix of vocational, social and everyday functioning. It remained unclear whether there was a differential association between specific domains of cognition and, for example, vocational functioning compared to everyday or social functioning. The distinction is important when determining the most appropriate interventions to aid functional recovery (M. F. Green, 1996; Strassnig et al., 2015). Additionally, a large proportion of the variance in functional outcome was left unaccounted for. Thus, on the basis of these studies, it was unclear whether cognitive functioning was the most appropriate

intervention target or whether another as yet unidentified factor would be more instrumental.

Table 2.2

Summary of Review Articles and Meta-Analyses Examining the Relationship Between Cognition and Functional Outcome

Author (Date)	Type	Studies (N)	Community Functioning	Social Problem Solving	Skills Acquisition	Social Behaviour in the Milieu
^a Green (1996)	Review	16	VerbM, R-PS	VerbM, AttnVig	VerbM, AttnVig	
^b Green, Kern, Braff, & Mintz (2000)	Meta- analysis	37	R-PS, VerbM, VerbF, PsyMot	VerbM, AttnVig, R-PS, PsyMot, VisPro	VerbM, R-PS, AttnVig, PsyMot	
Green, Kern & Heaton (2004)	Review	18	Various, not summarised			
^b Fett, Viechtbauer, Dominguez, Penn, van Os, & Krabbendam (2011)	Meta- analysis	48	VerbF: $\mu_p = 0.32$; VerbL&M: $\mu_p = 0.26$; SoP: $\mu_p = 0.25$; CogComp: $\mu_p = 0.25$; WM: $\mu_p = 0.22$; VisL&M: $\mu_p = 0.20$; R-PS: $\mu_p = 0.19$; AttnVig: $\mu_p = 0.16$	R-PS: $\mu_p = 0.29$; VerbL&M: $\mu_p = 0.26$; AttnVig: $\mu_p = 0.25$; WM: $\mu_p = 0.25$	AttnVig: $\mu_p = 0.39$; R-PS: $\mu_p = 0.34$; VisL&M: $\mu_p = 0.28$; VerbComp: $\mu_p = 0.24$; VerbL&M: $\mu_p = 0.18$	VerbL&M: $\mu_p = 0.32$; VisL&M: $\mu_p = 0.30$; R-PS: $\mu_p = 0.23$

Note. Measures of social cognition have been excluded from the summary.

(N) = number; AttnVig = attention/vigilance; CogComp = cognitive composite; PsyMot = psychomotor ability/reaction time; R-PS = reasoning & problem solving; VerbComp = verbal comprehension; VerbF = verbal fluency; VerbL&M = verbal learning & memory; VerbM = verbal memory; VisL&M = visual learning & memory; VisPro = early visual processing; WM = working memory; μ_p = estimated average correlation in the population distribution.

^aCommunity functioning is inclusive of vocational and social functioning; only probable (replicated) findings have been summarised.

^bCommunity functioning is inclusive of vocational, social and everyday functioning.

Greater clarity regarding potential differential patterns of association between cognitive domains and functional outcome domains was provided in a series of innovative studies by Bowie and colleagues (Bowie et al., 2008, 2006). Using confirmatory path analysis, Bowie and colleagues modelled the influence of cognition, symptoms (positive, negative, depressive) and both functional and social capacity across three real-world functioning domains: interpersonal functioning, vocational functioning and everyday activities. Functional and social capacity, which reflect people's current skill level, were examined as possible mediators in the relationship between cognition and functional outcome. Results exposed a complexity of associations between cognition and real-world functioning, with evidence of both direct and indirect—via functional or social capacity—associations that differed at a cognitive and outcome domain level (Bowie et al., 2008, 2006). Attention/working memory, SoP, and executive functioning were either directly or indirectly associated with all outcome domains; VerbM was indirectly associated through functional capacity with vocational functioning and everyday activities (Bowie et al., 2008).

A theoretical model of predictors of real-world functioning emerged from this work and was later tested by the group (see Figure 2.5; Strassnig et al., 2015; refer to Appendix A for permissions). Strassnig et al. (2015) found support for the model across four separate cohorts representing 821 individuals with chronic schizophrenia. Overall, 23% of the variance in interpersonal skills, 28% of the variance in everyday activities, and 19% of the variance in vocational functioning was accounted for (Strassnig et al., 2015). The model and study results are notable for the lack of association between cognition and interpersonal functioning, which has previously been found to be largely independent of neurocognition (Mehta et al., 2013), and for the mediating role of functional capacity. It is possible that a proportion of the variance left unexplained in earlier studies was attributable to functional and social capacity.

Support for the major pathways in Strassnig et al.'s (2015) model was found in an independent, parallel study that used structural equation modelling to explore factors associated with the real-world functioning of people with schizophrenia (Galderisi et al., 2014). Galderisi et al. (2014) considered a wider range of predictors, including social cognition, engagement with services, positive and disorganised symptoms, incentives, and measures of resilience, which collectively

accounted for a greater proportion (54%) of the variance in functioning. However, in contrast to Strassnig et al., the model did not discriminate between outcome domains and thus failed to capture potential differences in association. Despite the wider range of predictors included in the model, neurocognition was the strongest predictor of outcome, acting indirectly through functional capacity, social cognition, service engagement and internalised stigma (Galderisi et al., 2014)

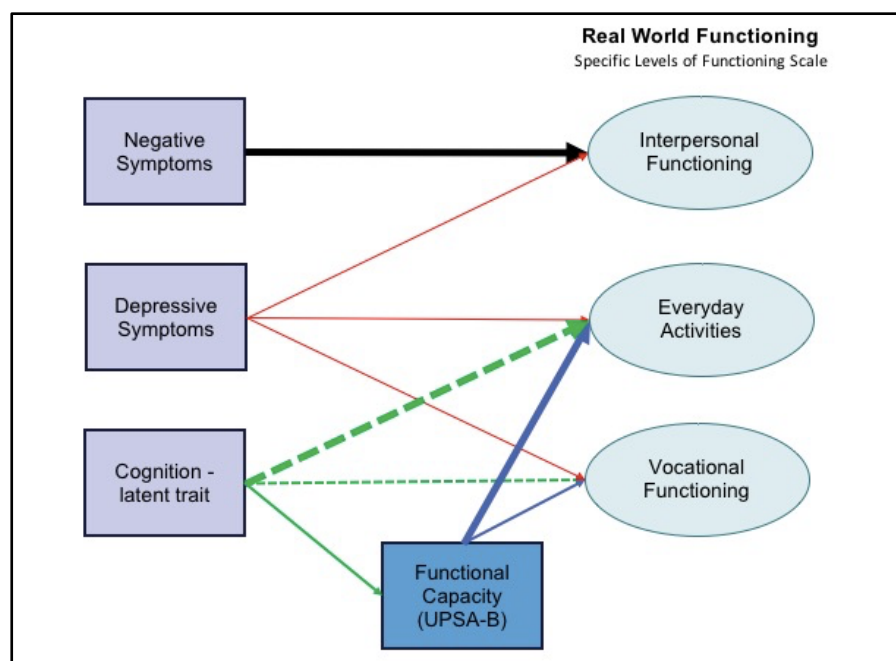


Figure 2.5. Modified version of Strassnig et al.'s (2015) theoretical model of predictors of real-world functioning. Solid lines reflect the theoretical model subsequently validated by confirmatory factor analysis. Thicker lines represent stronger reported correlations; broken lines reflect associations found but not included in the original theoretical model. Differences in line colours is to aid interpretation, e.g., depressive symptom associations are represented by red lines, cognition by green lines etc. UPSA-B = brief version of the UCSD Performance-based Skills Assessment. Adapted from “Determinants of different aspects of everyday outcome in schizophrenia: The roles of negative symptoms, cognition, and functional capacity”, by M. T. Strassnig, T. Raykov, C. O’Gorman, C. R. Bowie, S. Sabbag, D. Durand... and P. D. Harvey, 2015, *Schizophrenia Research*, 165, pp. 76-82, Copyright 2015, with permission from Elsevier.

While the link between cognition and functional outcome has been demonstrated, and differential patterns of association explicated, establishing that improvements in cognitive functioning can bring about concomitant improvements in functional outcome is more complicated. On the one hand, as illustrated nicely by Strassnig et al. (2015) and Galderisi et al. (2014), a large proportion of the variance in functioning that is explained by cognition is indirect; that is, the influence of cognition is mediated by such factors as functional and/or social capacity. On the other hand, the evidence presented thus far suggests that there is a differential pattern of association between specific domains of cognition and specific outcome domains. Studies that evaluate more broadly the association between cognition and functioning may fail to detect these more nuanced relationships. It is also important to acknowledge that functioning is influenced by a range of other internal and external factors, such as motivation, comorbidity, social supports, finances, and range of opportunities, that may attenuate, or enhance, the effects of cognition on outcome (M. F. Green, Kern, et al., 2004). As well, the appropriateness and sensitivity of the tools used to detect and measure change will influence what outcomes are found (Bakkour et al., 2014).

Notwithstanding the aforementioned points, there is evidence of an association between changes in cognition and changes in functional status. In a series of longitudinal studies that examined correlates of functional change in geriatric patients with schizophrenia over 2.5, 4.0 and 6.0 year intervals, cognitive decline was the strongest predictor of decline in functioning (Friedman et al., 2002; Harvey et al., 1999, 2003). Worthy of note, Friedman et al. (2002) observed a lag effect, with the change in cognition approximately 14 months after baseline associated with change in functional status at 48 months. It is possible that a similar lag occurs in response to treatment, with improvements in cognition not immediately evident in measures of functional outcome. A similar pattern of association was also found in a 10-year longitudinal study of a first episode psychosis cohort; decline on two cognitive measures and improvement on a third correlated with poorer and improved outcomes respectively, albeit at a trend level (Stirling, 2003).

When considered across shorter time frames, evidence suggests that cognition and functioning remain relatively stable without specific intervention (Miles et al., 2014). In the absence of effective pharmacological interventions that act to strengthen cognitive processes (Opler, Medalia, Opler, & Stahl, 2014), one

intervention that has gained increased attention over the past two decades is CRT. Evidence of associations between changes in cognition and changes in functioning in response to CRT will be presented in Chapter 3.

2.4 Pulling It All Together

The literature presented thus far paints a bleak picture of the consequences of a diagnosis of schizophrenia. The disorder typically manifests at a pivotal period in the lifespan, as individuals navigate through higher levels of education or into the workforce. For most, the disorder pervades and disrupts all domains in life, from internal states and cognitive processes, to the way in which the world is experienced, to external social and educational/vocational pursuits and everyday living. While periods of symptomatic remission and even recovery is achieved by some, the benefits do not extend to other outcome domains, where the prognosis remains poor.

In the past two decades there has been increased focus on the cognitive deficits that manifest in schizophrenia and that appear more closely associated with functional outcome than symptoms. As awareness of the associations between specific cognitive domains and outcome domains has developed, so too have efforts to improve functional outcomes with specific interventions that target cognition.

Chapter 3. Cognitive Remediation Therapy (CRT)

3.1 Chapter Guide

This chapter introduces to the reader CRT and some of its underlying principles. For brevity, this will not be an exhaustive review of the various CRT interventions; rather, a sense of the heterogeneity of CRT approaches available is provided. Evidence of neurobiological, cognitive-behavioural, and functional change in response to CRT will be presented. Given the large number of randomised controlled trials (RCT) to investigate CRT outcomes (100+ articles), this chapter will again draw on summary data provided in meta-analyses and systematic reviews. Discussion will however be supplemented where appropriate with examples drawn from the literature.

The final section of this chapter is a critical bridge between the contextual information presented thus far, and the primary purpose of this thesis; to arrive at a better understanding of factors that influence individual response to, and the efficacy of, CRT in people diagnosed with schizophrenia. The final section introduces empirical evidence that not everyone realises cognitive benefit from CRT. This realisation, and the clinical implications thereof, was the impetus for this body of work.

3.2 CRT: Origins and Underlying Principles

The early development of interventions targeting cognitive symptoms of psychiatric disorders, such as schizophrenia, has been described by Merzenich, Van Vleet, and Nahum (2014) as following two broad paths: pharmacological and cognitive-behavioural. In terms of pharmacology, the utility of antipsychotic medication in ameliorating cognitive deficits has been shown to be equivocal. Positive effects on cognition are small and possibly due to practice effects (S. K. Hill et al., 2010; Keefe et al., 2007). Moreover, the anticholinergic burden attributable to a range of medications prescribed to individuals with schizophrenia has been found to negatively impact cognitive performance, with poorer cognitive performance in turn associated with reduced engagement in, and benefit from, psychosocial interventions (O'Reilly et al., 2016). While a range of cognitive enhancing pharmacologic interventions have been trialled, none so far have withstood replication (Goff, Hill, & Barch, 2011).

In reference to the cognitive-behavioural path, CRT has emerged as an alternative to pharmacological interventions in the treatment of cognitive impairment in schizophrenia. Various referred to as cognitive rehabilitation, cognitive enhancement, and cognitive training, CRT has been defined as “an intervention targeting cognitive deficit (attention, memory, executive function, social cognition or meta cognition) using scientific principles of learning with the ultimate goal of improving functional outcomes.” (Cognitive Remediation Experts Working [CREW] Group, 2012; as cited in McGurk et al., 2013, p. 134). The CREW Group emphasised that to optimise functional gains, CRT was most effective when provided “in a context (formal or informal) that provides support and opportunity for improving everyday functioning” (2012; as cited in McGurk et al., 2013, p. 134).

3.2.1 Underlying principles: Neuroplasticity. Arising from a long history of research and practice involving the rehabilitation of brain injured patients (e.g., traumatic brain injury, stroke; see Brewer-Mixon & Cullum, 2013 for overview), CRT is underpinned by the science of neuroplasticity (Merzenich et al., 2014). Neuroplasticity refers to the brain’s ability to change in response to external experiences, such that neural networks “alter their structure, function and connectivity” (Kaneko & Keshavan, 2012, p. 126). It has been suggested that alterations in neural plasticity could in part underpin the cognitive deficits found in schizophrenia, with key neuromodulators (acetylcholine, serotonin, and dopamine)

and receptors (*N*-methyl-D-aspartate) associated with synaptic plasticity found to be disordered in schizophrenia (Daskalakis, Christensen, Fitzgerald, & Chen, 2008; Stephan, Friston, & Frith, 2009). According to a pioneer of brain plasticity, Professor Michael Merzenich (2014, p. 7), the dysregulation of underlying brain processes in schizophrenia results in brains that are,

poor signal resolvers, operate sluggishly, struggle to generate sustained activities supporting top-down (working memory, selective attention, associative memory, predictive) processes in prefrontal cortex (Minzenberg et al., 2009), and in frontal, posterior parietal and inferior and medial temporal areas (Heckers, 2001)... and have changes in fundamental neuronal processes that we associate (along with working memory degradation) with very noisy brain system processing (e.g., Hinkley et al., 2011).

The degradation of brain processes extends to lower order sensory processing systems. As summarised in Figure 3.1, deficits in auditory and visual sensory processing contribute to the brain noise by degrading the quality and salience of information fed forward to higher order processes (Javitt, 2009a, 2009b; Vinogradov, Fisher, & de Villers-Sidani, 2012). This in turn undermines the efficiency and functioning of such higher order processes as working memory and long-term memory encoding, as well as the quality of information fed back to lower order systems (Vinogradov et al., 2012).

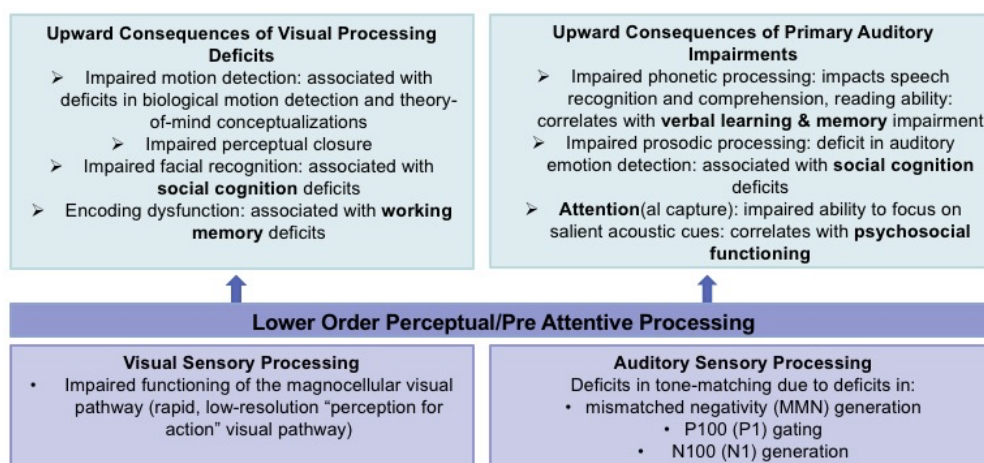


Figure 3.1. Summary of upward consequences of impaired auditory and visual sensory processing. Created by MPR based on text from “When Doors of Perception Close: Bottom up Models of Disrupted Cognition in Schizophrenia”, by D. Javitt, 2009, *Annual Review of Clinical Psychology*, 5, pp. 249-275. Copyright 2009 Annual Reviews.

CRT has been said to drive behavioural and neurobiological change, acting at functional and structural levels of the brain to bring about improvements in cognitive functioning (Fisher, Herman, Stephens, & Vinogradov, 2016; Merzenich et al., 2014). Its effectiveness in doing so will be reviewed in Section 3.4.

3.2.2 Underlying principles: Scientific principles of learning. CRT interventions are, by definition, underpinned by scientific principles of learning. While various models of learning exist (see Tenison, Fincham, & Anderson, 2016), information compiled from imaging studies support there being three key learning stages, characterised by differences in patterns of brain activation and deactivation (Chein & Schneider, 2012; Tenison et al., 2016). As detailed in Figure 3.2, which models stages defined by Chein and Schneider (2012), the first formation stage represents an initial period of task familiarisation, likely only lasting 5-6 task iterations (Tenison et al., 2016). The second stage, controlled execution, represents an extended training period during which stimulus-response associations are strengthened by repeated practice. As task performance reaches an asymptote, or the point where no further gains are realised, task execution becomes automatic. This final stage of learning is characterised by the reorganisation of underlying regions of activity, with reductions in attentional and control processes and increased activation in sensory or motor cortices (Chein & Schneider, 2012; Kelly & Garavan, 2005; Patel, Spreng, & Turner, 2013; Tenison et al., 2016; Vinogradov et al., 2012).

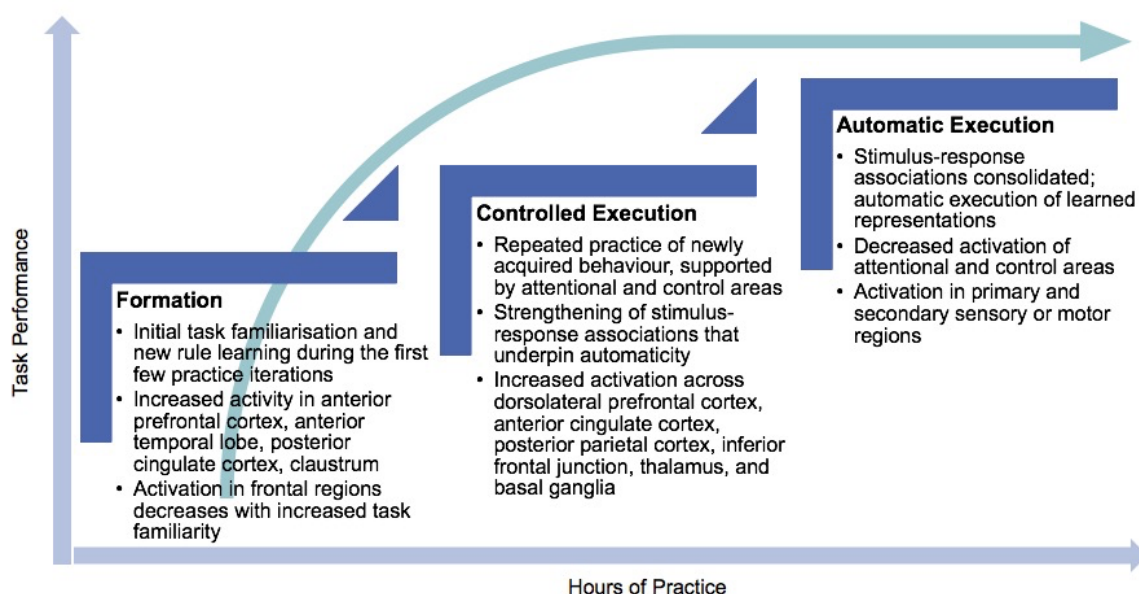


Figure 3.2. Key stages of new task learning with illustrative learning curve reflecting the relationship between hours of practice and task performance. As indicated by the arrow, the initial hours of practice are characterised by rapid task improvement into the controlled execution stage, after which visible gains slow towards an asymptote. The transition to the automatic execution stage is characterised by a functional reorganisation of patterns of brain activation. Created by MPR based on text from “The Brain’s Learning and Control Architecture”, by J. Chein & W. Schneider, 2012, *Current Directions in Psychological Science*, 21, pp. 78-84. Copyright 2012 The Author(s); “Human Functional Neuroimaging of Brain Changes Associated with Practice”, by A. Kelly & H. Garavan, 2005, *Cerebral Cortex*, 15, pp. 1089-1102. Copyright 2005 Oxford University Press; “Cognitive Training for Impaired Neural Systems in Neuropsychiatric Illness”, by S. Vinogradov, M. Fisher, E. de Villers-Sidani, 2012, *Neuropsychopharmacology*, 37, pp. 43-76. Copyright 2012 American College of Neuropsychopharmacology.

While the specific amount of training required to affect the transition from the second to third stage of learning is unclear, a number of neuroplasticity informed factors are thought to optimise the learning process. In their article “Cognitive Training for Impaired Neural Systems in Neuropsychiatric Illness”, Vinogradov, Fisher, and de Villers-Sidani (2012, pp. 61–62) concluded that cognitive training needed to:

- address impaired perceptual and pre-attentive processes in addition to the distributed neural networks of interest, while also facilitating generalisation to real-world settings;
- comprise learning trials that were well-defined, adaptive to the performance level of the individual so as to maintain a high level of success while remaining suitably challenging, and be of sufficient intensity and duration;
- engage selective attention and reward systems in the brain, ensuring active trial-by-trial engagement that was frequently rewarded.

Vinogradov et al. (2012) argued that the varying degree to which interventions addressed such factors might account for some of the reported heterogeneity in the effectiveness of CRT.

3.3 Overview of CRT Approaches

There is a great deal of diversity in approach across CRT interventions. As observed by McGurk et al. (2013), interventions can range from computer-based programs that require minimal, if any, facilitation (e.g., Posit Science's BrainHQ) through to pen and paper interventions that are individualised, facilitator led, and incorporate strategy training to promote generalisation to real-world settings (e.g., CRT; Delahunty & Morice, 1993). Some programs incorporate both cognitive and social cognitive training (e.g., Cognitive Enhancement Therapy; Hogarty & Flesher, 1999), while others include adjunctive rehabilitative therapies such as work (e.g., Thinking Skills for Work; McGurk, Mueser, & Pascaris, 2005) or functional skills training (e.g., Action-Based CR; Bowie, Grossman, Gupta, Holshausen, & Best, 2017). Illustrative of the number of CRT approaches available, 10 different types of intervention were found across the 11 studies included in the most recent CRT meta-analysis, which considered the efficacy of CRT in first episode schizophrenia (Revell, Neill, Harte, Khan, & Drake, 2015). In their broader examination of CRT efficacy in schizophrenia, Wykes et al. (2011) had earlier reported that 14 different interventions had been used across the 40 studies included.

CRT interventions have been delineated across a number of interrelated dichotomies (Medalia & Choi, 2009; Vita, Barlati, Bellani, & Brambilla, 2014). These serve to illustrate the range of CRT approaches available and have been summarised in Table 3.1.

Table 3.1

Overview of Major Dichotomies Used to Delineate CRT Approaches

Dichotomy	Key Features	Reference(s)
Drill & practice	Repeated, titrated practice across core tasks; seeks to capitalise on implicit and procedural memory.	Wykes & Spaulding (2011)
Drill plus strategy	Repeated, titrated practice coupled with explicit strategy training to aid generalisation.	
Restorative	Seeks to repair cognitive deficits using drill & practice techniques.	Medalia & Choi (2009)
Compensatory	Seeks to bypass cognitive deficits by developing alternate cognitive skills and by teaching use of external, environmental supports.	Kaneko & Keshavan (2012)
Broad-based	Training across a range of higher-order cognitive domains; top-down approach.	Fisher et al. (2016)
Targeted training	Neuroplasticity informed, intensive training; bottom-up approach.	Reddy et al. (2014)
Top-down / feed-back	Focused on such higher-order processes as attention, reasoning & problem solving.	Keshavan et al. (2014)
Bottom-up / feed-forward	Focused on sensory and pre-attentive processes.	

Each of these can, in turn, be delivered across a mix of modalities (computer, pen and paper, mixed), formats (group, individual, mixed), type of instruction (facilitated, supervised, unsupervised), as well as duration and intensity of training. Drawing on data reported across three meta-analyses (McGurk, Mueser, Feldman, Wolfe, & Pascaris, 2007; Revell et al., 2015; Wykes et al., 2011), Figure 3.3 provides an indication of the percentage of CRT interventions used by modality, technique, format, and whether adjunctive therapies were included.

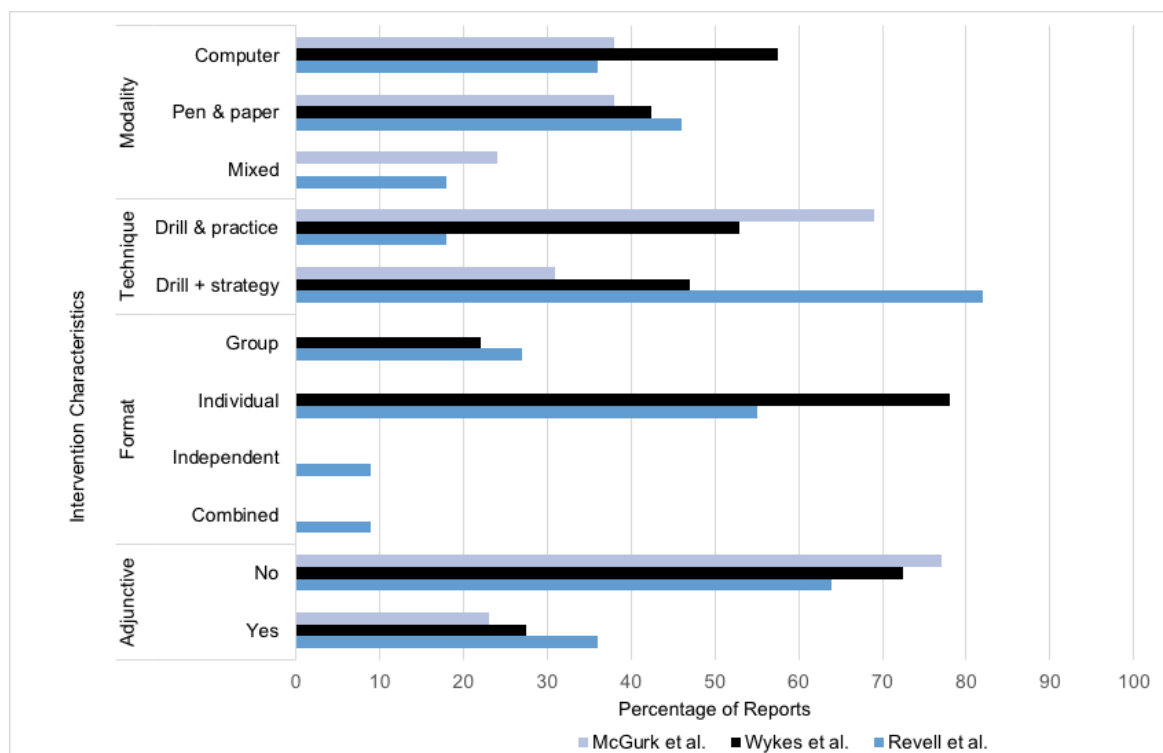


Figure 3.3. Percentage of CRT interventions used in research studies by modality, technique, format, and use of adjunctive therapies. The light purple (top) bar represents data drawn from “A Meta-Analysis of Cognitive Remediation in Schizophrenia”, by S. McGurk, E. Twamley, D. I. Sitzer, G. J. McHugo, and K. T. Mueser, 2007, *The American Journal of Psychiatry*, 164, pp. 1798-1801. Copyright 2007 American Psychiatric Association; this included 26 randomised controlled trials. The black (middle) bar represents data drawn from “A Meta-Analysis of Cognitive Remediation for Schizophrenia: Methodology and Effect Sizes”, by T. Wykes, V. Huddy, C. Cellard, S. R. McGurk, and P. Czobor, 2011, *The American Journal of Psychiatry*, 168, p. 475. Copyright 2011 American Psychiatric Association; this included 40 randomised controlled trials published up to June 2009. The blue (bottom) bar represents data drawn from “A Systematic Review and Meta-Analysis of Cognitive Remediation in Early Schizophrenia”, by E. R. Revell, J. C. Neill, M. Harte, Z. Khan, and R. J. Drake, 2014, *Schizophrenia Research*, 168, p. 217. Copyright 2015 Elsevier B.V.; this included 11 first episode schizophrenia studies.

Note. Computer modality reported by Wykes et al. included combined computer-based activities and other techniques, such as pen and paper activities.

There appears to have been a shift towards combined drill and practice plus strategy training, though whether this is specific to the first episode schizophrenia cohort is unclear. There has also been a gradual increase in the use of adjunctive therapies. Regarding the high percentage of computer-based therapies reported by Wykes et al. (2011), interventions that combined computer-based activities with other techniques were classified as computerised rather than mixed.

Broad-based, top-down CRT approaches tend to be delivered 2-3 times a week, with intervention durations averaging between 20-30 sessions. In contrast, targeted, bottom-up, neuroplasticity informed CRT approaches more typically involve intensive training regimes of 4-5 sessions a week, totalling 30-50 sessions (Fisher, Herman, et al., 2016). With broad-based approaches predominating, CRT trials average 2.2 sessions per week (range = 0.6–5), totalling 32.2 hours of training (range = 4–130) delivered across 16.7 weeks (range = 2–104; Wykes et al., 2011).

Despite the considerable heterogeneity of CRT approaches, intervention characteristics have not been found to account for reported heterogeneity in cognitive response to CRT (Grynszpan et al., 2011; McGurk, Mueser, et al., 2007; Wykes et al., 2011).

3.4 CRT Efficacy: Neurobiological, Cognitive-Behavioural, and Functional Outcomes

Evidence of the effectiveness of CRT in ameliorating cognitive deficits can be found at multiple levels. Neurobiological evidence is likely the strongest, being more proximal to the functional and structural systems that underpin cognitive performance (Rose & Donohoe, 2013). Cognitive-behavioural measures, such as neurocognitive test batteries, would rank next, though with some variability depending on the appropriateness and sensitivity of the tool(s) selected to measure cognitive change (Heinrichs, 2005). Most distal are measures of functional outcome (M. F. Green, Kern, et al., 2004), results of which can be confounded by the range of factors discussed in Section 2.3.4., including the indirect effect of cognition and a potential time lag between cognitive and functional change.

3.4.1 Neurobiological evidence of change. Evidence that CRT can bring about positive changes at functional and structural levels of the brain, and that these are associated with positive behavioural changes, can be found in studies examining the neuro-physiological and -anatomical effects of CRT. Of the former, studies

using neuroimaging techniques to measure cerebral activity following CRT commonly report increased brain activation in prefrontal, occipital, anterior cingulate, and thalamic regions of the brain (Isaac & Januel, 2016; Penadés et al., 2017; Thorsen, Johansson, & Løberg, 2014). Corresponding behavioural improvements, as measured by independent tests of cognition, are frequently reported (Isaac & Januel, 2016). Bor et al. (2011), for example, reported increased frontal and parietal activation in the left inferior/middle frontal gyrus (Broca's area), cingulate gyrus, and inferior parietal lobule/precuneus during a spatial WM task after 28 hours of CRT, an effect not found in the control group. Increased activation in Broca's area correlated with improvements on cognitive measures of AttnVig (Bor et al., 2011). More recently, Ramsay, Nienow, and MacDonald (2017) reported that 48 hours of WM focused CRT increased functional connectivity between the thalamus and prefrontal cortex, with a significant correlation reported between the right middle frontal gyrus and improvement on the MCCB cognitive composite. No significant effect was found on an active control group matched on training time, computer exposure, and facilitator attention (Ramsay et al., 2017).

Support for the association between regions of increased brain activity and post-intervention cognitive change has been found in two recent meta-analyses which, using Activation Likelihood Estimation, were able to identify neural substrates associated with cognitive response to CRT (Ramsay & Macdonald, 2015; Wei et al., 2016). The respective meta-analyses were however limited to a small number of studies ($N = 9$) and limited by heterogeneity across study design, intervention, imaging technique, and analytic approach (Penadés et al., 2017). Further support was found in a systematic review of neural correlates of cognitive improvement following CRT; 11 of the 15 included reports had formally assessed the association, with 10 reporting statistically significant correlations between areas of activation and cognitive change scores (Isaac & Januel, 2016).

Positive changes at a structural level have also been reported. For example, in a 2-year CRT intervention involving a cohort of early course schizophrenia and schizoaffective disorder patients ($N = 53$; average illness duration of 3.22 years, $SD = 2.20$), Eack et al. (2010) reported that, relative to a non-CRT control, CRT participation resulted in both preservation of grey matter in areas implicated in cognitive impairment, specifically medial temporal regions including the left hippocampus, left parahippocampal gyrus, and left fusiform gyrus, and increases in

left amygdala grey matter. Eack et al. further reported that preservation of grey matter in the parahippocampal gyrus and fusiform gyrus was associated with significantly greater improvements in cognitive functioning by treatment end compared to control participants receiving psychoeducation and coping skills training. Structural increases are not limited to those in the early course of illness. Increased white matter integrity, for example, measured using fractional anisotropy maps, was found in the genu of the corpus callosum in patients with chronic schizophrenia (average illness duration of 11.59 years, $SD = 9.79$) after completing a four-month course of CRT (Penadés et al., 2013).

Given that functional and structural brain changes can be identified in patients diagnosed with schizophrenia following CRT, and that those changes have been associated with improvements in behavioural measures of cognitive functioning, highlights two important points: (1) CRT can differentially, when compared to non-CRT interventions, induce a beneficial neuro-plastic response in the brain; and (2) those changes are of sufficient magnitude to drive improvements on measures of cognitive functioning.

3.4.2 Cognitive-behavioural evidence of change. There is a growing body of evidence in support of the positive effects of CRT on cognitive functioning. As summarised in Table 3.2, eight meta-analyses have been conducted since 2001, considering studies published from as early as 1973 through to early 2015 (Grynszpan et al., 2011; Krabbendam & Aleman, 2003; Kurtz, Moberg, Gur, & Gur, 2001; McGurk, Twamley, Sitzler, McHugo, & Mueser, 2007; Pilling et al., 2002; Revell et al., 2015; Twamley, Jeste, & Bellack, 2003; Wykes et al., 2011). The most recent was limited to first-episode schizophrenia cohorts (Revell et al., 2015), while Grynszpan and colleagues (Grynszpan et al., 2011) included only computer-assisted CRT studies. Kurtz, Moberg, R. C. Gur, and R. E. Gur (2001) sought to determine whether CRT could improve performance on the Wisconsin Card Sorting Test (WCST), however the reported effect size was likely over stated as the WCST was used for both cognitive training and measurement purposes. The meta-analysis conducted by Pilling et al. (2002) was the first to limit study inclusion to RCTs. While no positive effect was found on cognition, the overly restrictive selection criteria, which excluded a number of studies later included by Twamley, Jeste, and Bellack (2003), meant it was unlikely to be representative of the field.

Table 3.2

Summary of Meta-Analyses Measuring Cognitive Response to CRT

Author (Year)	Domain	Studies (N)	Participants (N)	Effect Size (<i>d</i>)	95% CI ^a
Kurtz et al. (2001)	R-PS	10	181	0.98	0.80,1.16
Pilling et al. (2002)	Attn	2	87	0.11	-0.31,0.53
	VerbM	4	117	0.14	-0.23,0.50
	VisM	2	48	0.35	-0.46,1.16
Twamley et al. (2003)	GlobalCog	15		0.32	
Krabbendam et al. (2003)	GlobalCog	12	543	0.45	0.26,0.64
McGurk et al. (2007)	GlobalCog	26	1,214	0.41	0.29,0.52
	AttnVig		659	0.41	0.25,0.57
	SoP		655	0.48	0.28,0.69
	WM		428	0.52	0.33,0.72
	VerbL&M ^e		858	0.39	0.20,0.58
	VisL&M ^e		424	0.09	-0.26,0.43
	R-OS		564	0.47	0.30,0.64
Grynszpan et al. (2011) ^b	Non-specific	17		0.38	0.20,0.55
	AttnVig	6		0.29	0.09,0.49
	SoP	9		0.36	0.07,0.65
	WM	8		0.29	0.10,0.47
	VerbL&M ^e	12		0.30	0.03,0.58
	VisL&M ^e	3		-0.09	-1.29,1.11
	R-PS ^d	7		0.48	-0.15,1.10
Wykes et al. (2011)	GlobalCog ^e	38	1,982	0.45	0.31,0.59
	AttnVig	16	901	0.25	0.08,0.42
	SoP ^e	24	1,332	0.26	0.07,0.45
	WM	20	1,029	0.35	0.19,0.51
	VerbL&M	23	1,346	0.41	0.27,0.55
	VisL&M	10	547	0.15	-0.08,0.38
	R-PS ^e	25	1,389	0.57	0.22,0.92

Revell et al. (2015) ^c	GlobalCog		0.13 ^d	-0.04,0.31
	AttnVig	4	0.06	-0.31,0.44
	SoP	7	0.19	-0.01,0.40
	WM	9	0.19	-0.00,0.38
	VerbL&M	9	0.23	0.01,0.46
	VisL&M	9	0.23	-0.10,0.29
	R-PS	7	0.21	-0.03,0.45

Note. CRT = cognitive remediation therapy; *d* = Cohen's *d*; 95% CI = 95% confidence interval; Attn = attention; AttnVig = attention/vigilance; GlobalCog = global cognition; R-PS = reasoning and problem solving; SoP = speed of processing; VerbL&M = verbal learning and memory; VerbM = verbal memory; VisL&M = visual learning and memory; VisM = visual memory; WM = working memory.

^aEffect size confidence intervals that span 0 are not statistically significant. ^bLimited to computer-assisted CRT. ^cLimited to first-episode schizophrenia cohorts. ^d*d* = 0.19, 95% CI [0.00, 0.38] after significant baseline differences were excluded.

^eSignificant heterogeneity of effect reported.

Overall, small-to-medium effect sizes have been reported across all but the VisL&M domain, and with the exception of the first-episode schizophrenia cohort where response appeared attenuated. Heterogeneity of effect was reported across CogComp, SoP, VerbL&M, VisL&M, and R-PS domains (Grynszpan et al., 2011; McGurk, Twamley, et al., 2007; Wykes et al., 2011). However, moderator analysis considering such factors as study methodology (trial quality, randomisation, masking, control group), participant characteristics (age, gender, diagnosis, baseline symptom severity, inpatient/outpatient status), and treatment characteristics (length, weekly frequency, therapy type [drill and practice versus drill and strategy, domain specific versus non-specific], computer-assisted, use of adjunctive therapies) failed to identify the source of the variability.

While the relative consistency of the meta-analytic results supports the veracity of the reported effect sizes, also apparent is the lack of change in effect size since 2003. It has been close to a decade since the efficacy of CRT was quantified; the Wykes et al. (2011) meta-analysis included publications up to June 2009. It

remains to be seen whether the emergence of such innovations as neuroplasticity informed therapy (e.g., auditory training by Posit Science; Fisher, Holland, Merzenich, & Vinogradov, 2009), web-based meta-cognitive CRT (e.g., CIRCuiTS by Reeder et al., 2017), and CRT combined with role-play and simulated activities (e.g., action-based CR; Bowie et al., 2017) has improved the efficacy of CRT.

3.4.3 Functional evidence of change. The overarching goal of CRT is to improve the functional outcomes of individuals diagnosed with schizophrenia. While it is intended to do that by driving change in cognitive performance, as discussed in Section 2.3.4, the path between cognition and real-world outcomes is likely to be as indirect as it is direct.

Evidence that CRT more generally brings about functional improvement can be found in several of the aforementioned meta-analyses. As presented in Table 3.3, small-to-moderate effect sizes have consistently been reported across an increasing number of studies and study participants. Results in first-episode schizophrenia were attenuated (Revell et al., 2015).

Table 3.3

Summary of Meta-Analyses Measuring Functional Response to CRT

Author (Year)	Domain	Studies (N)	Participants (N)	Effect Size (<i>d</i>)	95% CI
Twamley et al. (2003)	Functioning			0.51	
McGurk et al. (2007)	Functioning ^a	11	615	0.35	0.07,0.62
Wykes et al. (2011)	Functioning ^a	19	1,036	0.42	0.22,0.62
Revell et al. (2015)	Functioning	11		0.18	0.01,0.36

Note. CRT = cognitive remediation therapy; *d* = Cohen's *d*, mean weighted effect size; 95% CI = 95% confidence interval.

^aSignificant heterogeneity of effect reported.

Heterogeneity of effect was reported across two studies (McGurk, Twamley, et al., 2007; Wykes et al., 2011). Moderator analysis indicated that this was partly attributable to training approach and adjunctive therapy status. Larger effect sizes were reported in studies that used a drill and practice plus strategy intervention, and that included adjunctive therapies, both of which appear to confer additional benefit

to functional but not cognitive outcomes. In a later review of whether CRT for schizophrenia improved functional outcomes, Medalia and Saperstein (2013) concluded that CRT potentiated the impact of functional skills training, enhancing functional gains.

The direct relationship between CRT, cognitive improvement, and functional improvement has been examined less frequently. Improvement on measures of global functioning has been associated with improvements in WM (Vita et al., 2011) and global cognition (Sánchez et al., 2014) following approximately 48 sessions of CRT, while increased time spent in structured activities was associated with improved executive functioning following a median 28 sessions of CRT (Reeder et al., 2017). The planning aspect of executive functioning was also found to mediate improvements in work quality, though only a small percentage of the variance was explained ($d = 0.08$) after an average 30 sessions of CRT (Wykes et al., 2012). More recently, Bosia et al. (2017) sought to determine how large an improvement in cognition was required to improve daily functioning. Ninety-five participants completed 36 sessions of CRT, combined with standard rehabilitation. Bosia et al. found that the proportion of “normalised” cognitive domain scores, relative to a normal population and excluding participants who were within a normal range at baseline, predicted functional outcome, though it was unclear how many domains had to achieve normalisation to affect this change. Of note, while a diverse range of interventions were used across these studies, each incorporated an element of either social skills training or strategy training to promote the transfer of cognitive gains to real-world settings.

3.5 Efficacious, But Not Everyone Realises Cognitive Benefit

Although evidence regarding the efficacy of CRT in bringing about neurobiological, cognitive, and functional change is encouraging, there are indications that not everyone realises cognitive benefit from CRT. That does not mean that other benefits are not realised, though no one to-date has examined the potential consequences for this subset of participants. However, it calls into question whether sufficient change has occurred in underlying disrupted neural networks to enable improvements in more distal areas of functional capacity and outcome.

Variability of individual response to CRT can be difficult to detect. A majority of RCTs evaluating CRT efficacy restrict their analysis to group-level

comparisons of pre-post cognitive change scores. As a result, potential variability gets masked in tests of statistical significance calculated over group averages (Jacobson, Follette, & Revenstorf, 1984). This point was made by Medalia and Richardson (2005) with an example from one of their own clinics. At a group level, 47 participants improved 0.5 standard deviation on tests of memory. However, closer examination revealed that 13 of the 47 participants realised no improvement; the remaining 34 participants improved 1.0 standard deviation on the memory tests. Only a handful of CRT studies have reported the proportion of participants to realise cognitive benefit from CRT. These are summarised in Table 3.4.

Table. 3.4

Number of Participants to Realise Cognitive Benefit from CRT, as Calculated by Measures of Reliable Change or Proxy Thereof

Author (Year)	Intervention	No. Sessions	Reliable Change Method	CRT Participants N	Improved n (%)	Not Improved n (%)
Wykes et al. (1999)	CRT (D&M) ^a	40 planned	Index = change score/std error of sample's b/line; if $\geq 50\%$ of within category tests improved by at least one std error of whole sample's b/line, categorised as improved	17	10.7 ^g (63%)	6.3 (37%)
Medalia et al. (2001)	NEAR ^b	10	J&T; 95% CI; change in at least one domain meeting threshold	36	18 (50%)	18 (50%)
Choi et al. (2005)	NEAR ^b	26	J&T; 95% CI; change in at least one domain meeting threshold	55	22 (40%)	33 (60%)
Medalia et al. (2005)	NEAR ^b	20	J&T; 95% CI; change in at least one domain meeting threshold	26	18 (69%)	8 (31%)
Penadés et al. (2006)	CRT (D&M) ^a	40 planned	Chelune adjusted J&T; 90% CI; change in at least one domain meeting threshold; adjusted for practice effects	16	14 ^h (87.5%)	2 (12.5%)
Hodge et al. (2010)	NEAR ^b	20 – 30 planned	J&T; 68% CI; change in at least one domain meeting threshold	40	15 (37.5%)	25 (62.5%)
Vita et al. (2013)	IPT/CACR ^c	42 (ave.)	Global cognitive change $\geq z = 0.5$	52	24 (46%)	28 (54%)
Lindenmayer et al. (2017)	COGPACK ^d MRIGE ^e BrainHQ ^f aud.	36 (approx.)	J&T; 95% CI; change in at least one domain meeting threshold; maintenance across other domains	137	86 (62.8%)	51 (37.2%)
Bryce et al. (2018)	COGPACK ^d	13 (ave.)	J&T; 90% CI; change in at least one domain meeting threshold; adjusted for practice effects	22	17 (77%)	5 (23%)
Reser et al. (unpublished)	BrainHQ ^f vis.	24	Chelune adjusted J&T; 95% CI; change in at least one domain meeting threshold; maintenance across other domains; adjusted for practice effects	22	12 (55%)	10 (45%)
Total:				423	237	186
Percentage of Total:					(56%)	(44%)

Note. Std = standard; b/line = baseline; J&T = Jacobson and Truax (1991) reliable change calculation (calculated by deducting a participant's baseline score (T_1) from their post-intervention score (T_2), which derives a change score, and then dividing that value by the standard error of the difference (S_{diff})); 95% CI = 95% confidence interval; Chelune adjusted J&T = Chelune et al. (1993) modification of J&T calculation to account for practice effects.

^aCRT by Delahunty and Morice (1993); ^bNEAR = Neuropsychological Educational Approach to Remediation; ^cIPT/CACR = Integrated Psychological Therapy/COGPACK; ^dCOGPACK by Marker Software®; ^eMRIGE = Mind Reader: An Interactive Guide to Emotions; ^fBrainHQ by Posit Science: aud. = auditory program, vis. = visual program; ^gbased on cognitive flexibility tasks, where 63% of CRT participants were reported to have improved on at least 3 of 6 tests; ^hdata was presented by cognitive domain; we reported the highest domain level result, being executive function where 14 of 16 participants realised reliable change.

A majority of the studies in Table 3.4 used Jacobson and Truax's (1991) reliable change index (RCI) to determine whether CRT had resulted in cognitive improvement. RCIs are calculated at an individual level and provide a measure of whether clinically meaningful change has occurred (Jacobson & Truax, 1991). Details of the calculation are provided in Methods Section 6.13.1.

An overall estimate based on the studies listed in Table 3.4 suggests that around 40-50% of participants fail to realise cognitive benefit from CRT. That estimate is itself based on a low threshold. To be categorised as improved, most studies (9 of 10) only required that reliable change be realised on a single cognitive domain; only two studies required that performance levels be maintained across other cognitive domains. The actual number of improved domains is rarely reported. In our own study, only 4 of 12 (33.3%) improved participants realised reliable change on more than one cognitive domain (see Chapter 7). In their evaluation of whether size or breadth of cognitive response to CRT mattered, Bosia et al. (2017) reported that, of the participants categorised as normalised on at least one cognitive domain (56.5%), half normalised on only a single domain.

Although there is strong evidence in support of CRT, individual variability of response impacts its overall efficacy. Moreover, without understanding the sources of variability, or factors that might optimise individual response, the effectiveness of CRT in clinical practice is undermined. In Chapter 4 the evidence base is reconsidered in an effort to identify potential predictors of cognitive response to CRT.

Chapter 4. Factors That Influence the Efficacy of CRT: Systematic Review of Literature

4.1 Chapter Guide

Reser, M. P., Slikboer, R., & Rossell, S. L. (in submission). Factors that influence the efficacy of cognitive remediation therapy in schizophrenia: Systematic review of literature.

This chapter comprises the aforementioned article, currently in submission. It represents a synthesis of empirical research to examine factors that influence the efficacy of CRT. It has as its focus predictors of cognitive response to CRT. To ensure, as much as is possible, that reported associations are attributable to cognitive training, interventions that contained social cognition training and/or adjunctive rehabilitative therapies were excluded.

This systematic review informed the selection of variables examined in the empirical research presented in Chapters 7 and 8. Following the article, in Section 4.9, further detail is provided regarding those variables of interest.

4.2 Abstract

Objective: Cognitive remediation therapy (CRT) is a moderately effective intervention for ameliorating cognitive deficits in individuals with schizophrenia-related disorders. With reports of considerable variability in individual response to CRT, we need to better understand factors that influence CRT efficacy to realise its potential. A systematic review was conducted to identify and evaluate predictors of cognitive outcome.

Method: An electronic database search was conducted identifying peer-reviewed articles examining predictors of cognitive response to CRT.

Results: Forty articles accounting for 1,681 CRT participants were included. Eighty-one distinct predictors of cognitive response were identified. Data synthesis and discussion focused on 20 predictors examined a minimum 3 times in different studies. Few of the examined predictors of cognitive outcome following CRT were significant when examined through systematic review. A strong trend was found for baseline cognition, with reasoning and problem solving and working memory being strongly predictive of within-domain improvement. Training task improvement was the most notable cross-domain predictor of cognitive outcome.

Conclusion: It remains unclear why a large proportion of participants fail to realise cognitive benefit from CRT. There is a need to consolidate investigation of potential predictors of response to CRT, strengthening the evidence base through replication and collaboration.

4.3 Introduction

Impaired cognitive functioning is a core aspect of schizophrenia experienced by around 75% of those so diagnosed (Heinrichs et al., 2013). Cognitive deficits manifest across a broad range of domains (Schaefer et al., 2013) and have been associated with poorer functional outcomes in such areas as vocational and educational pursuits, independent living, and community and social relations (Bowie et al., 2008; Fett et al., 2011; M. F. Green, 1996; Strassnig et al., 2015). In the absence of approved pharmacotherapies targeting cognitive deficits, (Opler et al., 2014) there has been an acceleration of research investigating the efficacy of cognitive remediation therapy (CRT) in ameliorating cognitive deficits with the aim of improving functional outcomes. Meta-analyses quantifying the efficacy of CRT have reported small to moderate effect sizes, but have been unable to account for the heterogeneity detected across multiple cognitive domains (Grynszpan et al., 2011; $d=0.38$; McGurk, Twamley, et al., 2007; $d=0.41$; Revell et al., 2015; $d=0.13$; Wykes et al., 2011; $d=0.45$).

Available evidence regarding rates of reliable change following CRT indicate that approximately 44%⁴ of participants fail to realise a cognitive benefit (Bryce et al., 2018; J. Choi & Medalia, 2005; Hodge et al., 2010; Lindenmayer et al., 2017; Medalia et al., 2001; Medalia & Richardson, 2005; Penadés et al., 2006; Vita et al., 2013; Wykes et al., 1999). Such variability in response has the potential to undermine the effectiveness of CRT in real-world settings. To enable a more nuanced matching of individual needs and capacity for change to the most appropriate CRT tool, there is a need to better understand the factors that influence individual response to, and in turn the efficacy of, CRT (Vinogradov et al., 2012).

Efforts to identify factors that influence the efficacy of CRT have had limited success. McGurk et al. (2007; 26 studies; 1,151 participants), Grynszpan et al. (2011; 16 studies; 805 participants), and Wykes et al. (2011; 40 studies; 2,104 participants) each examined potential moderators of cognitive outcome in their respective meta-analyses. Collectively, neither key methodological, participant, or treatment effects were found. McGurk et al. found that increased training hours and treatment approach

⁴ Based on data obtained from the 9 referenced studies where either a reliable change index (i.e., Jacobson & Truax, 1991, or variant thereof; $n=7$) or proxy measure of change ($n=2$) was calculated over measure(s) of cognitive response to CRT. Across these studies we summed the number of individuals classified as not improved and divided this by the total number of participants who engaged in CRT.

(i.e., use of drill and practice) appeared to confer a greater benefit in the verbal learning and memory domain. Wykes et al. found that lower baseline psychotic symptoms influenced outcome, though poorer clinical presentation did not prevent improvements in global cognition. In their narrower examination of first episode psychosis, Revell et al. (2015; 11 studies; 615 participants) found that greater improvements in global cognition were realised in studies where more than 66% of participants were male. However, the primary objective of these meta-analyses was to evaluate the efficacy of CRT. Moderator analysis was undertaken to examine between-study variability only where heterogeneity was detected and did not consider the range of variables that have been investigated in the wider literature. In the absence of participant data, these meta-analyses failed to account for differential responses within respective study cohorts and excluded potentially rich sources of data in the form of single arm trials and secondary analyses exploring predictors of outcome.

Review articles are free from these constraints, and several have touched on the purported predictors and moderators of cognitive response to CRT (Cellard et al., 2011; Kaneko & Keshavan, 2012; Keshavan et al., 2014; Kurtz, 2012; McGurk et al., 2013; Wykes & Spaulding, 2011). Common themes to emerge include participant age, symptom stability, baseline cognition, motivation and genetic influence.

To our knowledge, no systematic review of the CRT evidence base has been conducted. With an acceleration of secondary predictor analysis over the last five years, there is no current, comprehensive synthesis of the literature that can be used to inform clinical decision-making or to guide future research in this important field.

4.4 Aims of the Study

With a focus on cognitive response to CRT in individuals diagnosed with schizophrenia, we aimed to (a) provide a systematic review of the predictor literature, (b) bring the field up-to-date by considering publications up to and including September 2017, and to (c) evaluate the strength of the evidence at a predictor level. We considered moderators, mediators and predictors [significant main effect] of cognitive outcome (Kraemer, 2016; MacKinnon, 2011) and, where examined, factors that differentiated subgroups of responders compared to non-responders. These are all factors that influence individual response to, and therefore the efficacy of, CRT and are collectively referred to as “predictors” of response or cognitive outcome. We limited the scope of the review to studies where CRT was the sole intervention, excluding those

that incorporated such adjunctive therapies as social cognition/skills training and vocational rehabilitation.

4.5 Methodology

4.5.1 Search strategy. Methods of the analysis and inclusion criteria were informed by PRISMA (Liberati et al., 2009) and registered with PROSPERO (<https://www.crd.york.ac.uk/prospero/> CRD42016037400). Studies were identified through electronic database searches and by examining reference lists of published meta-analyses and review articles. Search terms “cognitive training” OR “cognitive remediation” OR “cognitive rehabilitation” OR “cognitive enhancement” AND “schizophrenia” AND “predictor*” OR “mediator*” OR “moderator*” were applied to Scopus, Web of Science and PsycINFO databases and Cochrane Collaboration Controlled Trials Register for all years until 30/09/2017. As the examination of predictor variables is often exploratory and not directly referred to in article titles and abstracts, we also hand searched articles that had been identified in preparation for another manuscript using search terms “cognitive training” OR “cognitive remediation” OR “cognitive rehabilitation” OR “cognitive enhancement” AND “schizophrenia” AND “randomized” OR “clinical trial” OR “randomly assigned” for the period 2009 to 30/09/2017 across the abovementioned databases. Finally, articles comprising the most recent meta-analyses (Grynszpan et al., 2011; Revell et al., 2015; Wykes et al., 2011) were manually reviewed for evidence of covariate and/or post-hoc analysis.

4.5.2 Study selection. Search outputs were collated in spreadsheet format. Duplicates were removed, and articles not published in English excluded. Eligibility assessment was performed independently in an unblinded standardised manner by two reviewers, MPR and RS. Inclusion criteria were: 1. Peer-reviewed article; 2. Randomised controlled trial (RCT), or single arm trial, or retrospective review of such; 3. Majority ($\geq 70\%$) participants diagnosed with schizophrenia / schizoaffective disorder; 4. Inclusion of CRT treatment arm as defined by the Cognitive Remediation Expert Working Group, 2012 (McGurk et al., 2013); 5. At least one pre- post-intervention measure of cognition that was independent of the cognitive training tasks; 6. Analysis of at least one predictor/determinate of cognitive outcome. Studies that included social cognition/skills training and/or parallel rehabilitation activities (i.e., not treatment as usual activities outside of study control), such that the specific effects of each could not be distinguished, were excluded. Initial screening focused on article

titles and abstracts; for the remaining records, full articles were considered. Review results were coded, cross-tabulated, with disagreements resolved by consensus and/or consultation with a third party.

4.5.3 Data extraction and analysis. The first author extracted resultant study data into a spreadsheet template. Data included participant characteristics for CRT trial arm, study and intervention details, predictor and outcome measures, statistical methods and summary of pertinent results. Predictor summary information was collated by category (i.e., demographics, clinical presentation, baseline cognition, etc.). If an article reported both post-intervention and follow-up data, post-intervention results informed our discussion.

A meta-analysis was not conducted for two reasons. First, we combined data obtained from multiple study designs, including RCTs, randomised trials with multiple treatment arms and no control, quasi-RCTs, single arm trials, retrospective studies that included only the treatment arm or that combined single arm trial results with treatment arm results. Second, for a majority of included predictors, we had insufficient data to support subgroup or meta-regression analysis within a meta-analytic framework. To enhance the otherwise narrative review, a box-score analysis of predictor variables was conducted (B. F. Green & Hall, 1984). To complete the box-score analysis, for each article, a list of predictor variables and cognitive outcome domains was compiled. At a summary level, if a predictor was statistically significantly associated with any of the cognitive outcome domains examined, it was coded as ‘+’ to denote positive associations or ‘-’ to denote negative associations (no mixed associations were found). If no statistically significant associations were found, be that using correlations, analysis of covariance, regression, or modelling techniques, it was coded as ‘0’. If multiple analytic techniques were used, for example, correlations followed by regression, results from the final confirmatory analysis were reported. This process was repeated at a cognitive domain level. Predictor variables have been grouped by category to aid interpretation. Summary scores have been reported according to whether analysis was conducted at a Total Sample or CRT Subgroup level. These are mutually exclusive categories that when summed reflect the total number of articles to examine the predictor variable. To determine whether significant predictor by cognitive domain associations were only present if statistically significant change had been realised following CRT, results at the cognitive domain level were **bolded** if significant change was reported within the domain.

To further increase the rigor of the review, the strength of the predictor evidence was assessed by the first author. Criteria developed specifically to assess moderators within systematic reviews of randomised controlled trials, and endorsed by a consensus group of 21 international experts (Pincus et al., 2011), were applied. Where a criterion was not applicable, for example conducting assessments prior to randomisation in single arm trials, the overall rating was adjusted accordingly. Consideration was given to whether (a) a priori hypothesis framed the research; (b) the research was theory driven or evidence based; (c) predictor variables were measured pre-randomisation; (d) measures were valid; and (e) there was a direct test of interaction.

Consideration of the methodological issues associated with systematic reviews and subgroup analysis encouraged caution regarding interpretation of the results and conclusions drawn (Bender et al., 2008; Lagakos, 2006).

4.6 Results

Forty articles, considering 2,652 study participants, of whom 1,681 received CRT, were included in the final review. Figure 4.1 presents the flow of studies through the selection process. Two articles were combined due to examination of the same predictors at different time-points (J. Choi, Fiszdon, & Medalia, 2010; J. Choi & Medalia, 2010), as were another two articles due to them being different treatment arms on the same study examining the same covariates (Medalia, Revheim, & Casey, 2000; Medalia et al., 2001). Sixteen articles involved secondary analysis of either one (12 articles) or multiple (4 articles) trials, resulting in some overlap of study cohorts. An additional two were follow-up extensions of Fisher et al. (2009; Fisher, Holland, Subramaniam, & Vinogradov, 2010; Fisher, Mellon, Wolkowitz, & Vinogradov, 2016). With such secondary analysis encouraged (Furberg & Friedman, 2012), overlapping study cohorts were included where distinct predictors were examined. Where a cohort/predictor overlapped, it was included once in the box-score analysis and subsequent discussion. This occurred on four occasions—Fisher et al. (2015) and Bigianti et al. (2016) who were examining task engagement/progression; Wykes et al. (2007) and Greenwood et al. (2011) examining medication type; Twamley, Burton, and Vella (2011) and Burton et al. (2015) examining premorbid IQ and ethnicity; Reeder et al. (2017) and Cella and Wykes (2017) who both examined the average number of tasks completed per session—with consistency of reported associations. Also excluded from graphic and narrative summaries was Medalia et al.'s (2005) examination of baseline

symptoms, due to contradictory reporting, and Penadés et al.'s (2016) examination of baseline symptoms, due to lack of clarity around which subscales were used. On both occasions no association was found with cognitive outcomes. Other predictor variables examined by these authors were included.

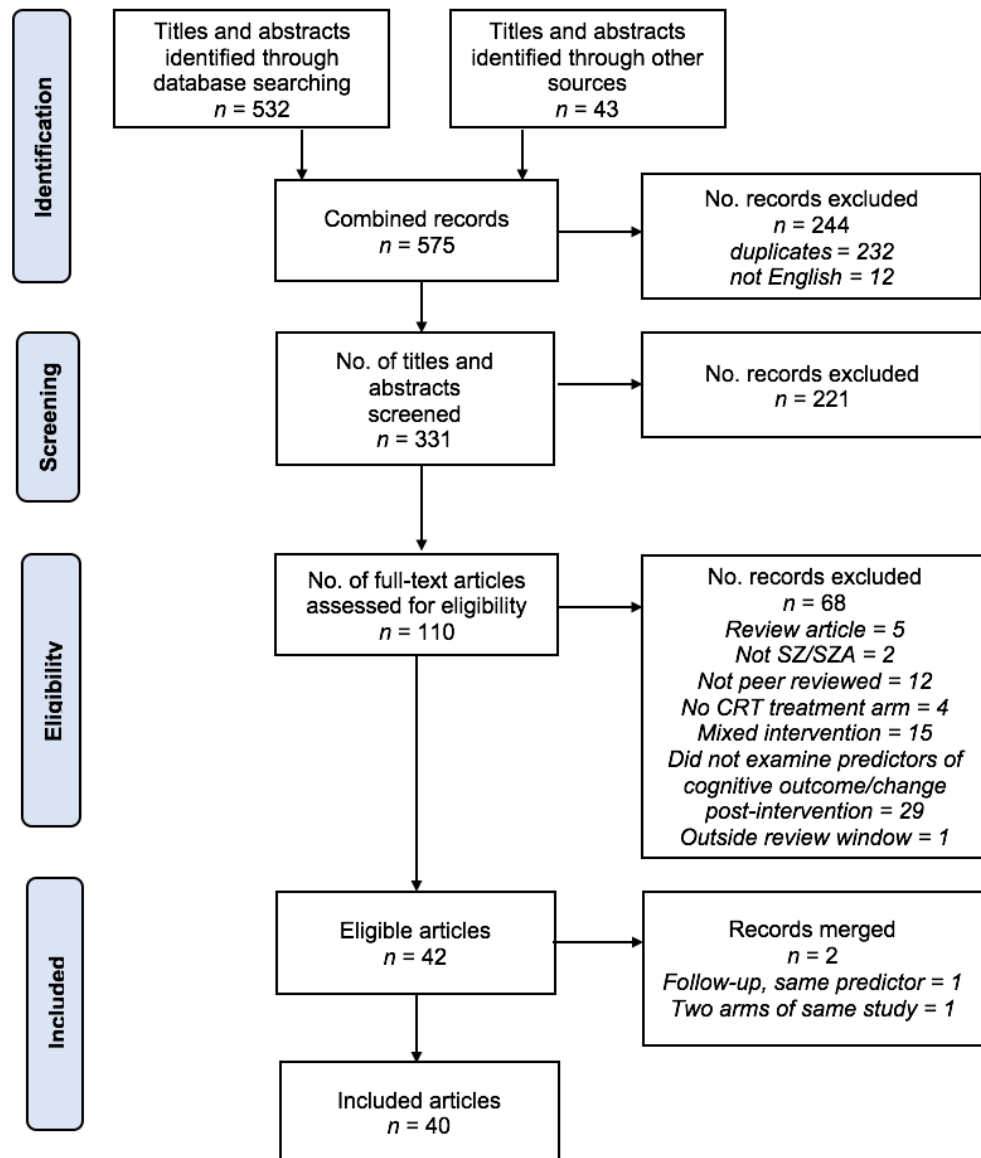


Figure 4.1. PRISMA flow diagram of article selection process. No. = number; CRT = cognitive remediation therapy; SZ = schizophrenia; SZA = schizoaffective disorder.

4.6.1 Study characteristics. A summary of participant and treatment characteristics for the CRT arm of included articles is provided in Table 4.1. Participant characteristics were similar to those reported in the Wykes et al. (2011, p. 474) meta-

analysis, being individuals aged in their mid-thirties, majority males, with approximately 12 years of education. CRT trial arm size averaged 43 participants (range=10-131). Fifteen different core treatment/training programs were considered: 8 articles used Posit Science's auditory/visual training, 7 articles Delahunty and Morice's (1993) cognitive remediation therapy, 5 articles CogPack (and once in combination with another treatment), 3 articles each NEAR and Compensatory Cognitive Training, and 2 articles each REPYFLEC and CIRCuiTS. CogRehab was used alone once and in combination twice.

Computer-based programs predominated, and a majority of the programs were facilitator led across a mix of group and individual formats. Treatment programs varied in duration and intensity; treatment sessions ranged from 25 to 120 minutes and were delivered 1 to 5 times a week. Appendix B provides at the article level, participant characteristics, active and control treatment details, a full list of predictor variables and a summary of cognitive outcome domains. Appendix C details statistical methodology and pertinent variable level results.

Table 4.1

Summary Characteristics of Included Articles for CRT Trial Arm

Measure	Articles ^a <i>N</i>	Mean (<i>SD</i>) / %	Range
Participant Characteristics			
Age (years)	36	37.01 (11.07)	18.8 – 48.0
Male	38	68.47%	46.34 – 92.0
Years of Education	28	12.10 (2.68)	9.3 – 13.50
Estimated Current IQ	14	93.55 (14.65)	84.23 – 103.55
Years of Illness	18	12.61 (11.09)	1.57 – 24.30
Chlorpromazine equiv. (mg/day baseline)	15	392.01 (336.59)	270.65 – 698.55
Treatment Characteristics^b			
Modality	40		
- computer		65%	
- pen & paper		33%	
- mix		3%	
Technique	40		
- drill & practice		43%	
- drill & practice + strategy		45%	
- strategy		5%	
- compensatory		7%	
Format	33		
- group		48%	
- individual		35%	
Instruction	36		
- facilitated		68%	
- supervised		20%	
- unsupervised		3%	
Intensity (planned) ^c			
- total hours	39	36.27	4.16 – 100
- total weeks	39	12.31	4 – 52
- intensity (hrs/wks)	39	2.95	0.83 – 5.0
Attrition (%)	26	17.52%	9.3% – 39.47%
Control Type	40		
Active		33%	
Social skills training		3%	
Treatment as usual		40%	
Subgroup secondary analysis		25%	

Note. Equiv. = equivalent; Mg = milligrams; Hrs = hours; Wks = weeks.

^aCount of articles that provided sufficient data to include in calculation. ^bPercentage calculations based on 40 articles; some values do not total 100 due to data not being available. ^c21 studies reported actual rates however, as these differed in metrics used (mean/median, sessions/hours), it was not possible to calculate representative actuals.

4.6.2 Predictor characteristics. Twenty-nine articles declared an intention to examine at least one predictor of response (Table 4.2). Of these, seven examined the influence of COMT polymorphisms on cognitive outcome, six with a specific focus on single nucleotide polymorphism rs4680. Three articles planned examination of a broad range of predictors of response. Four looked more specifically at whether treatment task engagement/progress predicted response, though only three were included in predictor summary tables due to the aforementioned overlapping predictor/cohort. Two articles each examined the influence of symptoms, age, cognitive insight and training dose. Single articles examined the influence of anticholinergic burden, correlates with cortical thickness, intrinsic motivation, serum BDNF levels, early versus later course of illness, and specific versus general cognitive training. The remaining articles conducted co-variate or post-hoc predictor analysis, at times incorporating the above-mentioned predictors.

Table 4.2

Author List with Corresponding Predictor Focus and Count of Predictors and Cognitive Domains Examined

Author (year)	Planned^a analysis?	Focus	Sample N (CRT)	Pred. N	Cog. Dom. N
Ahmed et al. (2015)	No		78 (42)	5	7
Bark et al. (2003)	Yes	Symptoms	54 (36)	8	2
Benoit et al. (2016)	Yes	Cognitive insight	20 (20)	3	7
Biagianti et al. (2016)	Yes	Task progress	131 (131)	3	6
Bosia et al. (2007)	Yes	COMT rs4680	50 (27)	1	6
Bosia, Bechi et al. (2014)	Yes	COMT rs4680, 5-HT1A	86 (86)	11	1
Bosia, Zanoletti et al. (2014)	Yes	COMT rs4680, antipsychotic type	98 (98)	4	6
Bowie et al. (2014)	Yes	Early vs later course illness	39 (39)	2	7
Burton et al. (2015)	Yes	COMT rs4680	41 (20)	3	4
Burton et al. (2011)	Yes	Cognitive insight, clinical insight	69 (23)	2	7
Buonocore et al. (2017)	Yes	Training dose	98 (98)	1	6
Cella & Wykes (2017)	Yes	Therapy characteristics	38 (38)	6	2
Choi and Medalia (2010)/ Choi et al. (2010)	Yes	Intrinsic motivation	72 (57)	5	2
Dickinson et al. (2010)	No		62 (34)	1	6
Farreny et al. (2016)	Yes	Various	62 (29)	16	1
Farreny et al. (2013)	Yes	Negative symptoms	62 (29)	2	1
Fisher et al. (2009)	Yes	Task progress	55 (29)	1	9
Fisher et al. (2010)	Yes	Training dose	32 (22)	1	6
Fisher et al. (2015)	Yes	Reward anticipation, task progress	86 (43)	2	2
Fisher et al. (2016)	Yes	Serum BDNF level	87 (46)	1	8
Fiszdon et al. (2016)	Yes	Task progress	75 (50)	3	7
Franck et al. (2013)	Yes	Specific vs general training	138 (92)	3	1
Gomar et al. (2015)	No		130 (43)	2	2
Greenwood et al. (2011)	Yes	COMT rs4680	87 (61)	2	2
Haut et al. (2010)	No		30 (10)	11	2
Kontis et al. (2013)	Yes	Age, cognitive reserve	134 (85)	6	3
Kurtz et al. (2007)	No		42 (23)	5	1
Lopez-Luengo et al. (2003)	No		24 (13)	6	3
Mak et al. (2013)	Yes	COMT rs4680	81 (41)	2	2
Medalia et al. (2000, 2001)	No		54 (36)	2	3
Medalia et al. (2005)	Yes	Various	36 (36)	17	2
Panizzutti et al. (2013)	Yes	COMT	48 (48)	6	1
Penadés et al. (2016)	Yes	Cortical thickness	35 (17)	12	5
Reeder et al. (2017)	No		93 (46)	4	4
Twamley et al. (2011)	Yes	Various	33 (23)	18	3
Vinogradov et al. (2009)	Yes	Anticholinergic burden	49 (25)	4	9
Wykes et al. (1999)	No		33 (17)	8	3
Wykes, Reeder et al. (2007)	No		85 (43)	1	3
Wykes, Newton et al. (2007)	No		40 (21)	1	3
Wykes et al. (2009)	Yes	Age	85 (43)	1	3

Note. Pred. = predictors; Cog. Dom. = cognitive domains.

^aReference made in article title, abstract, introduction and/or study aims.

An average of 4.8 predictor variables (range=1-18) were considered across an average 3.95 cognitive domains per article (range=1-9). Nine articles (Bark et al., 2003; Farreny et al., 2016; Haut et al., 2010; Kurtz et al., 2007; López-Luengo & Vázquez, 2003; Medalia & Richardson, 2005; Penadés et al., 2016; Twamley et al., 2011; Wykes et al., 1999), using a mix of correlational, analysis of (co)variance and regression techniques, had less than 5 participants per predictor. Overall, 81 distinct predictors of cognitive response were identified; 24 clinical, 12 each baseline cognition and treatment characteristics, 10 participant characteristics, 8 genetic, 7 demographic details, 5 subgroup (e.g., younger vs older age group), 2 baseline functioning and 1 cortical. Fifty predictors were analysed once and 11 were analysed twice. Our discussion focuses on the 20 (25%) predictors that were examined a minimum three times in different studies, with age group considered alongside the continuous variable “age”. Information regarding predictors examined less than three times is available in Supplementary Figure D4 (Appendix D).

There was little consistent evidence regarding associations between predictor variables and cognitive outcome measures (see Figure 4.2 and Table 4.3). Of the articles that examined the influence of ethnicity, sex, diagnosis (schizophrenia versus schizoaffective disorder), antipsychotic dose, and number of hospitalisations there were no associations found. The opposite was true for training task improvement and age group, where each article reported significant associations. The prognostic value of the balance of the predictors varied in strength. The influence of age on cognitive outcome was the most frequently examined association (17 studies). Of the predictor category groupings, the strongest trends towards an association were found in specific baseline cognitive domains, with reasoning and problem solving (R-PS; five positive associations) and working memory (WM; two out of three associations were positive) domains being more strongly predictive of within domain improvements, and in premorbid IQ. Training task improvement was the most notable cross-domain predictor of cognitive outcome. As shown in Table 4.3, there does not appear to be a direct correspondence between whether statistically significant cognitive change was realised and the prognostic value of examined predictors of response. Statistically significant change at a cognitive domain level (bolded values) did not result in only significant associations (+ or -).

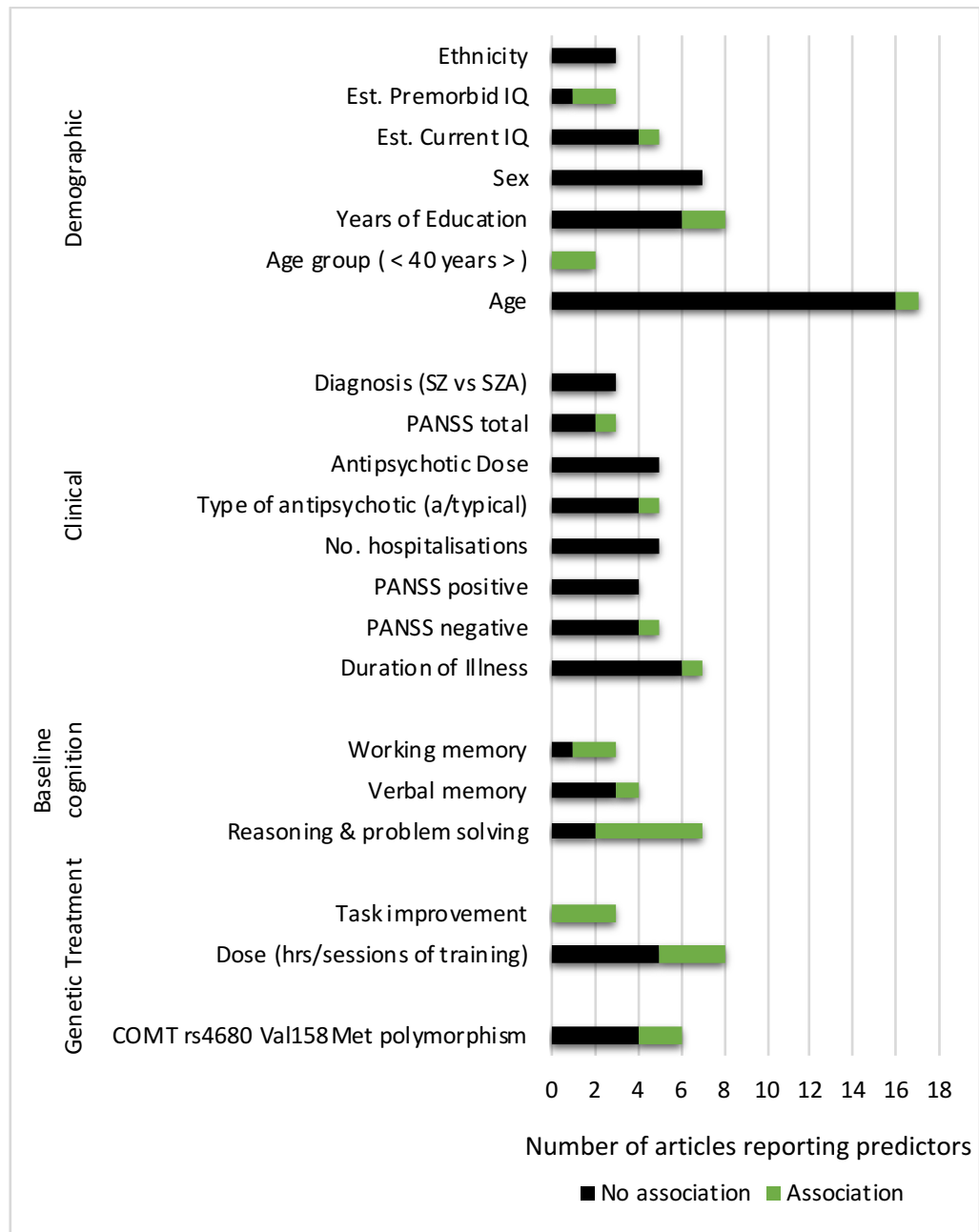


Figure 4.2. Horizontal bar graph showing count of articles that examined predictors of cognitive response to cognitive remediation therapy, grouped by category. Black = no statistically significant association found between the specified predictor and any of the cognitive outcomes examined in the article. Green = at least one statistically significant association found between the specified predictor and at least one the cognitive outcomes examined in the article.

Note. Figure reflects all the predictors reported in a minimum of 3 articles. Est. = estimated; BPRS = Brief Psychiatric Rating Scale; PANSS = Positive and Negative Syndrome Scale; SZ = schizophrenia; SZA = schizoaffective disorder; No. = number; hrs = hours.

Table 4.3

Box-Score Review of Predictors of Cognitive Response to Cognitive Remediation Therapy (CRT) at Summary and Cognitive Domain Level

Category / Predictor	Count of Articles	Predictor: Total sample ^a	Predictor: CRT subgroup ^b	Cog Comp	SoP	Attn Vig	WM	VerbL	VerbM	VerbF	VisL	VisM	R-PS, ExeFun
Demographics													
Age	17	- 0 0 0 0 0 0	0 0 0 0 0 0 0 0 0 0	0 0 0	0 0 0 0	0 0 0	- 0 0 0 0 0 0 0 0	0 0 0	0 0 0 0 0 0 0 0	0	0 0	0 0 0	0 0 0 0 0 0 0 0 0 0 0 0
Age group	2	-	+				- 0						- 0
Years of Education	8	+ 0 0 0	+ 0 0 0	0	0 0 0	0 0	+ 0 0 0	0 0	0 0 0 0	0	0	0	+ 0 0 0 0 0
Sex	7	0 0 0	0 0 0 0	0		0 0	0 0	0	0 0				0 0 0
Est. Current IQ	5	+	0 0 0 0	+ 0 0 0	0 0	+ 0	0 0	0 0	0		0 0	0	0 0 0
Est. Premorbid IQ	3	+ ^d -	0			0	+ ^a		0				- 0
Ethnicity	3	0	0 0	0		0	0		0				
Baseline clinical													
Duration of Illness	7	0 0	- 0 0 0 0	-	0 0	0 0	0 0 0		0 0 0 0	0		0	0 0 0 0 0
PANSS negative	5	0	+ 0 0 0			+		0	+ 0				0 0 0 0
No. hospitalisations	5	0 0 0	0 0		0	0	0 0 0	0	0 0			0	0 0
Antipsychotic type ^e	5	+ ^f 0 0 0	0 ^g		0 ^g		0 ^g 0 0 ^f 0	0	0 ^g 0	0 ^g			+ ^f 0 ^g 0 0 0
Antipsychotic dose	5	0 0	0 0 0	0	0	0	0		0 0 0			0 0	0 0 0
PANSS positive	4		0 0 0 0			0		0	0 0				0 0 0
PANSS total	3	- ^h	0 0	0			0						- ^h 0
SZ vs SZA	3	0	0 0			0 0		0	0 0				0
Baseline cognition													
R-PS	7	+ + 0	+ + + 0										+ + + + 0
VerbM	4		+ 0 0 0			0			+ 0				0
WM	3	+ 0	+				+ + 0						
Treatment													
Training dose	8	+ + 0 0	+ 0 0 0	+ 0	+ 0 0	0 0 0	0 0 0 0 0	0 0 0	0 0 0 0		0	0	+ + 0 0 0 0
Task improvement	3	+	+ ^j	+ 0	0 0	0	+ + 0	+ 0 0	0 0 0	0	+ 0	0 0	0 0
Genetic													
COMT Val158Met	6	+ 0 0	+ 0 0		0 0	0 0	0 0 0	0	0 0 0	0 0			+ + 0 0 0 0

Note. + = positive relationship with outcome ($p < .05$); - = negative relationship with outcome ($p < .05$); 0 = no relationship with outcome; **bolded** values = reported improvement in domain; unbolded values = no improvement in domain; *italics purple* = domain level outcomes not reported. Est. = estimated; PANSS = Positive and Negative Syndrome Scale; SZ = schizophrenia; SZA = schizoaffective disorder; BPRS = Brief Psychiatric Rating Scale; burd. = burden; CogComp = cognitive composite; SoP = speed of processing; AttnVig. = attention and vigilance; WM = working memory; VerblL = verbal learning; VerbM = verbal memory; VerbF = verbal fluency; VisL = visual learning; VisM = visual memory; R-PS = reasoning and problem solving; Exe Fun = executive functioning.

^aFor randomised controlled trials, analysis included control arm(s); ^bAnalysis performed on CRT trial arm only; ^cless than or greater than 40 years; ^dparticipants aged less than 40 years; ^etypical vs atypical unless otherwise specified; ^fclozapine + typical vs other atypicals; ^gclozapine vs other antipsychotics; ^hparticipants aged 40+ years; ⁱreductions (i.e., improvement) in auditory processing speed were associated with improvements in cognition.

4.6.3 Predictor strength of evidence. Assessment of the strength of predictor evidence is presented in Appendix E. Of the more frequently examined potential predictors of cognitive response, few were theory driven or evidence based, and fewer were undertaken with a priori hypotheses. A majority of predictor variables were said to be measured pre-randomisation and the validity and reliability of primary measures of cognitive outcome was largely acceptable, with most studies using neuropsychological tests and test batteries previously vetted in the Wykes et al. (2011) meta-analysis or assessed as appropriate for cognitive assessment in schizophrenia (Bakkour et al., 2014). However, few analyses included tests of interaction. While not included in the strength of evidence summary, only eight articles reported having accounted for multiple comparisons.

4.7 Predictor Results by Category

4.7.1 Demographics.

4.7.1.1 Estimated premorbid IQ. Evidence regarding the influence of estimated premorbid IQ on cognitive outcome was complicated by contrary associations across domains. Performing subgroup analysis, Kontis and colleagues (Kontis et al., 2013) reported the association was limited to participants aged under 40 years, with higher premorbid IQ, dichotomised at the median, positively associated with WM improvements. When re-analysed as a continuous variable across the full sample, higher premorbid IQ was positively associated with both WM and R-PS-planning improvements. Franck et al. (2013) reported a different pattern of association, with higher premorbid IQ associated with less post-intervention improvement on R-PS. Twamley et al. (2011) found no correlates with attention/vigilance (AttnVig), prospective memory, verbal learning or verbal memory domains (VerbL, VerbM) when examining CRT completers. Inconsistencies across domains examined and level of analysis (total sample, subgroup x age, subgroup x completers), along with methodological concerns regarding the use of dichotomies in regression (Royston, Altman, & Sauerbrei, 2006), precludes further interpretation.

4.7.1.2 Estimated current IQ. Less support was found for estimated current IQ as a predictor of response, with only one of five articles reporting an association. Ahmed and colleagues (Ahmed et al., 2015) reported current IQ predicted improvement in attention and a cognitive composite. Two other articles that

examined the influence of current IQ on a cognitive composite found no association, though Panizzutti et al.'s (2013) study cohort overlapped with that of Vinogradov et al. (2009) when pooling data from two RCTs. Neither Bosia, Bechi et al. (2014) or Benoit et al. (2016) found current IQ to influence cognitive response to CRT.

4.7.1.3 Years of education. Years of education has been examined across a broad range of cognitive domains, with two of eight articles reporting an association with cognitive outcomes. The positive correlation reported by Haut et al. (2010) with an untrained WM task ($r=0.32$, $n=21$, $p=0.22$) was weak and not significant. They reported no association with a lexical decision task. In modelling performed by Bosia, Bechi et al. (2014), a relationship was found between years of education and R-PS ($F=5.04$, $p=.033$), though it was unclear how much of the variance was explained. No association was reported by this group when conducting similar analysis examining a measure of attention across another sample (Bosia, Zanoletti, et al., 2014). The weight of evidence suggests years of education exerts little influence on cognitive response to CRT (Ahmed et al., 2015; Farreny et al., 2016; Medalia et al., 2000, 2001; Penadés et al., 2016; Twamley et al., 2011).

4.7.1.4 Age. When considered as a continuous variable, a majority ($n=16$) found no association between age and cognitive outcome. This was true even for the more rigorous studies with larger samples sizes using statistical modelling (Biagianti et al., 2016; Bosia, Bechi, et al., 2014; Bosia, Zanoletti, et al., 2014; Dickinson et al., 2010) with tests of interaction (Franck et al., 2013).

Two subgroup analyses failed to clarify the role of age on cognitive outcome. Interpretation is however limited by methodological concerns. In overlapping sample cohorts, Kontis et al. (2013) and Wykes et al. (2009) applied a somewhat arbitrary dichotomisation of age, being those aged $<$ or $\geq$ 40 years, in part to “achieve relatively balanced sample sizes” (Wykes et al., 2009, p. 254). Dichotomisation results in a loss of both information and power (Royston et al., 2006). Moreover, Kontis et al.'s use of multiple dichotomies (age, premorbid IQ, vocabulary, cognitive reserve) across multiple, unadjusted regression analyses, significantly increased the risk of spurious findings (Lagakos, 2006). Wykes et al. reported that CRT improved WM in both age groups, however only younger participants improved post-intervention on R-PS-planning. No effect was found on R-PS-cognitive flexibility. In comparison, Kontis et al. reported that CRT improved WM in younger but not older participants. No effect was found for cognitive

flexibility and planning aspects of R-PS. When Kontis et al. examined age as a continuous variable, increased age was associated with poorer post-intervention WM, independent of treatment.

4.7.2 Baseline clinical. Regarding clinical predictors of cognitive response to CRT, neither diagnosis (schizophrenia versus schizoaffective disorder), number of hospitalisations, nor antipsychotic dose was found to influence outcome.

4.7.2.1 Duration of illness. One of seven articles found an association between duration of illness and cognitive outcome. Analysing a sample of convenience comprising early versus long-term course of illness, Bowie et al. (2014) reported a negative relationship between duration of illness (range=1-43 years) and improvement on a cognitive composite ($r=-0.43$, $n=39$, $p=0.001$). It is not clear whether the absence of any other reported associations (Bosia, Bechi, et al., 2014; Farreny et al., 2016; Kurtz et al., 2007; López-Luengo & Vázquez, 2003; Penadés et al., 2016; Twamley et al., 2011) is due to there being less variability in illness duration as there was limited reporting of the range of illness duration. Using age as a proxy for duration of illness, it is possible Farreny et al. (2016, age range = 18-60 years) and Twamley et al. (2011, age range = 21-69) approximated the variability engineered by Bowie and colleagues, with no reported associations in these two studies.

4.7.2.2 Medication type. One of five articles found that medication type influenced outcome, with use of either clozapine or typical medication conferring a benefit on R-PS-planning not apparent in those taking other atypical medications (Wykes, Reeder, et al., 2007). No effect was found on measures of WM or R-PS-cognitive flexibility and the authors noted that participants taking Clozapine had more room for improvement, having a lower baseline planning score (Wykes, Reeder, et al., 2007). Where clozapine was compared with other antipsychotics (Bosia, Zanoletti, et al., 2014) or where typical were compared to atypical antipsychotics (Medalia et al., 2000, 2001; Wykes, Newton, et al., 2007; Wykes et al., 1999), no effect was found.

4.7.2.3 Baseline psychotic symptoms. The majority of articles reported no association between baseline symptoms and CRT cognitive outcomes. Eleven articles examined the predictive role of baseline symptoms, of which nine were included in the box-score analysis. Comparisons were facilitated by frequent use of Positive and Negative Syndrome Scale (PANSS; Kay, Fiszbein, & Opler, 1987)

subscale or factor scores, with Haut et al. (2010) and Wykes et al. (1999) using the Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1962). Kontis et al. (2013) reported that for both older adults and the full sample, higher overall symptomatology (PANSS total) was associated with less improvement in R-PS-planning; no association was found with R-PS-cognitive flexibility or WM. Two additional articles that analysed PANSS total (Bosia, Bechi, et al., 2014; Vinogradov, Fisher, Warm, et al., 2009), and two that examined BPRS total score (Haut et al., 2010; Wykes et al., 1999), found no associations with cognitive outcomes. No associations were reported between positive symptoms and cognitive outcomes in four articles (Bark et al., 2003; Bosia, Bechi, et al., 2014; Farreny et al., 2016; Twamley et al., 2011). Conversely, Twamley et al. (2011) found that higher PANSS negative symptom scores were correlated with greater improvements on measures of AttnVig and VerbM but not prospective memory. Bosia, Bechi et al. (2014) also reported a correlation between PANSS negative and cognitive outcome (R-PS), however it did not emerge as a predictor when included in general linear model analysis. Farreny and colleagues (Farreny et al., 2016) similarly found correlations ($p < .10$) between R-PS and PANSS factors (positive, excited, disorganised) that were not predictive when considered in regression analysis. Neither Bark et al. (2003) or Farreny et al. (2013), who sought to better understand the interaction between symptoms and treatment response, found symptoms to be predictive of cognitive response to CRT.

4.7.3 Baseline cognition. Nine articles examined the influence of baseline cognition on cognitive response to CRT, with a majority focused on within domain response (i.e., pre-intervention value predicting the corresponding post-intervention value). R-PS was the most frequently examined baseline predictor and had the strongest association with outcome. Biagianti et al. (2016), Bosia, Bechi et al. (2014), Farreny et al. (2016), and Kontis et al. (2013) all reported positive associations, with higher baseline R-PS predicting greater within domain improvement. This was irrespective of measure or CRT program. The two articles that did not replicate these results used more stringent measures of effective change, calculating either reliable change indices (RCI) that accounted for practice effects and measurement error (Medalia & Richardson, 2005) or improvement thresholds that required a minimum 50% of within domain measures to have improved at least one standard error of the sample's test baseline score (Wykes et al., 1999).

Of the other cognitive domains, a strong positive trend was also evident in WM (Biagianti et al., 2016; Kontis et al., 2013), though contrary results were reported by Wykes et al. (1999) when considering a more clinically rigorous improvement threshold. The opposite pattern emerged on measures of VerbM, with a majority of articles not finding baseline VerbM predictive of within domain change (Farreny et al., 2016; Medalia & Richardson, 2005; Twamley et al., 2011). On finding that increased training hours and a drill and practice approach were associated with improvements in verbal learning and memory, McGurk et al. (2007) hypothesised that the domain might be more sensitive to the method and length of treatment. Indeed, the only article in this review to report a positive association between baseline and VerbM outcome was Biagianti et al. (2016) in a pooled sample of 131 participants engaged in 40 hours of targeted drill and practice auditory training. In comparison, Farreny et al. (2016) analysed results from 29 participants engaged in a strategy-based CRT program, Medalia and Richardson (2005) applied a stringent RCI to a five hour intervention involving 36 participants, and Twamley and colleagues (Twamley et al., 2011) analysed 23 completers who completed 24 hours of compensatory training.

4.7.4 Treatment.

4.7.4.1 Treatment dose. Three of eight articles found that treatment dose, being the number of hours trained or sessions attended, influenced cognitive response to CRT. This was most apparent in studies that compared groups who differed in length of treatment. For example, Fisher et al. (2010) examined the differential responses of participants who received either 50 or 100 hours of targeted cognitive training. While both groups improved on VerbL, VerbM and R-PS, extended training conferred additional benefit in speed of processing (SoP) and cognitive composite (CogComp). A change from auditory to visual training across the two 50-hour blocks meant it was unclear what combination of training dose and spectrum of training conferred the reported benefit. However, support was recently found in a study that compared the differential effect of 3-months (36 sessions) compared to 6-months (72 sessions) of the same CRT protocol (Buonocore et al., 2017). Buonocore et al. (2017) reported that both groups improved across VerbM, WM, verbal fluency (VerbF), SoP and R-PS domains, however greater improvements were realised in R-PS by the group to receive 6-months CRT. From this, Buonocore et al. concluded that 36 sessions appeared sufficient to confer

maximal benefit in a majority of domains, with little further benefit realised after 3-months training.

Of the six studies to examine the association between number of sessions completed and cognitive outcome, only one reported a significant association. Reeder et al. (2017) reported that the number of sessions completed correlated with improvements in R-PS; study completers, being participants who completed a minimum 20 session, averaged 27.5, 45-minute sessions (range 20–41). Of the five articles to find no association, Farreny et al. (2016) reported a median (range) of 26 (20-32) sessions attended across 16 weeks, while López-Luengo and Vázquez (2003) reported a range of 19-90 sessions attended across 8 to 76 weeks. Kurtz et al. (2007) reported mean (SD) training hours of 67.4 (28.7) for the CRT group, with the large SD indicating greater variability around the mean. There was minimal variability in training dose reported by Ahmed and colleagues (Ahmed et al., 2015; mean=48.40, SD=4.11). Twamley et al. (2011) reported the lowest training dose, with an average attendance of 10.6-12.0 sessions.

4.7.4.2 Task engagement/performance. There is stronger evidence of an association between training task performance and cognitive response to CRT. Of the earliest studies to investigate this association, Fisher, Holland, Merzenich, and Vinogradov (2009) reported that improvement on a trained auditory processing task predicted post-intervention improvements across WM-verbal and cognitive composite. More recent analysis has explored underlying mechanisms of action. Biagianti et al. (2016) pooled results from three RCTs delivering 40 hours of computer-based auditory training to examine the relationship between auditory processing speed and cognitive outcome. They reported that, after controlling for baseline cognition, faster auditory processing speed (APS) at the point of APS plateau (i.e., the point after which gains no longer manifest) predicted improvements across CogComp, WM-visual and –verbal, VisL, VisM, SoP and R-PS domains (Biagianti et al., 2016). Fiszdon et al. (2016) have also explored mechanisms of treatment effect, examining the interaction between progress on PSS CogReHab training tasks, and cognitive response to CRT. Improvements on training tasks correlated with improvements in VerbL, VerbM, VisM, and WM.

4.7.5 Genetic. The influence of the Val¹⁵⁸Met polymorphism of the catechol-O-methyltransferase (COMT rs4680) gene is the most frequently analysed genetic predictor of cognitive response to CRT. The weight of evidence, being four

of six articles, suggests that purported associations between COMT rs4680 and cognition do not always extend to CRT response across attention, SoP, WM, Verbl, Verbm, or R-PS domains (Bosia, Zanoletti, et al., 2014; Burton et al., 2015; K. Greenwood et al., 2011; Mak et al., 2013). Of the two articles reporting an association, Boisa and colleagues (Bosia et al., 2007; Bosia, Bechi, et al., 2014) found that Met carriers made greater improvements on a measure of R-PS compared to Val/Val carriers. However, closer examination of their 2007 results reveals the effect was restricted to Met carriers receiving CRT compared to Val/Val carriers receiving no intervention; no difference was reported between Met versus Val/Val carriers receiving CRT (Bosia et al., 2007). As outlined by Greenwood et al. (2011), any number of factors might account for the variability in results, including small sample sizes comprising unequal groups that limits statistical power (Burton et al., 2015).

4.8 Discussion

This systematic review represents the first rigorous synthesis of the evidence base examining predictors of cognitive response to CRT. Through the application of strict criteria that excluded interventions that were found to incorporate social cognition or adjunctive rehabilitation, and that gave preference to post-intervention over follow-up results, it was possible to address some of the potentially confounding factors that could account for heterogeneity of results (McGurk et al., 2013). With a meta-analysis not possible due to study design variability and data limitations, the largely narrative accounting was enhanced by inclusion of a box-score analysis and assessment of the strength of predictor evidence. While this lacks the robustness and objectivity of a meta-analysis, and fails to account for the size of effects across included articles (B. F. Green & Hall, 1984), it provided a methodical way of recording and presenting a summary of the review outcomes.

When examined as a systematic review it is quickly apparent, from consideration of the evidence base, that very few of the currently examined predictors of cognitive response to CRT are significant. This supports results of earlier meta-analyses (Grynszpan et al., 2011; McGurk, Twamley, et al., 2007; Revell et al., 2015; Wykes et al., 2011), where no factors emerged as consistent moderators of treatment effect. It also draws attention to the limitations of more cursory reviews that often focus on findings of significance without adequate

consideration of the weight of studies that find no such associations. Through systematic review, it has been possible to identify a number of areas worthy of closer examination that would otherwise have been masked or overlooked using meta-analytic techniques.

4.8.1 Demographic considerations. There is little evidence to suggest that differences in gender, age, level of education, or current IQ effect the efficacy of CRT or would act as barriers to realising individual benefit from CRT. The influence of premorbid IQ on CRT efficacy was less clear cut. Premorbid IQ has previously been conceived of as both a risk factor and as a protective factor in the development of schizophrenia (Khandaker, Barnett, White, & Jones, 2011) and, as such, may operate at different levels on CRT outcome. It is possible that the relationship between premorbid and current IQ might be more predictive of CRT response. There is limited evidence that individuals with a comprised IQ trajectory, typically defined as premorbid and current IQ below 90 and within 10 points of each other, are less likely to generalise training effects to independent measures of cognition compared to those with preserved (premorbid and current IQ ≥ 90 and within 10 points of each other) or declined (estimated current IQ at least 10-points less than estimated premorbid IQ; Fiszdon, Choi, Bryson, & Bell, 2006) IQ trajectories. This proposal needs further investigation.

The lack of an effect of age on response to CRT is consistent with results of earlier meta-analyses. As per Wykes et al. (2011, p. 482), it is possible that the lack of association could be attributable to the narrow range of ages examined, with a majority of articles reporting mean ages in the 30s. While some evidence suggests that recent onset participants have greater potential to benefit from training (Bowie et al., 2014; Corbera, Wexler, Poltorak, Thime, & Kurtz, 2017), effect sizes from the recent meta-analysis of CRT efficacy in early schizophrenia (Revell et al., 2015) were smaller than those found in chronic schizophrenia. There is a risk of conflating evidence of cognitive decline across the lifespan (Harada, Love, & Triebel, 2013) with the ability of older adults to benefit from cognitive interventions. Evidence from healthy older adults (Kueider, Parisi, Gross, & Rebok, 2012) and those with mild cognitive impairment (N. T. M. Hill et al., 2017) suggests that the capacity to benefit from CRT remains intact across some, but perhaps not all, cognitive domains.

4.8.2 Baseline clinical considerations. The paucity of associations between clinical factors and cognitive outcome is in line with evidence of the relative

independence of clinical and cognitive domains (Heinrichs et al., 2013). Although small to moderate correlations have been found between both negative and disorganised symptoms and specific domains of cognition (de Gracia Dominguez, Viechtbauer, Simons, van Os, & Krabbendam, 2009; O’Leary et al., 2000; Ventura, Thames, Wood, Guzik, & Helleman, 2010), symptom severity appears at worst to attenuate rather than prevent gains from CRT (Wykes & Spaulding, 2011). Regarding medication effects, evidence of the relative effects of different types of antipsychotic medication remains equivocal (Goff et al., 2017) and it is difficult to tease out other factors that could confound results, such as dose and anticholinergic burden.

4.8.3 Baseline cognition considerations. One of the stronger trends to emerge was the influence of baseline cognition on within domain improvement following CRT. However, evidence was limited to three domains, with the strongest effects found in R-PS and WM. It is plausible to suggest that an individual’s baseline cognitive profile in part influences their ability to engage in and benefit from CRT, and a case has been made for both positive and negative associations. Some have suggested that stronger baseline performances aids target engagement and resultant treatment gains (Biagianti et al., 2016), while others have suggested that poorer baseline performance allows more room for improvement (Twamley et al., 2011). These are not mutually exclusive and might vary by domain, warranting further enquiry. There is a need to extend research in this area to consider the impact of CRT on a wider range of cognitive domains and to determine whether there is a threshold of performance below which participants are less likely to benefit from CRT.

4.8.4 Treatment considerations. Vinogradov, Fisher and de Villers-Sidani (2012) presented a persuasive argument that cognitive training needed to be of sufficient intensity and duration to drive the cortical reorganization associated with enduring change. Evidence to-date suggests there is a point at which further training is unlikely to confer additional cognitive benefit, being circa 20 hours. However, more follow-up studies are needed to determine whether the longer training periods result in more enduring cognitive change or drive greater functional improvements. It also remains unclear what role intensity of training plays in driving cognitive change and whether the influence of duration and intensity differs according to training type (see Popov et al., 2011).

The mediating role of training task engagement/performance on cognitive response to CRT is an emergent area of investigation being innovatively led by Vinogradov and colleagues (Biagianti et al., 2016; Fisher et al., 2015, 2009; Vinogradov et al., 2012). While the consistency in results to-date is encouraging, the evidence base is small and needs to be extended across a wider range of research groups considering a more diverse range of CRT interventions. Moreover, the prognostic value of training task performance is somewhat limited as it can only be measured subsequent to CRT commencement. A complimentary line of enquiry should examine potential correlates of task engagement, such as learning potential (Davidson, Johannesen, & Fiszdon, 2016; Kurtz & Wexler, 2006; Rempfer, Brown, & Hamera, 2011; Wiedl & Wienöbst, 1999), which could better inform treatment planning.

4.8.5 Genetic considerations. Interest in genetic influences on the efficacy of CRT in schizophrenia is natural given evidence of the high heritability of schizophrenia (Sullivan, Kendler, & Neale, 2003) and of neurocognitive traits (Husted, Lim, Chow, Greenwood, & Bassett, 2009). However, given the complex interaction of multiple genetic risk variants on cognitive endophenotypes (T. A. Greenwood et al., 2011; T. A. Greenwood, Light, Swerdlow, Radant, & Braff, 2012), coupled with evidence that measures of cognition may be more distal to underlying genetic risk and therefore less sensitive in detecting associations between cognitive change and purported genetic risk variants (Rose & Donohoe, 2013), it is unlikely that investigation of single risk variants will yield consistent results.

4.8.6 Methodological considerations. There are a range of more general limitations in CRT research that add complexity and challenge interpretation when examining predictors of CRT response. These have been comprehensively explicated by others (McGurk et al., 2013) and will not be restated here.

Use of a systematic review has exposed a number of methodological issues that, in limiting what conclusions can be drawn, should be addressed in ongoing efforts to understand factors that influence the efficacy of CRT in individuals with schizophrenia. First is the large number of potential predictors of response that have been assessed only once or twice. Of the included literature, it was only possible to review a quarter of the examined variables. While there is publication pressure to identify and highlight unique findings, lack of replication renders a large proportion of the predictor literature inconclusive.

Variability in methodological approach and rigor was apparent across the evidence base, in part explained by the sometimes exploratory nature of the analysis being undertaken and by the potentially misinformed use of covariates to control for baseline between group differences (see Kraemer, 2016). Only eight articles reported controlling for multiple comparisons and fourteen reported using tests of interaction. A more specific methodological concern relates to multiplicity issues associated with systematic reviews and the risk of over-interpreting pooled results (Bender et al., 2008; Wang, Lagakos, Ware, Hunter, & Drazen, 2007). Multiplicity issues are compounded when examining multiple groups, subgroups and time-points. While it was not possible to control for these, we identified whether full sample or subgroup analysis was performed and have been cautious in our interpretation of outcomes.

4.8.7 Future direction. Having reviewed the evidence base thus far, we still do not know why some people do not appear to receive cognitive benefit from CRT. There is a need to both extend and consolidate the promising lines of enquiry to emerge from this review, being the influence of premorbid IQ, baseline cognition and training task engagement on the efficacy of CRT. We need to move beyond the “obvious suspects”, such as age and duration of illness (Biagianni et al., 2016), in considering the neurobiology of neuropsychiatric illness and neurobiology of learning and learning potential (Vinogradov et al., 2012). No study has investigated all predictors with the same data set. There might be cross cultural, education, or socioeconomic differences that influence CRT outcomes differently internationally. We need to conduct large scale investigations informed by a priori hypotheses, ideally involving cross-research group collaboration or international data pooling initiatives (indeed, where appropriate ethical approvals have been given to re-analyse existing data sets, the international community might consider such an initiative straight away). How we define and measure improvement (Medalia & Richardson, 2005) also needs further consideration. Last, in the face of evident interindividual variability, we need to reconsider whether traditional group level analysis is sufficiently sensitive to detect predictors of such differential patterns of response (Jacobson et al., 1984).

4.9 Variables of Interest

A strong theme emerged from the systematic review of factors that influence the efficacy of CRT in individuals with schizophrenia. When considering only those variables where a majority of articles reported a statistically significant association with cognitive response to CRT, three stand out: premorbid IQ, baseline cognition, and task engagement/progress. It could be argued that each of these relates in some way to an individual's capacity or potential for change.

4.9.1 Intellectual status.

4.9.1.1 Premorbid IQ. Individuals who go on to develop schizophrenia have, on average, one-half a standard deviation impairment in premorbid IQ relative to their peers (Woodberry, Giuliano, Ph, & Seidman, 2008). The link between premorbid IQ and risk of developing schizophrenia has been characterised as a dose-response; for each point of decline in premorbid IQ, the risk of developing schizophrenia increases approximately 3.7-3.8% (Kendler, Ohlsson, Sundquist, & Sundquist, 2015; Khandaker et al., 2011); the greater the decline, the earlier the age of illness onset (Khandaker et al., 2011). It has been theorised that deficits in premorbid IQ may be a marker of abnormal neural connectivity, reflective of underlying neurodevelopmental abnormality (Khandaker et al., 2011). That being the case, it is possible that differences in the degree of impairment may differentially influence individual response to CRT.

4.9.1.2 IQ change. With evidence of continued intellectual decline from premorbid levels to illness onset (Meier et al., 2014), another way of examining the influence of intellectual status on response to CRT would be to consider IQ change, or trajectory. IQ trajectory operationalises differences between current and premorbid IQ. Participants are categorised as either intellectually preserved (premorbid IQ $\geq$ 90) or compromised (premorbid IQ $<$ 90) when there is a less than 10-point difference between current and premorbid IQ; where the difference is $\geq$ 10-points, they are categorised as intellectually declined (T. W. Weickert et al., 2000). IQ trajectory has previously been associated with vocational and functional competency. Leeson et al. (2011), for example, reported that 31% of a first-episode schizophrenia cohort categorised as intellectually preserved had better vocational outcomes at 3-year follow-up compared to intellectually compromised (25%) and deteriorated (44%) subgroups. Ammari et al. (2014) reported the same pattern across a measure of functional competency, with intellectually compromised (19%) and

deteriorated (36%) subgroups performing significantly more poorly than intellectually preserved participants diagnosed with schizophrenia; groups were however equally impaired on a measure of community functioning.

A single study has examined the relationship between IQ trajectory and response to CRT. Fiszdon, Choi, Bryson, and Bell (2006) measured both rates of training task normalisation and change scores on independent measures of cognition. Although participants categorised as intellectually compromised (29%) improved on training task performance, they were unable to generalise the gains to independent measures of cognition. In contrast, both the preserved group (23%) and the deteriorated group (48%) realised significant improvements on independent measures of cognition. The authors surmised that the preserved and deteriorated groups might have had greater cognitive reserves for generalising CRT benefits to untrained tasks (Fiszdon, Choi, et al., 2006).

4.9.2 Baseline cognition. The act of learning is underpinned by some of the same cognitive processes CRT seeks to improve, including attentional control and memory systems (Chein & Schneider, 2012). It is therefore easy to conceive of an individual's baseline cognition influencing their ability to engage in and receive benefit from CRT. An individual's capacity for change may in part be influenced by the domain(s) and degree of baseline impairment experienced (Medalia & Choi, 2009). Attentional capacity, for example, has been singled out as a key element in the success of CRT (Fiszdon, Cardenas, Bryson, & Bell, 2005; Silverstein et al., 2009). It has been proposed that impairments might compromise the processing of "salient stimuli required for training progression" (Biagianti et al., 2016, p. 1006), undermining the ability to benefit from feedback, rehearsal, and repeated practice (Kurtz & Wexler, 2006), and in turn slowing the acquisition of skills (Kurtz, Seltzer, Fujimoto, Shagan, & Wexler, 2009). The contrary results identified in the systematic review could reflect a threshold effect, whereby improvement is more limited when baseline performance on cognitive domains critical to the learning process falls below a requisite level. Tarasenko and colleagues (Tarasenko et al., 2016) alluded to this when discussing the relative sensitivity of different measures of baseline cognition as potential indices of "plasticity potential". In their study, the California Verbal Learning Test-II (CVLT-II) was identified as a potential index of an individual's capacity to benefit from auditory-targeted cognitive training (Tarasenko et al., 2016). To-date, the potential influence of baseline cognition on cognitive

response to CRT has been limited to only a few of the domains known to be impaired in schizophrenia, with little focus on the domains that underpin learning.

4.9.3 Learning potential. Learning potential reflects an individual's capacity to learn and improve in response to training (Boosman, Bovend'Eerd, Visser-Meily, Nijboer, & van Heugten, 2016). It is considered dependent on, but distinct from cognitive performance (M. F. Green et al., 2000). While traditionally assessed pre-intervention, training task progress also provides a measure of an individual's ability to engage in and benefit from training. Given the more limited prognostic value of task performance, as it presupposes training commencement, I sought to extend the evidence base by determining whether a pre-intervention measure of learning potential was as predictive of response to CRT.

4.9.3.1 Training task performance. Measuring CRT task performance over time is akin to measuring an individual's position on the learning curve illustrated in Figure 3.2. A failure to manifest task performance improvements in the early stages of training may have prognostic value regarding the likelihood of realising benefit by training end. On plotting the trajectory of auditory processing speed (APS) over 40 sessions of auditory-targeted training, Biagianti et al. (2016) found evidence of initial rapid gains in APS that plateaued at 20 sessions. APS plateau in turn predicted improvement on independent measures of cognition, with variability in individual APS performance likened by the authors to differences in "sensory system 'learning potential'" (Biagianti et al., 2016, p. 1005). Using the same auditory-targeted training, Murthy and colleagues (Murthy et al., 2012) found that participants who failed to make sufficient APS gains by treatment end (i.e., ≥ 40 ms improvement), also failed to realise cognitive benefit from CRT. In contrast, participants whose APS improved by at least 40 ms also improved on independent measures of cognition (Murthy et al., 2012). While APS improvements are evident after a single hour of training (Tarasenko et al., 2016), it is not known what the predictive threshold is, or whether the same pattern of association is evident in other forms of CRT.

4.9.3.2 Measures of learning potential. The prognostic value of learning potential in guiding therapeutic decision making was introduced by Green, Kern, Braff, and Mintz (2000) in their seminal paper, "Neurocognitive Deficits and Functional Outcome in Schizophrenia: Are We Measuring the 'Right Stuff'?". Green et al. (2000) theorised that learning potential could mediate the effect of CRT

on skills acquisition and, in turn, on functional outcomes. The measurement of learning potential is, traditionally, a dynamic process administered in a single session, involving pre- and post-training assessments either side of an intervening period of instruction (Boosman et al., 2016). Rather than an emphasis on acquired knowledge, the focus is on whether participants benefit from instruction (M. F. Green et al., 2000). The most common tool used in the test-train-test model is the Wisconsin Card Sorting Test (WCST), though list-learning tasks such as the CVLT have also been used (Boosman et al., 2016). In schizophrenia rehabilitation research, dynamic measures of learning potential have been predictive of post-intervention skills acquisition (Rempfer et al., 2011; Sergi, Kern, Mintz, & Green, 2005; Wiedl & Wienöbst, 1999), work capability (Watzke, Brieger, Kuss, Schoettke, & Wiedl, 2008; Watzke, Brieger, & Wiedl, 2009), and CRT task improvement (Davidson et al., 2016), but not of social skills training outcome (Tenhula, Strong Kinnaman, & Bellack, 2007) or social functioning (Woonings, Appelo, Kluiters, Slooff, & van den Bosch, 2002). A summary of these and other studies to investigate the predictive value of learning potential and task performance in schizophrenia cohorts is provided in Appendix F.

It has been argued that learning potential can also be measured using static methods of assessment that mimic the dynamic process (M. F. Green et al., 2000). Static methods involve assessment at a single time point across repeated task trials, but without an intervening period of instruction. It is said that repetition of the task provides participants with the opportunity to “implement an adaptive strategy which will increase their recall” (Vaskinn et al., 2008, p. 180), thus providing a measure of within-task learning (M. F. Green et al., 2000). List-learning tests such as the CVLT and the Hopkins Verbal Learning Test (HVLT) come with procedures for calculating learning slopes or scores. In schizophrenia rehabilitation research, static measures of learning potential have been predictive of readiness for psychosocial rehabilitation (Fiszdon, McClough, et al., 2006), work skills acquisition (Sergi et al., 2005), and improvement in social functioning following rehabilitation (Woonings et al., 2002).

There is ongoing debate regarding the relative merits of dynamic versus static measures of learning potential and the predictive validity of different measures of learning potential (see Boosman et al., 2016; Davidson et al., 2016; Fiszdon & Johannesen, 2010). Advantages of static over dynamic measures of learning potential include a reduction in assessment time and a reduced risk of confounding

future use of a measure through having provided active instruction on how to optimise performance. However, it is possible that static measures fail to capture responsiveness to or benefit from instruction (Davidson et al., 2016) and might therefore be better suited to CRT interventions with minimal instruction. In their recent systematic review of dynamic measures of learning potential, Boosman et al. (2016) concluded that further research was needed to better understand the relationship between learning potential and rehabilitation outcome.

Chapter 5. Empirical CRT Study Aims and Objectives

5.1 Chapter Guide

As stated in the introductory chapters, the overarching goal of this research project was to arrive at a better understanding of factors that influence individual response to, and the efficacy of, CRT in people diagnosed with schizophrenia. A logical starting point and essential objective in pursuit of that goal was to complete a systematic review of empirical research that had examined mediators, moderators and predictors [that is, a significant main effect] of cognitive outcome following CRT. No comprehensive synthesis of the predictor literature had previously been undertaken. Drawing on primary, secondary and co-variate analysis, the review compiled a profile of each of the more frequently examined purported predictors. From this, it was more readily apparent which factors appeared to have greater prognostic value. Premorbid IQ, baseline cognition, and training task performance emerged as potential predictors of an individual's capacity to benefit from CRT.

Through the process of synthesising the CRT predictor literature, a number of initiatives were identified that had the potential to further progress the field. Future directions outlined in Section 4.8.7 included (a) consolidating and extending on the factors that emerged as having greater prognostic value, (b) giving consideration to how cognitive improvement was defined and measured, and (c) re-evaluating whether group level analysis was sufficiently sensitive to detect predictors of differential patterns of response. These initiatives were subsumed in the empirical research papers presented in Chapters 7 and 8.

5.2 Chapters 7 and 8 General Study Aims

The CRT study (Study 2) undertaken in support of this thesis aimed to (a) identify individual patterns of cognitive response to CRT using a measure of clinically meaningful change, (b) characterise emergent responder subgroups, and (c) verify the value of intellectual status, baseline cognition, and learning potential as potential predictors of differential response to CRT.

5.3 Chapters 7 and 8 Research Objectives

In support of the CRT study aims, key research objectives included:

- i. To deliver a minimum 24-session, neuroplasticity informed CRT intervention in an Australian-based schizophrenia cohort.
 - ii. To establish whether use of a computer-aided, drill and practice approach with minimal facilitation was sufficient to drive group level improvements in cognition, as measured on the MCCB. While this was not an efficacy study, group level analysis facilitated cross-study comparisons.
 - iii. To determine whether differential patterns of cognitive response could be identified through use of reliable change indices, adjusted for practice effects. Use of this more clinically meaningful measure of change addressed the limitations of group level analysis, better exposing the variability in individual response to CRT.
 - iv. To characterise potential responder subgroups through provision of baseline demographic, clinical, cognitive, IQ, and learning potential information. Such responder group profiles will better inform clinical practice than group level characteristics.
 - v. To ascertain whether the variables of interest to emerge from the systematic review were predictive of CRT responder status.
- Outcomes from the systematic review were consolidated through consideration of premorbid IQ, MCCB baseline cognition, and CRT task performance and were extended upon through additional consideration of IQ trajectory and static measures of verbal and visual learning potential.

Specific hypotheses in support of these aims and objectives are detailed in the respective chapters.

Chapter 6. Methods

6.1 Chapter Guide

This chapter details the methodology for the articles presented in Chapters 7 and 8. While there is some overlap with the material contained in the respective articles' methods sections, they were necessarily more succinct as is the requirement for publication in scientific journals. Statistical analysis methods specific to the respective chapters are covered in sufficient detail within the chapters for replication and will not be restated here. Rather, the focus in statistical analysis Section 6.15 will be on the generic steps preceding data analysis, such as data preparation, screening, and resolution of missing values.

6.2 Study Design

This was a single-arm, pre- post-test design in which participants were assessed at baseline, completed a minimum 24 sessions of CRT, and were then re-assessed post-intervention. This design allowed for the calculation of cognitive domain-level change scores, which were then used to: (a) calculate reliable change indices, (b) categorise individual response to CRT, and (c) undertake statistical analysis of predictors of response group membership.

Single-arm trials have several limitations that can complicate interpretation of results, including potentially confounding factors such as history and maturation effects, regression to the mean, and practice effects (Evans, 2013; Marsden & Torgerson, 2012). However, consideration of the following factors supported selection of this study design: (a) this study did not seek to assess efficacy; (b) over four decades of randomised controlled CRT efficacy studies have established that treatment effects are largely attributable to the active intervention (Fisher, Herman, et al., 2016), over and above small, non-specific effects that have been reported in control groups (Radhakrishnan, Kiluk, & Tsai, 2016); (c) the intervention to be carried out was of relatively short duration, reducing the risk of maturation effects; (d) the reportedly small practice effects found in the cognitive test battery used to assess cognitive response to CRT were controlled for (Georgiades et al., 2017; Nuechterlein et al., 2008); and (e) the need to optimise statistical power in an anticipated small sample size.

6.3 Study Locations

Study activities, including the recruitment, assessment, delivery of the CRT intervention, and data storage, were conducted across multiple sites.

6.3.1 Swinburne University of Technology (SUT). The candidate was enrolled at SUT during the tenure of this thesis, thus SUT was the primary site overseeing the administration of the study. Recruitment also took place at SUT, via referrals from internal collaborators. It was also a site for administering pre- and post-intervention assessments, as well as the thrice weekly CRT sessions that were offered to study participants. Study data was stored at this site, including signed participant consent forms, de-identified case report forms (CRFs), and electronic data files.

6.3.2 Monash Alfred Psychiatry Research Centre (MAPrc). MAPrc was a recruitment and assessment site. Recruitment at MAPrc was limited to use of

participant databases and self-referrals in response to promotional flyers. A majority of the assessment sessions were conducted at MAPrc and the thrice weekly CRT sessions were available to study participants.

6.3.3 St Vincent's Hospital. St Vincent's permitted recruitment across three of their sites, two located at outpatient mental health care centers and one a community care unit (CCU) providing medium-term supported residency in the inner Melbourne region. Referrals were also received from St Vincent's prevention and recovery service (PARC), which provides short-term residential services for people with mental illness.

6.3.4 Mind Australia. Direct recruitment occurred across three supported residencies in the inner Melbourne region. Assessments and CRT sessions were conducted at each site. Participants were also recruited through self-referrals in response to Mind Australia's promotion of the study.

6.3.5 Peninsula Health. Recruitment occurred across two sites, one an outpatient mental health care clinic and the other a CCU that provided integrated care to medium-term residents.

6.3.6 Monash Health. Recruitment occurred across two outpatient community mental health services. Assessment and CRT sessions were to be conducted on site.

6.3.7 Baker IDI Genomics and Systems Laboratory. De-identified material (blood and saliva) collected for genetic analysis was stored and analysed at this site.

6.4 Ethics

To ensure the study complied with Australia's *National Statement on Ethical Conduct in Human Research* (National Health and Medical Research Council, 2007; updated 2015) and with the principals set out in the Helsinki Declaration, approval was obtained from the following primary and ancillary (whereby approval was contingent on primary committee approval) review bodies:

I. St Vincent's Hospital (Melbourne) Human Research Ethics Committee-A (101/14, 17/09/2014), with approval received to recruit across three sites: Hawthorn Community Mental Health Centre, Hawthorn VIC; Clarendon Community Mental Health Centre, East Melbourne VIC; Footbridge Community Care Unit, Fitzroy North VIC.

- i. Swinburne Human Research Ethics Committee (2014/251, 29/09/2014);
- ii. Monash Health Governance (16245X, 03/06/2016), with approval received to recruit across three sites: Monash Medical Centre, Clayton VIC; Clayton Community Mental Health Service, Clayton VIC; Southern Community Mental Health Service, Moorabbin VIC.
- II. The Alfred Hospital Ethics Committee (373/14, 30/09/2014).
 - i. Mind Australia Research and Evaluation Committee (18/08/2015);
 - ii. Peninsula Health Human Research Ethics Committee (16/11/2015), with approval received to recruit across two sites: Peninsula Community Mental Health Service, Frankston VIC and Peninsula Health Mental Health Service Community Care Unit, Frankston VIC.

Copies of certificates of approval are provided in Appendix G1-6. Final report acknowledgments from St Vincent's Hospital, The Alfred Hospital, and Swinburne University of Technology can also be found in Appendix G (7-9).

6.5 Recruitment

6.5.1 Source of participants. The study sample was drawn from a population of community and supported residency dwelling individuals diagnosed with schizophrenia-related disorders residing in the Melbourne, Australia region. Potential participants were recruited by the author through hospital based mental health care services, community sector mental health care services, and internal collaborators over a two-year period between February 2015 to January 2017.

Potential participants were primarily obtained through self-referral in response to recruitment material. In addition to study flyers, this included advertising on a local community Gumtree website, advertising through Melbourne's public transport network, and an online presence hosted by Swinburne University of Technology and MAPrc. The author was also provided with opportunities to present to residents during team meetings in supported residencies.

A subset of individuals was referred to the project by case-managers, healthcare professionals, and internal collaborators. To facilitate referrals to the study, the author delivered information/education sessions to teams of health care professionals, delivered a colloquium to Mind Australia, a major community mental health service provider (<https://www.mindaustralia.org.au/resources/our-evidence->

base), and provided recruitment material to mental health care service sites. Another group was identified on volunteer databases managed by research teams at MAPrc. These databases comprised previous study participants who had expressed interest in future studies and who had provided consent for their details to be held and contact to be made. Access to the databases was restricted and rigorously governed, with formal approval processes and mandatory training and reporting requirements.

6.5.2 Eligibility criteria. To participate in the study, individuals had to be:

- diagnosed with a schizophrenia-related disorder, meeting criteria set out in the Diagnostic and Statistical Manual of Mental Disorders, (DSM-IV-TR; American Psychiatric Association, 2000) for schizophrenia, schizoaffective disorder, or schizophreniform disorder;
- aged between 18 and 65 years;
- fluent in spoken English;
- stable on medication for at least eight weeks prior to baseline assessment;
- assessed as having an estimated premorbid IQ ≥ 75 (participants not meeting this criterion would be accepted into the study but would not be included in final analysis);
- of sufficient level of functioning to be able to provide informed consent and to communicate with the research team.

Exclusion criteria included:

- Having uncorrected hearing or vision impairments such that training tasks could not be undertaken;
- Having undergone electroconvulsive therapy in the past six-months;
- A history of head trauma with prolonged loss of consciousness;
- A history of neurological (e.g., epilepsy) or neuro-degenerative (e.g., Huntington's disease) illness that might independently affect cognitive performance;
- Current or recent history of a significant and habitual substance abuse or dependence, as confirmed by structured clinical interview.

6.5.3 Recruitment procedure. On first contact either in person, by phone or by e-mail, potential participants received a brief overview of the study and were

provided the opportunity to ask any initial questions. Subsequent to this, with verbal consent, individuals completed a short screening questionnaire, comprising a series of simple questions intended to assess the eligibility criteria detailed in Section 6.5.2. Arrangements were then made to provide those still interested with a copy of the participant information and consent form (PICF; Appendix H), which contained more detailed information about all aspects of the study. Individuals were encouraged to discuss their possible participation with a family member, support person, case manager, or general practitioner. A follow-up time approximately four days after provision of the PICF was agreed on, at which point any additional questions could be responded to. If the individual made the decision to participate, the author coordinated with the assessment team to schedule the two baseline assessment sessions. Once mutually agreed upon times were arranged, participants and, where appropriate, case-managers, were sent confirmation of arrangements by post or e-mail.

Standardised templates were used for all forms of written communication. A generic study e-mail address and mobile phone number were made available to participants to streamline communication and to keep associated activities distinct from the author's personal communication mediums.

6.6 Assessment Procedure

Participants were assessed prior to CRT engagement (baseline) and on completion of a minimum 24 sessions of CRT (post-intervention). At baseline, clinical presentation, intellectual status, and neuropsychological performance was assessed and demographic details were collected across two, three-hour sessions. At post-intervention, clinical presentation and neuropsychological performance was re-assessed in a single, three-hour session.

The author, whose primary role during this phase of the project was to manage recruitment activities, coordinate assessment times and materials, and to facilitate CRT sessions, remained blind to all assessment data until participant completion in the study.

Testing took place at a location most convenient to each study participant. At all sites, interview rooms that allowed for privacy and that were a safe environment for both the participants and researchers were used.

If time permitted, a demographic/questionnaire pack was sent to participants prior to their first assessment session for completion in their own time. It was made

clear that completion of the questionnaires would be taken as consent to participate in the pre-assessment phase of the project. If not completed prior, the information was collected during the scheduled assessment sessions.

At the outset of the first testing session, individuals met with the author who talked through each section of the PICF, encouraging any further questions and seeking confirmation of understanding by having individuals repeat back key aspects of the study. Perceived risks and benefits to study participants were outlined. The individual's right to withdraw at any point during the study, without consequence to their ongoing care or future opportunities to participate in research, was emphasised. The author then invited the participant to sign the informed consent form, which was witnessed by someone independent of the study. This was taken as their agreement to participate in the study. Participant consent was determined by the author according to the following criteria:

- Meeting eligibility criteria (subject to outcome of clinical assessment)
- Able to understand the purpose of and procedures required for the study
- A demonstrated willingness and availability to participate

A copy of the signed and witnessed consent form was given to the participant for their own records, along with a copy of the withdrawal of consent form. After obtaining informed consent, the participant was introduced to the researcher responsible for administering the baseline assessment.

6.7 Assessment Materials

To capitalise on project synergies and to maximize participant opportunities, the CRT study protocol was aligned with that of a parallel project, of which Professor Susan Rossell was the Principal Investigator. This section details the subset of the broader assessment pack that was used in the CRT study only.

6.7.1 Demographic details. Basic demographic information such as gender, age, ethnicity, and years of education was gathered. Information collected was used to characterise the study sample.

6.7.2 Clinical assessment. Clinical information was collected through use of a semi-structured clinical interview. In the first instance, diagnosis was verified, and participants were screened for current or recent substance dependence, to ensure eligibility to participate (Section 6.7.2.1). Then, after gathering information about length of illness and current medication, depressive and psychotic symptoms were assessed (Sections 6.7.2.2 & 6.7.2.3):

6.7.2.1 Mini International Neuropsychiatric Interview for Schizophrenia and Psychotic Disorder Studies. (M.I.N.I Version 5.0.0; Sheehan et al., 1998). The M.I.N.I is a short, semi-structured diagnostic interview that was used to confirm diagnosis of a schizophrenia-related disorder according DSM-IV-R criteria and to screen for substance dependence. Responses to a series of probe questions guided subsequent diagnostic screening questions.

Two studies to evaluate the validity, inter-rater and test-retest reliability of the MINI reported good to very good results (Lecrubier et al., 1997; Sheehan et al., 1997). Regarding diagnostic validity, when compared to the Composite International Diagnostic Interview (CIDI), Lecrubier et al. (1997) reported kappa coefficients of 0.75 and 0.82 for lifetime psychotic syndrome and symptoms respectively. Test-retest reliability was Kappa = 0.90. Kappa coefficients of 0.82 and 0.81 were reported for alcohol and drug dependence respectively, with a test-retest reliability of Kappa = 0.93 for dependence in general. When compared to the Structured Clinical Interview for Patients (SCID-P), Sheehan et al. (1997) reported a Kappa coefficient of 0.76 for lifetime psychotic disorder; inter-rater reliability was Kappa = 0.81 and test-retest reliability was Kappa = 0.77. For current alcohol dependence, Sheehan et al. reported a Kappa coefficient of 0.60, inter-rater reliability of 1.00, and test-retest Kappa of 0.86. For current drug dependence, Sheehan et al. reported a Kappa coefficient of 0.30, inter-rater reliability of 0.91, and test-retest Kappa of 0.96.

6.7.2.2 Calgary Depression Scale for Schizophrenia (CDSS; Addington, Addington, & Schissel, 1990) was used to assess participant depressive symptoms. The CDSS is a nine-item rating scale intended to assess depressive symptoms, as distinct from positive, negative, and extrapyramidal symptoms, in people with schizophrenia (Addington et al., 1990). Items such as ‘Depression’ and ‘Pathological Guilt’ are rated on a 4-point scale ranging from 0 (absent) to 3 (severe). Item scores are summed to generate an overall rating, with higher scores reflecting increased depressive symptomatology over the past week.

The CDSS has been found to have high internal consistency across inpatient and outpatient populations (Cronbach’s $\alpha = 0.79$), has excellent criterion related validity when compared to the Brief Psychiatric Rating Scale (BPRS; $r = 0.87$), the Hamilton Depression Rating Scale (HDRS; $r = 0.82$), and the Beck Depression Inventory (BDI; $r = 0.79$; Addington, Addington, Maticka-Tyndale, & Joyce, 1992). The CDSS has been found to effectively discriminate depressive symptoms from

negative psychotic symptoms (Kontaxakis et al., 2000), and a majority of items are sensitive to change (intervention response) over time (Santen, Danhof, & Della Pasqua, 2009). As item level responses were not captured, it was not possible to assess the internal reliability of the measure in this study.

6.7.2.3 Structured Clinical Interview for the Positive and Negative Syndrome Scale (SCI-PANSS; Kay et al., 1987). The SCI-PANSS is a semi-structured interview comprising 57 questions assessing the presence and severity of psychopathology experienced over the prior week. Based on responses received, the 30 items comprising the PANSS are rated on a seven-point scale ranging from 1 (absent) to 7 (extreme). Seven items each comprise a positive symptom subscale and a negative symptom subscale (potential score range of 7-49); 16 items (potential score range of 16-112) comprise the general psychopathology subscale (Kay et al., 1987). This was used to measure symptom severity across the three subscales.

Kay, Opler, and Lindenmayer (1988) reported good inter-rater reliabilities (mean Intraclass Correlation Coefficients [ICC_{2,1}] ranging from 0.83 to 0.87) across the three subscales and the composite score and good criterion related validity when compared to the Scale for the Assessment of Positive Symptoms and the Scale for the Assessment of Negative Symptoms (Andreasen, 1981, SAPS & SANS respectively; 1984). Cronbach's alpha values for the current study sample were as follows: positive = 0.45, negative = 0.61, general psychopathology = 0.52.

6.7.3 Intellectual status. To support calculation of intelligent quotient (IQ) change scores (detailed in Section 6.13.2), both premorbid and current IQ was measured.

6.7.3.1 Wechsler Test of Adult Reading (WTAR; Weschler, 2001) was used as a measure of premorbid IQ, or the degree of intellectual function prior to the onset of illness or disease (Wechsler, 2001). Reading ability is thought to reflect levels of premorbid IQ; it is highly correlated with IQ and is resistant to cognitive decline (Franzen, Burgess, & Smith-Seemiller, 1997). Participants are asked to pronounce, in order, a list of 50 words presented to them. Responses are scored 0 (incorrect) or 1 (correct), and then summed to provide an overall rating. In the absence of Australian norms, scores were standardised using United Kingdom norms.

The WTAR has been widely used as a measure of premorbid IQ in studies involving schizophrenia populations (e.g., Leeson et al., 2010; Sharip et al., 2013). It was found to be a valid measure of premorbid IQ in a TBI population, where post-

injury improvements were noted across measures of current IQ but where ratings on the WTAR remained stable (R. E. A. Green et al., 2008).

6.7.3.2 Wechsler Abbreviated Scale of Intelligence (WASI; Weschler, 1999) was used as a measure of current IQ. The WASI comprises four subtests similar in format to the Wechsler Adult Intelligence Scale (WAIS; Wechsler, 1999): Vocabulary, Block Design, Similarities, and Matrix Reasoning. Administered in either a two-subtest or four-subtest format, conversion tables are available to calculate an estimated Full-Scale IQ (FSIQ). The two-subtest version comprising Vocabulary and Matrix Reasoning was used.

Split-half reliabilities for the WASI FSIQ in an adult population was 0.98, test-retest reliability was 0.92, and convergent validity with the WAIS FSIQ score was excellent at $r_{12} = 0.92$ (Homack & Reynolds, 2007). The WASI was recently used in a study evaluating the cognitive and clinical correlates of the MATRICS Consensus Cognitive Battery (MCCB), credentialing its use as a measure of FSIQ in schizophrenia populations (August et al., 2012).

6.7.4 Neuropsychological assessment. Cognitive functioning was assessed using the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS™) Consensus Cognitive Battery (MCCB; Nuechterlein et al., 2008). The MCCB was selected due to its specific development for use in clinical trials assessing the efficacy of cognitive-enhancing treatments for individuals diagnosed with schizophrenia (Nuechterlein et al., 2008). With increased use of the MCCB in CRT studies (e.g., Biagiante et al., 2016; Lindenmayer et al., 2017), its use in the current study facilitated cross study comparisons.

The MCCB is comprised nine tests representing six cognitive domains commonly found to be impaired in schizophrenia, along with one test representing social cognition (Nuechterlein et al., 2004, 2008). Raw test scores were converted into age- and gender-corrected, domain-level *T*-scores using the MCCB scoring tool (see Kern et al., 2008). Cognitive composite scores, which represented the average of domain-level *T*-scores, were used for analysis of response to CRT.

Individual tests comprising the MCCB are described in Table 6.1, referencing information provided in the MATRICS™ Consensus Cognitive Battery Manual (Nuechterlein & Green, 2006). Psychometric properties published in a recent study involving a large cohort ($N = 2,616$) of patients diagnosed with schizophrenia (Georgiades et al., 2017) have been included to attest to the suitability of the MCCB.

Table 6.1

MCCB Tests by Cognitive Domain

Domain, <i>Subtest</i>	Baseline <i>T</i> -Score Mean (SD)	Test-Retest Reliability ICC (95% CI)	Practice Effects Mean (SD), Cohen's <i>d</i> ^a
Speed of Processing	33.4 (12.20)	0.81 (0.80, 0.82)	2.2 (7.06), 0.18
<i>Trail Making Test, Part A (TMT-A)</i> . Participants are asked to draw a continuous line to connect a series of numbered circles in numeric order from 1-25. Raw score = time taken in seconds.			
<i>BACS Symbol Coding</i> . Participants are asked to cross-reference a series of nonsense symbols with a corresponding number (1-9), using the key provided. Raw score = total number of correctly cross-referenced symbols in 90 seconds.			
<i>Category Fluency Test, animal naming</i> . Participants are asked to name as many animals as they can in a 60 second trial. Raw score = total number correctly named.			
Attention-Vigilance	37.1 (12.19)	0.78 (0.76, 0.79)	1.3 (7.79), 0.11
<i>Continuous Performance Test, identical pairs</i> . In this computer-based task measuring sustained attention, participants are presented with blocks of 2-digit, 3-digit, and then 4-digit numeric combinations. They are required to indicate when the presented combination matches exactly the preceding combination. Participants complete a practice block before the main tasks. DPRIME scores for 2-, 3-, and 4-digit blocks represented the participant's ability to discriminate identical from nearly identical numeric combinations.			
Working Memory	35.4 (11.51)	0.80 (0.79, 0.82)	1.4 (7.07), 0.12
<i>Letter-Number Sequencing</i> . Participants are verbally presented with increasingly sized spans of alternating number-letter combinations and asked to repeat them back, numbers sorted lowest to highest, then letters in alphabetical order (e.g. 4-L-9-A would be repeated 4, 9, A, L).			
<i>WMS-III Spatial Span subtest</i> . On a board comprising ten blocks of different heights, the test administrator touched a series of increasingly sized sequence of blocks. Participants are asked to touch the same sequence of blocks.			
Verbal Learning	36.2 (7.91)	0.61 (0.59, 0.63)	0.8 (6.69), 0.11

Hopkins Verbal Learning Test-Revised (HVLT-R). Participants are read a list of 12 words and are then asked to recall as many as possible. This is repeated two times (trials 1-3), with total words recalled recorded for each trial. Raw score = sum of total words recalled correctly across the three trials. Alternate forms were used to mitigate the risk of practice effects; form 1 was administered at baseline and form 4 post-intervention.

Visual Learning	36.1 (11.99)	0.69 (0.67, 0.71)	1.5 (9.34), 0.13
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Brief Visuospatial Memory Test-Revised (BVM-T-R). Participants are shown an array of six geometric shapes for 10 seconds, after which they are provided a blank piece of paper and asked to reproduce from memory each shape in the correct location. This is repeated two times (trials 1-3), with up to two points awarded per shape for reproduction and placement accuracy. Raw score = sum of total points awarded across the three trials. Alternate forms were used to mitigate the risk of practice effects; form 1 was administered at baseline and form 5 post-intervention.

Reasoning and Problem Solving	40.8 (9.31)	0.76 (0.74, 0.77)	0.8 (6.27), 0.09
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NAB Mazes subtest. This activity is said to measure foresight, planning, and impulse control. Participants are presented with a series of mazes of increasing difficulty and are instructed to draw a continuous line from the “start” to “end” point as quickly as they can without lifting the pen or crossing lines. Points are awarded for each maze successfully completed based on the time taken to complete.

Social Cognition	36.3 (13.10)	0.76 (0.75, 0.77)	0.2 (8.92), 0.02
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MSCEIT, managing emotions branch. Participants are read a series of short vignettes and, for each, are asked to rate how effective they thought the protagonist’s response was on a 5-point scale (1 = very ineffective to 5 = very effective). Responses are scored through use of a computer-scoring program.

Cognitive Composite	28.2 (12.41)	0.88 (0.87, 0.89)	1.9 (5.54), 0.15
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Note. MCCB = MATRICS Consensus Cognitive Battery; SD = standard deviation; ICC = intra-class correlation coefficients; CI = confidence interval; WMS-III = Wechsler Memory Scale III; NAB = Neuropsychological Assessment Battery; MSCEIT = Mayer-Salovey-Caruso Emotional Intelligence Test.

^aCohen’s *d* = mean difference divided by the pooled SD from screening and baseline.

6.8 Reimbursement

Participants were reimbursed \$40 per 3-hour assessment session for their time and associated travel expenses, totalling a potential \$120 across the course of the study. No reimbursement was provided for attendance of CRT intervention sessions.

6.9 Blood Collection and Management

Blood or saliva was collected by certified venepuncturists at either MAPrc or Swinburne University of Technology and then stored at the Baker IDI with project collaborator Dr Bozaoglu.

For the gene of interest, DTNBP1, rs1018381 and rs2619522 single-nucleotide polymorphisms (SNPs) were selected based on prior evidence suggestive of associations with IQ and cognition (reviewed in Chapter 9). While a range of other SNPs influence the dysbindin gene, to reduce risk of Type 1 errors, analysis was constrained to those SNPs with established major functional variants.

Genotype frequencies for rs1018381 and rs2619522 respectively were predicted to be 8% and 19% for dysbindin at-risk allele carriers (National Center for Biotechnology Information, 2014b, 2014a). Homozygous risk-allele carriers were grouped with heterozygous risk-allele carriers.

⁵DNA from venous blood was extracted using the QIAamp DNA Blood Mini Kit as per manufacturer's instructions (QIAGEN, Hilden Germany). DNA from saliva samples was purified using the PrepIT-L2P DNA purification protocol as per manufacturer's instructions (DNAGENOTEK, Ottawa, Canada). SNP assays were designed using the Agena Assay Design Suite 1.0 software (Agena, San Diego, CA). Genotyping for rs1018381 and rs2619522 was performed using the MassArray system as per manufacturer's standard protocols (Agena, San Diego, CA). The MassArray platform relies on a primer extension reaction in combination with a mix of mass-tagged dideoxy-nucleotides (iPlex chemistry) to generate a pool of oligo products that are analysed by chip-based matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF). Adherence to Hardy-Weinberg equilibrium (HWE) and allele frequency was examined. For efficiency, the two SNPs were genotyped in a single reaction.

6.10 Cognitive Remediation Therapy Intervention

⁵ Methodology for the processing of genetic material was provided by K. Bozaoglu (personal communication, 22 February, 2018).

CRT was undertaken using BrainHQ's (Posit Science™) VISUAL Intensive, a commercially available, web-based cognitive training tool. Its selection was not an arbitrary choice. Of the range of programs available, BrainHQ's CRT modules are grounded in principles of neuroplasticity and are designed to target both lower and higher order processing deficits, combining bottom-up with top-down training (Adcock et al., 2009). The exercises have been described by Adcock et al. (2009, p. 1134) as:

- Intensive, with thousands of trials per exercise.
- Attentionally engaging, with self-paced initiation of each learning trial and closely regulated task difficulty.
- Adaptive, with the critical content of each exercise adjusting trial by trial to user performance.
- Rewarding, with entertaining embellishments to reinforce correct responses, which occur frequently due to the adaptive structure of the exercise.

The visual exercises have been found to specifically target and bring about improvements in visual learning and visual memory (Surti, Corbera, Bell, & Wexler, 2011). Intensive training on the BrainHQ CRT programs—which also includes social- and meta-cognition exercises—has been found to restore neural activity within the reality monitoring network of the medial prefrontal cortex (Subramaniam et al., 2012), an effect not found in an active control. It has similarly been found to normalise brain-derived neurotrophic factor (BDNF) levels, implicated in neurodevelopment and plasticity, with a concomitant improvement in quality of life in a group of participants diagnosed with schizophrenia; again, no such improvements were found in the active control (Vinogradov, Fisher, Holland, et al., 2009). These successes suggest that remediation of lower order sensory processing systems in order to drive changes at the higher level is an effective approach in bringing about improvements in cognitive functioning (Javitt, 2009a).

BrainHQ's CRT programs are accessible to clinicians and participants outside of research settings and, with minimal resources required, could be implemented as a CRT solution in community mental health care settings.

A total of 16 BrainHQ licenses were procured at a reduced rate for research purposes of 25% off the normal price. Licenses could be reallocated on participant

completion and were active for 12 months after first use. Licenses were funded by a Seeding Grant made available to the author by Swinburne University of Technology.

6.10.1 Visual intensity training tasks. Participants work through up to 40 levels of visual processing training, with each level comprising two of the five training tasks. Each level of a task comprises multiple sets that differ in task complexity and therefore difficulty. Training tasks target attention, visual processing speed, and visual working memory. The training tasks detailed below can be trialled on the BrainHQ website (<https://www.brainhq.com/why-brainhq/brain-training-your-way/brainhq-courses-challenges/visual-intensive>). Permission was obtained to include a screenshot of each task in the examinable thesis copy only (Appendix I).

6.10.1.1 Visual sweeps. Targeting visual acuity and visual processing speed, participants are presented with two consecutive spatial frequency sweeps (Gabor patterns; see Figure 6.1) and need to indicate in which direction each sweep moved (e.g., inward or outward). Incorrect responses slow the speed at which sweeps are presented; correct responses increase the speed of presentation. Task response is measured by the speed in milliseconds of the movement of the sweeps. Differences in background colour, orientation, and spatial frequency across task sets increased task complexity.

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Figure 6.1. Visual Sweeps task, BrainHQ from Posit Science. Participants click on the inward or outward pointing arrows to indicate the direction of the first and then second Gabor pattern sweep. Reprinted from Visual Sweeps, in Why BrainHQ? > About the Brain HQ Exercises > Brain Speed Exercises, n.d. Retrieved 20th April, 2018, from <https://www.brainhq.com/why-brainhq/about-the-brainhq-exercises/brainspeed/visual-sweeps>. Copyright 2018 by Posit Science. Reprinted with permission.

6.10.1.2 Target tracker. Targeting divided attention, participants are presented with a number of moving objects that they must track amidst identical looking distractor objects that appear several seconds after the target objects. When all objects stop moving, the participant must click on the objects they were to track

(see Figure 6.2). Successive incorrect responses results in a reduction in the number of objects presented to track; multiple correct responses increase the number of objects to track. Task response was measured by the number of objects tracked on completion of each task set. Task sets differ in the speed at which objects move and in the degree of contrast between the objects being tracked and the background.

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Figure 6.2. Target Tracker, BrainHQ from Posit Science. Participants track target objects (circled in yellow) amidst a number of identical looking distractor objects. Reprinted from Target Tracker, in Why BrainHQ? > About the Brain HQ Exercises > Attention Exercises, n.d. Retrieved 20th April, 2018, from <https://www.brainhq.com/why-brainhq/about-the-brainhq-exercises/attention/target-tracker>. Copyright 2018 by Posit Science. Reprinted with permission.

6.10.1.3 Double decision. Targeting visual processing speed and peripheral vision, participants are required to divide their attention across two on-screen activities. In the center of the screen, participants are briefly presented one of two similar looking vehicles. At the same time, on the periphery of the screen, a “Route 66” road sign is briefly presented. After a short masking interval, two cars appear in the center of the screen. The participant must click on the car that was presented seconds earlier and then must click on the section of the screen that the “Route 66” road sign appeared (see Figure 6.3). Incorrect responses results in the objects being presented for a longer period of time. Correct responses results in the car and road sign being presented for shorter periods of time. Task response was measured by the speed in milliseconds that objects were presented on correct response. Task complexity was increased by the degree of contrast between the objects being presented and the background, by the width of the circumference around which the road sign was presented (i.e., narrow or wide), by the eventual appearance of distractor signs from which the “Route 66” sign needs to be distinguished, and by a gradual increase in similarity in the vehicles to be discriminated between.

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Figure 6.3. Double Decision, BrainHQ from Posit Science. Participants must click on which of two vehicles was presented towards the middle of the screen and in what section of the screen the Route 66 sign appeared (circled in yellow). Reprinted from Double Decision, in Why BrainHQ? > About the Brain HQ Exercises > Attention Exercises, n.d. Retrieved 20th April, 2018, from <https://www.brainhq.com/why-brainhq/about-the-brainhq-exercises/attention/double-decision>. Copyright 2018 by Posit Science. Reprinted with permission.

6.10.1.4 Eye for detail. Targeting visual processing speed and visual working memory, participants are briefly presented with three (or five) successive images (e.g., butterflies, flowers) at different positions on the screen. Two of the three (or three of five) images are identical. After all images have been presented, they are replaced with generic placeholders in the locations of the previously presented objects. The participant needs to remember and click on the location of the matching objects (see Figure 6.4). Incorrect responses results in objects being presented for a longer period of time. Correct responses increased the speed at which objects were presented. Task response was measured by the speed in milliseconds that objects were presented on correct response. Task complexity was increased by the degree of contrast between the objects being presented and the background, by the width of the circumference around which the objects were presented (i.e., narrow or wide), and by the gradually increased similarity of the objects they needed to discriminate between.

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Figure 6.4. Eye for Detail, BrainHQ from Posit Science. Participants must click on the positions in which two of three or three of five matching objects were briefly presented on screen. Reprinted from Eye for Detail, in Why BrainHQ? > About the Brain HQ Exercises > Brain Speed Exercises, n.d. Retrieved 20th April, 2018, from

<https://www.brainhq.com/why-brainhq/about-the-brainhq-exercises/brainspeed/eye-detail>. Copyright 2018 by Posit Science. Reprinted with permission.

6.10.1.5 Hawk eye. Targeting visual speed and precision, participants are briefly presented with a flock of birds that are identical except one. They must identify and locate the odd bird during the flock's brief presentation. When the birds disappear, participants must click on the section of the screen in where the odd bird was located (see Figure 6.5). Incorrect responses resulted in objects being presented for a longer period of time. Correct responses increased the speed at which objects were presented. Task response was measured by the speed in milliseconds that objects were presented on correct response. Task complexity was increased by a reduction in contrast between the birds and their background, by the width of the circumference around which the birds were presented (i.e., narrow or wide), and by the gradually increased similarity of the odd bird to the rest of the flock.

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Figure 6.5. Hawk Eye, BrainHQ from Posit Science. Participants must identify and then locate the section of the screen in which the unmatched bird appeared (circled in yellow). Reprinted from Hawk Eye, in Why BrainHQ? > About the Brain HQ Exercises > Brain Speed Exercises, n.d. Retrieved 20th April, 2018, from <https://www.brainhq.com/why-brainhq/about-the-brainhq-exercises/brainspeed/hawk-eye>. Copyright 2018 by Posit Science. Reprinted with permission.

6.10.2 Equipment Procurement. In support of the CRT intervention, five laptops were allocated to the author, procured by the Centre of Mental Health, Swinburne University of Technology, using funds obtained through an equipment grant awarded to Professor Rossell. A 25 gigabyte per month mobile broadband data plan was obtained, accessed via pocket Wi-Fi, to ensure internet access when providing CRT sessions away from the main study sites. This was funded by a Barbara Dicker Foundation grant awarded to the author.

6.11 Ongoing Review of Capacity to Consent and Engage

Participants' ongoing capacity to consent and to actively engage in the intervention was monitored during and between CRT sessions. During sessions, if any of the participants appeared to demonstrate a diminished capacity to consent, for example, through confusion regarding the experimental procedure, they were referred for independent assessment by a member of the research team. Between sessions, if a participant unexpectedly missed successive CRT sessions or was unable to complete the allotted session time of 45-60 minutes, they were gently probed about potential reasons for any difficulties and the potential benefit versus harm of continued involvement was discussed.

It is likely that deterioration in capacity to consent and participate in the study would be associated with an overall deterioration in clinical state. This would indicate that the best course of action would be withdrawal from the study. Where this was indicated, the author first consulted with senior research team members before raising such concerns with participants.

6.12 Data Collection, Storage and Security, and Confidentiality

6.12.1 Data collection. Data was collected by members of the research team under the direct supervision of Professor Susan Rossell. Only authorised personnel, being members of the research team, had access to raw data.

Assessment data was either collected manually, through self-report and interview notes recorded in participant CRFs, or automatically, through computerised programs by researchers. Summary scores from computerised tasks were transcribed into the participant CRFs. Genetic material was collected by blood or saliva samples and was submitted for processing and storage at the Baker IDI. CRT training task data was collected automatically on the provider's host website and was available to download in .csv format through a secure login provided to the author.

6.12.2 Data storage and security.

6.12.2.1 *Hardcopy and electronic assessment data.* Participants were assigned a unique, 3-digit numeric study code that only they and authorised project personnel were able to identify as belonging to them. To ensure anonymity, documents that contained identifying information, such as the PICF, did not include this code number. Hardcopy data was stored securely in a locked filing cabinet, with identified and non-identified data stored separately. Electronic data was stored in

password protected files on a secure network drive that was only accessible by the research team. Access to the network drive was managed by a senior member of the research team and was reviewed periodically.

A password protected document, made available only to the research team, contained a cross reference between each participant's name and corresponding code. This was to be used to identify a given case in the event a participant wished to withdraw their consent to use of their data. On study completion, unless separate consent had been given to store information indefinitely for use in future studies, there was no further need to retain the participants' identifying details. Documentation linking personal information to code number was to be destroyed, restoring anonymity.

All data will be stored for a minimum of 7 years post publication at Swinburne University of Technology, in line with standard policy.

6.12.2.2 *Electronic CRT task data.* Participant CRT task data was automatically captured and stored by Posit Science. Task data was accessible by the author through use of a secure login provided for study administration purposes. To ensure participant anonymity, training was conducted using a set of generic user profiles (i.e., CRT1, CRT2 etc.) that contained no information about the participant. User profiles were linked to a generic e-mail address set-up and maintained by the author. The author maintained a password protected cross-reference document linking each participant's CRF study code to the CRT user profile so that information could be linked for analysis purposes. On study completion, a de-identified version of the file was archived on the research team's secure network drive.

6.12.2.3 *Genetic material.* Blood and saliva samples collected during the course of the study were allocated a six-digit code that was distinct from that assigned to assessment data contained in the CRF. Samples were labelled with the code at the time of extraction and, apart from the date of extraction, was the only information provided to Baker IDI Genomics and Systems Laboratory. Analysis outcomes were provided back to the research team using these codes. For the duration of the study, genetic material was stored in coded form such that it was re-identifiable. This was necessary in the event a participant withdraw their consent for use of their genetic data. A single document contained both the participant's name and unique code for the purposes of being able to link them with their genetic

material. The password protected electronic document was accessible only by senior members of the research team. At the conclusion of the study, unless separate consent had been given to store genetic information indefinitely in a bio-databank, the participant's entry on the document was to be deleted, rendering the blood samples de-identified. The blood samples are stored securely at the Baker IDI Genomic and Systems Laboratory as per the site's storage procedures.

6.12.3 Confidentiality. To ensure participant confidentiality, all data, genetic and otherwise, will be de-identified by the conclusion of the study to protect the privacy and confidentiality of consenting participants. However, if a participant separately provided consent for their information to be stored in the Cognitive and Genetic Explanations of Mental Illnesses (CAGEMIS) bio-databank, it was possible to re-identify them. This is necessary because (a) future research using information from or adding to the CAGEMIS bio-databank would need to be able to identify participants, particularly if adding new information from a participant who had already donated information to the databank; (b) if an individual who had previously consented to their information being stored in the CAGEMIS bio-databank later decided to withdraw that consent, they could be re-identified so their information could be deleted from the database.

In any publication or presentation, all participants remain anonymous, with results presented as pooled group or subgroup data only.

6.13 Operationalisation of Variables of Interest

In support of the analysis of potential predictors of cognitive response to CRT, the following variables were operationalised.

6.13.1 Reliable change index (RCI): Individual response to CRT was measured by reliable change indices, calculated across MCCB change scores. The RCI provides a measure of whether clinically meaningful change has occurred and the amount of change beyond that attributable to measurement error (Jacobson & Truax, 1991). A modified version of Jacobson and Truax's (1991) calculation was used to account for practice effects (Chelune, Naugle, Lüders, Sedlak, & Awad, 1993), using test-retest estimates and correlations published by Gray et al. (2014).

As described by Jacobson and Truax, the RCI is calculated by deducting a participant's baseline score (T_1) from their post-intervention score (T_2), which derives a change score, and then dividing that value by the standard error of the

difference (S_{diff}) between the two scores, or $\frac{T_2 - T_1}{S_{diff}}$. The standard error of the difference, which “describes the spread of the distribution of change scores that would be expected if no actual change had occurred” (Jacobson & Truax, 1991, p. 14), is calculated using the standard error of measurement (S_E) as follows: $S_{diff} = \sqrt{2(S_E)^2}$. In turn, the S_E is calculated using the formula $SD_1\sqrt{1 - r_{1,2}}$, where SD_1 is the baseline standard deviation and $r_{1,2}$ is the correlation between the mean baseline and post-intervention scores of an untreated group.

To account for practice effects, the adjustment described by Chelune et al. (1993) is applied to the numerator, whereby the practice effect value is deducted from the change score, or $\frac{(T_2 - T_1) - (M_2 - M_1)/SDD}{S_{diff}}$ where M_2 is the mean post-test score of an untreated group, M_1 is the mean pre-test score of the untreated group, and SDD is the standard deviation of the untreated group’s test-retest difference (Horswill, n.d.).

6.13.2 IQ change: IQ change was used as a proxy for IQ trajectory. IQ trajectory considers the difference between current and premorbid IQ scores and has previously been defined as a categorical variable comprising three levels: preserved, which reflects stable, average IQ scores, being ≥ 90 and within 10 points of each other; compromised, which reflects stable, below average IQ scores, being ≤ 89 and within 10 points of each other; declined/deteriorated, which represents all cases where current IQ is at least 10 points less than premorbid IQ (Kremen, Seidman, Faraone, & Tsuang, 2008; Leeson et al., 2011). For our purposes, current IQ was deducted from premorbid IQ to create a continuous variable that was more powerful than a categorical variable and was suitable for inclusion in discriminant analysis.

6.13.3 Learning potential: Several indices of learning potential (introduced in Section 4.9.3) were calculated.

6.13.3.1 Verbal and visual learning scores. Benedict and colleagues’ learning score calculation was applied to the HVLT-R (Benedict, Schretlen, Groninger, & Brandt, 1998) and the BVMT-R (Benedict, Schretlen, Groninger, Dobraski, & Shpritz, 1996) as static measures of verbal and visual learning potential respectively. Learning scores reflected the greater of trial 2 or trial 3 scores minus trial 1 score. Higher scores reflect better performance. Learning scores were

standardized by age group using normative data published by the test developers (Benedict et al., 1998, 1996).

6.13.3.2 Visual Sweeps change score. As described in Section 6.10.1.1, BrainHQ's Visual Sweeps task (Posit Science, 2018), which targets visual acuity and processing speed, was selected to assess training task performance, purportedly reflective of sensory systems learning potential (Biagianti et al., 2016). Change scores reflected the average threshold achieved on the final presentation of the Visual Sweeps task minus the average threshold achieved on its second presentation. The first presentation is a reduced set of stimuli and was used for familiarisation purposes.

6.14 Sample Size and Power Analysis

Based on an initial review of factors associated with cognitive outcomes following CRT, where an effect is found, moderate to large effect sizes are anticipated. For example, with regards to baseline cognition, Rodewald et al. (2014) reported a moderate sized correlation between the reasoning and problem solving domain and change in problem-solving capacity ($r = 0.38$); Twamley, Burton and Vella (2011) reported a large sized correlation between baseline attention/vigilance and post-intervention attention/vigilance following 12 weeks of CRT ($r = 0.73$). With regards to negative symptoms, correlations between $r = 0.45$ and $r = 0.50$ have been reported with post-intervention attention/vigilance (Twamley et al., 2011).

Using g*power, with effect size f^2 set at 0.25 (0.15 = moderate, 0.35 = large), alpha set at 0.05, and calculated on the basis of linear multiple regression involving 5 predictor variables, we estimated a sample size of 60 participants would be required to have 80% power of detecting effect sizes of this magnitude. Allowing for attrition and to account for the lack of information on some predictor variables of interest, a sample of 75 was sought.

6.15 Statistical Analysis

6.15.1 Data preparation. Data was either entered directly into IBM[®] SPSS[®] Statistics Version 25.0.0 or was converted to SPSS format from Excel for the tasks requiring the computerised collection of data. All scoring in the pre- and post-intervention CRFs was cross-checked and data in the physical files was checked against data held in SPSS databases.

MCCB age- and gender-corrected domain and composite *T*-scores were calculated using the test battery's scoring program and were manually entered into SPSS. Subsequent data activities were performed on the subset of participants who completed both baseline and post-intervention assessments.

6.15.2 Data screening. Categorical variables were reviewed to ensure only valid entries were present and continuous variables were reviewed to ensure they fell within expected ranges.

For continuous variables of interest, univariate outliers were identified through examination of box-plots and by calculating standardised (*z*) scores for each of the measures. A conservative $p < .001$ (two-tailed test) level was applied, with standardised *z*-score values exceeding ± 3.29 examined more closely (Tabachnick & Fidell, 2013). Outliers were resolved by score adjustment, such that they equalled a unit of measure increase or decrease to the next closest score (Tabachnick & Fidell, 2013, p. 77). This was done to avoid transformation of single MCCB domain-level scores, which would have complicated graphical presentation of data and interpretation of scores in relation to the normative mean.

A combination of graphic, i.e. histograms with normality curves and Q-Q plots, and descriptive, i.e. skewness and kurtosis values, mean versus 5% trimmed mean, Kolmogorov-Smirnov test of normality, inputs were reviewed to ensure adherence to the normal distribution. Standardised skewness and kurtosis values were calculated (for example, $z\text{-skewness} = [S - 0] / S_s$, where *S* is the reported skewness value and *S_s* is the standard error for skewness; Tabachnick & Fidell, 2013, p. 79) to aid evaluation of normality. Variables that did not meet the assumption of normality were resolved when outliers were addressed, requiring no further action.

In support of analysis for Chapter 7, to assess for multivariate outliers, Mahalanobis distance was calculated through regression techniques for each response group (Tabachnick & Fidell, 2013). Participant ID was used as the dummy dependent variable. A threshold of 13.82 was set, representing the critical value for chi-square (χ^2) at $\alpha < .001$ with 2 degrees of freedom to account for the independent variables to be included in a Discriminant Analysis function.

6.15.3 Missing values. Missing values were identified across several measures comprising the MCCB. Specifically, CPT (MCCB attention) raw scores were missing for three participants and MSCEIT (MCCB social cognition) raw

scores were missing for one participant. CPT 2-*d*, CPT 4-*d* and MSCEIT had less than 5% missingness; CPT 3-*d* had 9.1% missingness.

The MCCB manual recommends use of data imputation to resolve missing raw scores, which are then used to generate *T*-scores (Nuechterlein & Green, 2006, p. 84). Thus, to reduce estimation bias, SPSS's MVA (missing values analysis) was used to resolve the missing values. As values were not found to be missing completely at random (Little's MCAR $\chi^2 [128] = 29551.84, p < .001$), the expectation maximization method was selected. Pre- and post-intervention raw scores across all MCCB measures were included in the imputation process. The resultant replacement values were used to calculate MCCB age- and gender-corrected domain and composite *T*-scores. Sensitivity analysis was performed by repeating all statistical analysis in Chapter 7 on the subset of participants for whom full datasets were available.

Chapter 7. Predictors of Individual Response to Cognitive Remediation Therapy

7.1 Chapter Guide

Reser, M. P., Rossell, S. L. (in submission). What predicts individual response to cognitive remediation therapy?

This chapter comprises the aforementioned article, which has been submitted for publication. The article draws on outcomes from the systematic review presented in Chapter 4. The reader is referred to Section 4.9 of that chapter, which discusses in greater depth the specific variables of interest, to Chapter 5, which sets out the aims and objectives of Study 2, and Chapter 6, which details the study methodology.

7.2 Abstract

Background: Variability in individual response to cognitive remediation therapy (CRT) undermines its potential as a treatment of cognitive deficits in schizophrenia-related disorders, with approximately 44% of participants failing to realise clinically meaningful change following CRT. Predictors of response have, to-date, proved elusive. We sought to determine whether measures of intellectual status, cognitive ability and learning potential were predictive of a stringent measure of individual response to CRT.

Method: Twenty-two participants diagnosed with schizophrenia-related disorders completed a minimum 24 sessions of CRT. Reliable change indices (RCI) were calculated across MATRICS Consensus Cognitive Battery (MCCB) change scores and participants classified as Improvers or Non-improvers. Potential predictors of response, identified using Pearson correlations, were entered into a direct discriminant analysis.

Results: Twelve participants realised reliable change across at least one cognitive domain. Baseline MCCB attention/vigilance and pre-treatment verbal learning potential discriminated Improvers from Non-improvers, explaining 28% of the variance in RCI Status and correctly classifying 63.6% of original and cross-validated cases. Individuals who, at baseline, scored more poorly on attention/vigilance and who demonstrated greater verbal learning potential, were more likely to realise benefit from CRT.

Conclusions: Our results highlight the value in assessing both baseline cognition and learning potential when attempting to discern those most likely to benefit from CRT. A simple measure of learning potential, derived from the MCCB, proved the strongest measure of whether an individual had the requisite cognitive capacity for reliable change. In a clinical setting, using these results will allow for more informed treatment decisions.

7.3 Introduction

Variability in individual response to cognitive remediation therapy (CRT) undermines its potential as a treatment of cognitive deficits in schizophrenia-related disorders. On average, 44% of participants do not realise clinically meaningful cognitive change from CRT⁶, with improvement rates ranging from 38% (Hodge et al., 2010) to 77% (Bryce et al., 2018) across inconsistent measures of reliable change. While the need to better understand factors that influence CRT outcomes is well documented (Keshavan et al., 2014; McGurk et al., 2013; Wykes & Spaulding, 2011), predictors of response have proved elusive.

Results from meta-analyses examining the efficacy of CRT have failed to identify moderators or mediators of effect (Grynszpan et al., 2011; Wykes et al., 2011). Similarly, despite a twofold increase in the number of articles published over the past two decades examining predictors of cognitive response to CRT, a recent systematic review of the literature by our group concluded that few of the more frequently examined predictors were significant (Reser, Slikboer, & Rossell, 2018). Reser et al. (2018) collated evidence from 40 articles examining 81 distinct predictors; results indicated a trend for baseline cognition to predict within-cognitive-domain improvement. Estimated premorbid IQ and learning potential as measured by training task performance also showed prognostic value, though both were limited to three studies.

A majority of articles included in Reser et al. (2018) assessed correlates at the group level with pre-post change scores before undertaking further modelling of associated, purported predictors. There are limitations to this approach when seeking to understand individual response to CRT. It fails to account for whether change is of sufficient magnitude to be clinically meaningful, and does not consider variability in response (Jacobson & Truax, 1991); both are important if looking to inform clinical practice. Moreover, examination of change scores does not account for the known measurement error or practice effects associated with commonly used cognitive test batteries (e.g., Gray et al., 2014; Heaton et al., 2001).

In this pilot study we sought to determine whether intellectual status, cognitive ability and learning potential were predictive of a stringent measure of

⁶ Calculation based on percentage of improvers reported across nine CRT studies to use a measure of reliable change.

individual response to CRT. We used a modified version of Jacobson and Truax's (1991) reliable change index that adjusted for practice effects (Chelune et al., 1993). For intellectual status, in addition to premorbid IQ, we included IQ change, a dimensional measure of IQ trajectory, which has previously been associated with response to CRT (Fiszdon, Choi, et al., 2006) and with vocational and functional competency (Ammari et al., 2014; Leeson et al., 2011). For cognitive ability, we examined baseline domain and cognitive composite scores from the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB). For learning potential, in addition to a measure of training task performance, we included pre-treatment, static measures of verbal and visual learning potential. Static measures have been found by some (Vaskinn et al., 2008), but not all (Kurtz, Jeffrey, & Rose, 2010; Rempfer et al., 2011), to differentiate learners from non-learners. We selected standard measures from the MCCB to see whether existent cognitive measures were sufficiently sensitive to detect differences in treatment response.

We anticipated that a combination of intellectual status and cognitive ability would be predictive of reliable change. Moreover, based on the strength of previous associations between both auditory (Biagiante et al., 2016; Fisher et al., 2015, 2009; Murthy et al., 2012) and visual (Surti et al., 2011) processing training task performance and CRT outcomes, we hypothesised that visual processing training task performance would be predictive of reliable change. Examination of pre-treatment, static measures of learning potential was exploratory.

7.4 Methods

This pre-post, single arm pilot study was approved by hospital (The Alfred, St Vincent's Hospital Melbourne, Monash Health) and university (Swinburne University of Technology) human research ethics committees and conducted in accordance with the Declaration of Helsinki.

7.4.1 Participants. Outpatient participants were recruited by the first author between February 2015 and January 2017 across seven sites in the Melbourne Australia region, including public mental health care services and community sector support groups, and through local advertisements. Participation was open to individuals diagnosed with schizophrenia-related disorders, aged 18 to 65 years, stabilised on medication, and fluent in English. Participants with estimated

premorbid IQ below 75 were excluded, as were those with premorbid conditions (e.g., acquired brain injury, neurological disorder) or recent substance abuse that could independently compromise cognitive functioning. After being fully briefed, participants provided written, informed consent.

7.4.2 Assessment. The CRT facilitator remained blind to all assessment outcomes until participant completion.

7.4.2.1 Clinical. Participant's mental health status was assessed, and diagnosis confirmed, using the Mini International Neuropsychiatric Interview Screen 5.0.0 (Sheehan & Lecrubier, 2006). The Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) was administered to assess positive, negative and general psychotic symptoms.

7.4.2.2 Neuropsychological. Premorbid IQ was assessed using the Wechsler Test of Adult Reading (WTAR; Wechsler, 2001). Current IQ was assessed using the Wechsler Abbreviated Scale of Intelligence (WASI)-2 subtest version (Wechsler, 1999). The MCCB (Nuechterlein et al., 2008) was used to assess domain level and composite cognitive functioning. Domains included speed of processing, attention/vigilance, working memory, verbal learning, visual learning, reasoning and problem solving, and social cognition. Details of measures comprising these domains have been published elsewhere (Nuechterlein et al., 2008). Age- and gender-adjusted standardised *T*-scores (mean = 50, *SD* = 10; Kern et al., 2008) were used in the analysis.

7.4.3 Reliable change index (RCI). Individual response to CRT was measured by reliable change indices, calculated across MCCB change scores. The RCI provides a measure of whether clinically meaningful change has occurred and the amount of change beyond that attributable to measurement error (Jacobson & Truax, 1991). We used a modified version of Jacobson and Truax's (1991) calculation to account for practice effects (see Chelune et al., 1993), using estimates published by Gray et al. (2014). Individuals were categorised as improvers if they evidenced reliable change on at least one domain, being an $RCI \geq 1.96$ (95% confidence interval), and if they maintained performance in all other domains. If no change ($RCI's < 1.96$), or a significant decline in performance was evident ($RCI \leq -1.96$), individuals were categorised as non-improvers. This resulted in a dichotomous variable for RCI Status representing Improvers and Non-improvers.

7.4.4 IQ change. IQ change (current IQ - premorbid IQ) was calculated as a proxy for IQ trajectory, a continuous variable suitable for inclusion in discriminant analysis.

7.4.5 Learning potential. Several indices of learning potential, being the ability to improve in response to training (Fiszdon & Johannesen, 2010), were calculated.

7.4.5.1 Verbal and visual learning scores. We applied Benedict and colleagues' learning score calculation to the Hopkins Verbal Learning Test-R (HVLTR; Benedict et al., 1998) and the Brief Visuospatial Memory Test-R (BVMTR; Benedict et al., 1996) as static measures of verbal and visual learning potential respectively. On the HVLTR, participants are read a 12-word list and asked to recall as many as possible. This is repeated two times (trials 1-3), with total words recalled recorded for each trial. On the BVMTR, an array of six geometric shapes is presented for 10 seconds, after which participants are asked to reproduce from memory each shape in the correct location. This is repeated two times (trials 1-3), with up to two points awarded per shape for reproduction and placement accuracy. Learning scores reflect the greater of trial 2 or trial 3 scores minus trial 1 score. Higher scores reflect better performance. Learning scores were standardized by age group using normative data published by the test developers (Benedict et al., 1998, 1996).

7.4.5.2 Visual Sweeps change score. BrainHQ's Visual Sweeps task (Posit Science, 2018), which targets visual acuity and processing speed, was selected to assess training task performance, purportedly reflective of sensory systems learning potential (Biagianti et al., 2016). Participants determine whether two spatial frequency sweeps (Gabor patterns) are moving inward or outward. Differences in colour, orientation, and spatial frequency optimise neural response, with task performance (threshold) measured in milliseconds. Improvement is reflected in faster (lower) response times. Change scores reflected the average threshold achieved on the final presentation of the Visual Sweeps task minus the average threshold achieved on its second presentation. The first presentation is a reduced set of stimuli and was used for familiarisation purposes.

7.4.6 Cognitive Remediation Therapy. CRT was undertaken using BrainHQ's (Posit Science™) VISUAL Intensive, a commercially available, web-based tool. Participants work through up to 40 levels of visual processing training,

with each level comprising two of five training tasks: Visual Sweeps, Target Tracker, Double Decision, Eye for Detail, and Hawk Eye. Training tasks targeted attention, visual processing speed, and visual working memory. BrainHQ's cognitive training tasks have been described as theoretically grounded in neuroplasticity-based learning principles, being intensive, neuro-adaptive, attentionally engaging and rewarding (Fisher et al., 2010). Task difficulty is dynamically responsive to individual performance so as to maintain 80-85% task success rate. Detailed task information is available on the BrainHQ website (<https://www.brainhq.com/why-brainhq/brain-training-your-way/brainhq-courses-challenges/visual-intensive>).

7.4.7 Procedure. Potential participants were screened for eligibility before meeting with the first author, who obtained informed consent. Baseline assessments (demographic, clinical and cognitive) were completed over two, three-hour sessions by a team of trained doctoral-level students and post-doctoral researchers who were otherwise uninvolved in the study. The senior author regularly performed inter-rater reliability checks. CRT was offered across multiple sites up to three times a week. Participants attended 1-3 group or individual sessions a week, working independently at their own pace for 45-60 minutes a session. A single participant worked from home and was monitored remotely. Training sessions were supervised by the first author, a Doctor of Psychology (Clinical) candidate. On completion of a minimum 24 sessions, participants attended a single, 3-hour post-intervention assessment session (clinical, cognitive). Participants were reimbursed for assessment sessions (\$40 per 3-hour session) only.

7.4.8 Statistical analysis. Data analysis was undertaken using IBM[®] SPSS[®] Statistics Version 25.0.0 and was conducted on the completer sample. Measures were screened for univariate and multivariate normality and outliers. Missing values were resolved using single imputation. As data was not missing completely at random (Little's MCAR test was significant at $p < .001$), the expectation maximisation method was selected. Sensitivity analysis performed to verify results. Group differences across baseline variables and mean RCI scores were examined using independent-samples t -tests and χ^2 tests. Cohen's d was used as a measure of effect for between-sample analyses.

To select potential predictors of response, we first determined across which MCCB domains Improvers and Non-improvers significantly differed. Pearson

product-moment correlations were then used to assess associations between the identified MCCB domains and 13 potential predictor variables: premorbid IQ and IQ change, MCCB baseline domain and cognitive composite scores, HVLT-R and BVMT-R learning scores, and Visual Sweeps change score. Variables that correlated at $p < .05$ significance were included in the analysis. Direct discriminant analysis was used to determine whether the selected variables predicted group membership, RCI Status (Improvers, Non-improvers). Jackknifed classification (leave-one-out method) was used to cross-validate the solution (Lance, Kennedy, & Leberg, 2000). This involved an iterative process of removing then re-classifying a single case at a time based on the discriminant function derived from the remaining sample.

7.5 Results

MCCB age- and gender-corrected domain and composite *T*-scores calculated. Single outliers on MCCB verbal learning and reasoning and problem-solving domains were resolved by score adjustment. No multivariate outliers were detected.

7.5.1 Sample characteristics. Of 50 individuals screened for eligibility, 30 commenced and 22 completed CRT. The flow of participants through the study phases is presented in Figure 7.1. Of those who commenced CRT, study completers performed significantly better on baseline MCCB visual learning ($M = 36.68$, $SD = 11.10$) compared to non-completers ($M = 24.50$, $SD = 16.88$; $t[28] = 2.31$, $p = .029$, $d = 0.92$). There were no other differences between completers and non-completers across baseline demographic, clinical, IQ or cognitive measures.

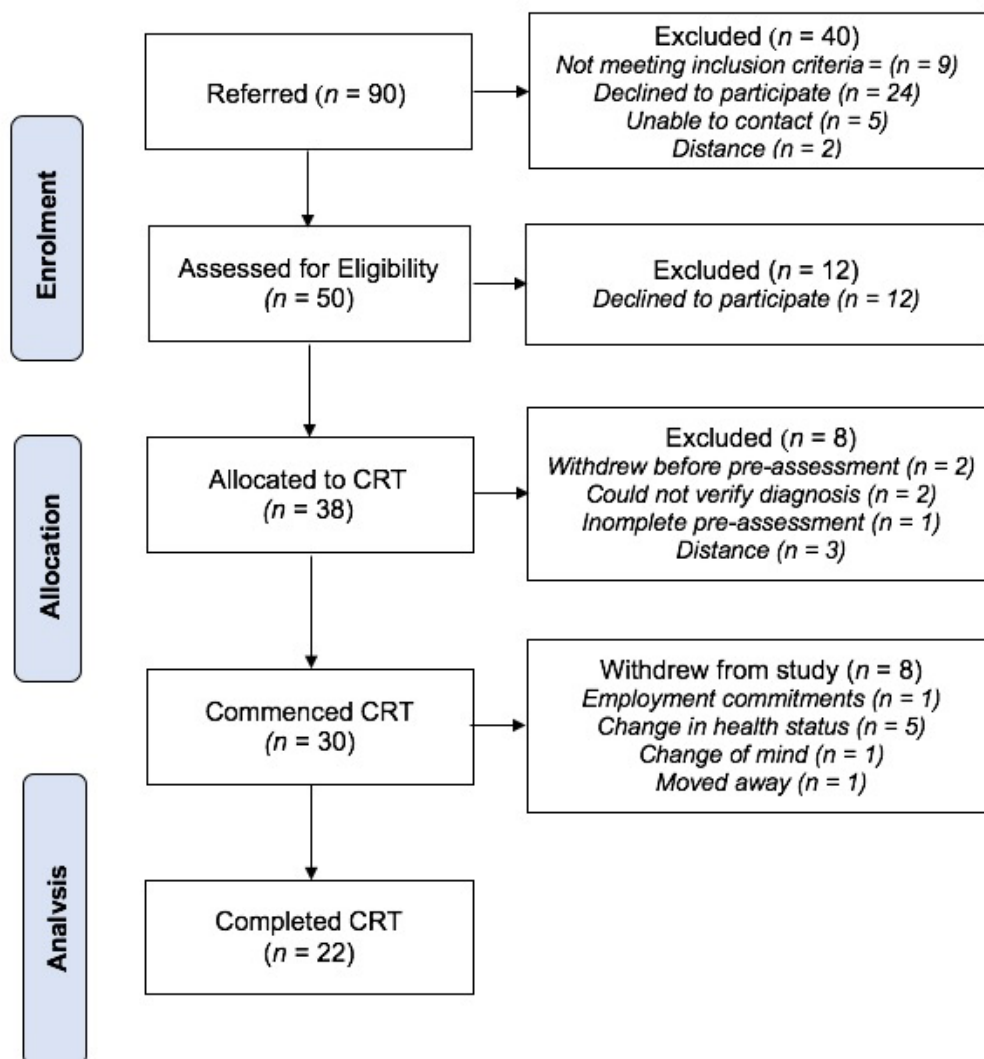


Figure 7.1. CONSORT 2010 Flow Diagram.

Sample characteristics for study completers are presented in Table 7.1. Improvers had significantly lower premorbid IQ and higher HVLT-R learning scores than Non-improvers. There were no other significant group differences across RCI Status.

Table 7.1

Baseline Demographic, Clinical, and Cognitive Characteristics by RCI Status

Characteristic	Improvers (<i>n</i> = 12)		Non-improvers (<i>n</i> = 10)		<i>t</i> / χ^2	<i>df</i>	<i>p</i>
	<i>n</i> (%)	Mean (SD)	<i>n</i> (%)	Mean (SD)			
<i>Demographics</i>							
Age (years)		38.17 (11.72)		38.10 (7.65)	-.02	20	.988
Gender (male)	7 (58.3)		5 (50.0)		.00	1	1.000
Ethnicity					1.30	2	.521
Caucasian	11 (91.7)		8 (80.0)				
Asian	0		1 (10.0)				
Other	1 (8.3)		1 (10.0)				
Years of Education		13.58 (1.83)		14.22 (1.72)	.81	19	.427
<i>Clinical</i>							
Age of onset (yrs)		26.08 (8.20)		25.60 (6.04)	-.16	20	.879
Years of illness		12.03 (9.51)		12.60 (10.28)	.14	20	.893
Diagnosis					.892	2	.640
Schizophrenia	8 (66.7)		7 (70.0)				
Schizoaffective	3 (25.0)		3 (30.0)				
Schizophreniform	1 (8.3)		0				
Medication (CPZ mg/day)		845.83 (629.17)		683.30 (496.95)	-.60	15	.561
PANSS positive		15.58 (4.23)		15.40 (5.58)	-.09	20	.931
PANSS negative		12.33 (4.08)		13.50 (6.01)	.54	20	.595
PANSS general		29.33 (7.44)		29.60 (6.60)	.09	20	.931
<i>Intellectual status</i>							
Premorbid IQ ^a		102.75 (10.13)		111.10 (5.45)	2.34	20	.030
Current IQ ^b		94.58 (10.84)		98.20 (13.53)	.697	20	.494
IQ change ^c		-8.17 (13.89)		-12.90 (14.62)	-0.78	20	.446
<i>Cognition (MCCB)</i>							
Speed of processing		41.17 (11.27)		44.90 (11.28)	0.77	20	.448
Attention/vigilance		38.58 (9.32)		44.20 (10.63)	1.32	20	.201
Working memory		42.50 (6.64)		43.90 (9.42)	0.41	20	.688
Verbal learning		36.75 (9.64)		39.20 (7.50)	0.66	20	.520
Visual learning		35.42 (7.59)		38.20 (14.58)	0.55	20	.595
Reasoning & PS		43.08 (9.24)		44.70 (10.29)	0.39	20	.702
Social cognition		39.75 (12.90)		39.10 (8.72)	-0.14	20	.894
Cognitive composite		33.33 (7.55)		37.00 (11.30)	0.91	20	.374
<i>Learning potential</i>							
HVLT-R learning ^d		0.21 (1.29)		-1.01 (1.42)	-2.10	20	.048
BVMT-R learning ^d		-0.04 (1.15)		0.08 (1.34)	0.22	20	.825
Visual Sweeps ^e		3.31 (124.99)		-18.32 (113.48)	-0.42	20	.678

Note. RCI = reliable change index; Improvers = reliable change index of ≥ 1.96 , being the 95% confidence interval, in at least one domain and performance

maintained across other domains; Non-improvers = reliable change index of ≤ 1.96 or ≥ -1.96 ; CPZ = Chlorpromazine equivalent; PANSS = Positive and Negative Syndrome Scale. MCCB = MATRICS Consensus Cognitive Battery; PS = problem solving; HVLT-R = Hopkins Verbal Learning Test-Revised; BVMT-R = Brief Visual Memory Test-Revised.

^aPremorbid IQ was measured with the Wechsler Test of Adult Reading (WTAR).

^bCurrent IQ was measured with the Wechsler Abbreviated Scale of Intelligence (WASI)-2 subtest version; ^cIQ change = Current IQ minus Premorbid IQ; ^dlearning score = greater of Trial 2 or Trial 3 score - Trial 1 score, standardised; ^eMeasured post-intervention, Posit Science, BrainHQ Visual Sweeps change score = average task response time (milliseconds) from final task presentation minus average task response time from second task presentation.

7.5.2 Response to Cognitive Remediation Therapy. Twelve participants evidenced reliable change across at least one MCCB domain (Figure 7.2). Attention/vigilance was the most frequently improved domain, with large effect sizes seen in attention/vigilance and cognitive composite. Comparing mean RCI scores across Improvers and Non-improvers, Improvers had significantly greater reliable change on attention/vigilance ($M = 1.34$, $SD = 1.34$) compared to Non-improvers ($M = -0.07$, $SD = 1.19$; $t[20] = -2.58$, $p = .018$) and on the cognitive composite ($M = 1.52$, $SD = 0.96$) compared to Non-improvers ($M = 0.09$, $SD = 0.70$; $t[20] = -3.89$, $p = .001$).

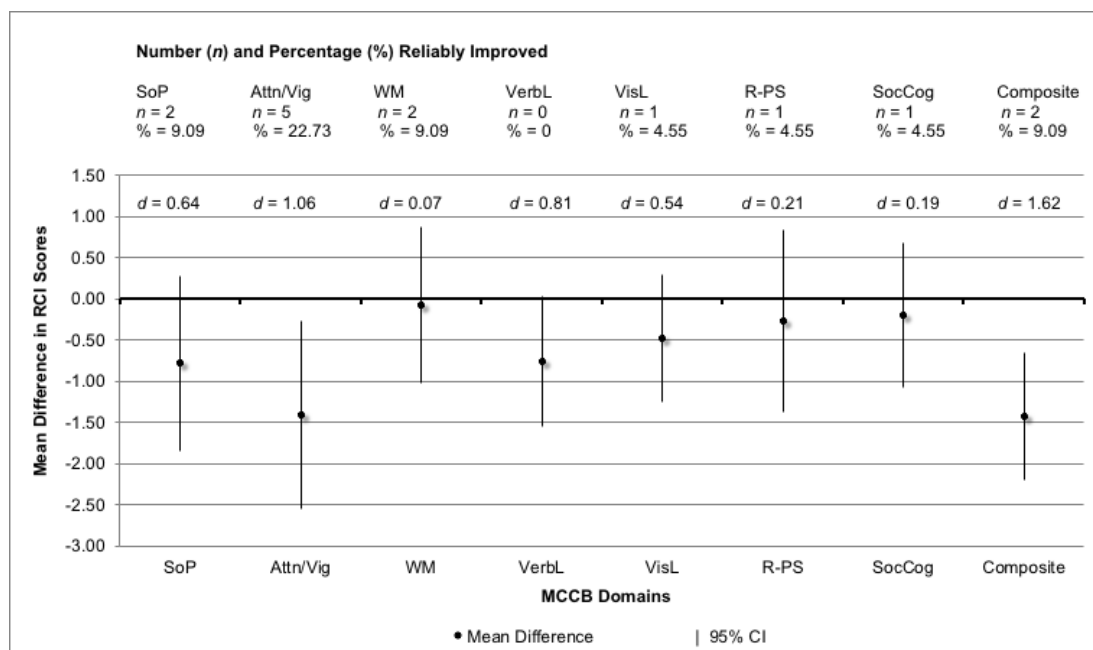


Figure 7.2. Error bars with 95% confidence intervals (CI) comparing Improvers (reliable change ≥ 1.96 in at least one domain with performance maintained across other domains) with Non-Improvers (reliable change index of ≤ 1.96 or ≥ -1.96) across MATRICS Consensus Cognitive Battery (MCCB) domains and cognitive composite. SoP = speed of processing; Attn/Vig = attention/vigilance; WM = working memory; VerbL = verbal learning; VisL = visual learning; R-PS = reasoning and problem solving; SocCog = social cognition; composite = cognitive composite. d = Cohen's d effect size.

7.5.3 Discriminant analysis. The results of Pearson correlations used to identify potential predictors are presented in Table 7.2. Baseline MCCB attention/vigilance and HVLT-R learning, which were not strongly correlated with each other ($r = .12, p = .597$), were included in the direct discriminant analysis as potential predictors of RCI Status.

Table 7.2

Pearson Correlations (R) Between Select RCI Domain Scores and Variables of Interest

Variable of Interest	Attention/Vigilance		Cognitive Composite	
	Mean RCI		Mean RCI	
	<i>R</i>	<i>p</i>	<i>R</i>	<i>p</i>
<i>Intellectual status</i>				
Premorbid IQ (WTAR)	0.02	.918	-0.21	.360
IQ change ^a	0.13	.568	-0.003	.988
<i>Baseline cognition</i>				
MCCB Speed of processing	-0.02	.927	-0.20	.369
MCCB Attention/vigilance	-0.53	.012	-0.23	.294
MCCB Working memory	-0.08	.720	-0.21	.339
MCCB Verbal learning	-0.28	.205	-0.16	.470
MCCB Visual learning	-0.12	.585	0.009	.969
MCCB R-PS	-0.17	.452	-0.36	.100
MCCB Social cognition	0.11	.623	0.18	.430
MCCB Composite	-0.25	.271	-0.22	.317
<i>Learning potential</i>				
HVLT-R learning score ^b	0.12	.597	0.48	.024
BVMT-R learning score ^b	-0.27	.227	0.03	.890
Visual Sweeps change score ^c	-0.17	.441	-0.04	.876

Note: RCI = reliable change index; WTAR = Wechsler Test of Adult Reading; MCCB = *MATRICES Consensus Cognitive Battery*; R-PS = Reasoning and Problem Solving; HVLT-R = Hopkins Verbal Learning Test-Revised; BVMT-R = Brief Visual Memory Test-Revised. **Bolded** *p* values = significant at < .05.

^aCurrent IQ (Wechsler Abbreviated Scale of Intelligence-2 subtest version) minus Premorbid IQ; ^blearning score = greater of Trial 2 or Trial 3 score minus Trial 1 score, standardised; ^cPosit Science, BrainHQ Visual Sweeps change score = average task response time (milliseconds) from final task presentation minus average task response time from second task presentation.

The single discriminant function significantly differentiated those who improved from those who did not show reliable improvement in response to CRT (Wilks' Lambda = 0.716, $\chi^2 [2] = 6.34$, $p = .042$, $\eta^2_p = .28$). The model explained 28.41% of the variance in RCI Status (canonical correlation = .533). HVLT-R learning was a more important predictor than baseline MCCB attention/vigilance (standardised canonical coefficient = .909 and -.685 respectively). The structure matrix indicated the discriminant function was positively correlated with HVLT-R learning (loading = .747) and negatively correlated with baseline MCCB attention/vigilance (loading = -.469). Participants with lower attention/vigilance scores and higher verbal learning potential (HVLT-R learning score) at baseline were more likely to improve in response to CRT. The model correctly classified 63.6% of original and cross-validated cases (Table 7.3), which is more than chance alone (50.4%).

7.5.4 Sensitivity analysis. The analysis was repeated on the subset of 19 completers who had no missing data (Improvers $n = 9$, Non-improvers $n = 10$). The model remained significant, Wilks' Lambda = 0.612, $\chi^2 [2] = 7.86$, $p = .020$, $\eta^2_p = .39$). Results were very similar to those of the full completer sample, explaining 38.81% of the variance in RCI Status (canonical correlation = 0.623) and correctly classifying 68.4% of the original and cross-validated cases (Table 7.3).

Table 7.3

Summary of Classification Results^a for Main and Sensitivity Analysis

Group membership	RCI Status	Predicted group membership <i>n</i> (%)		
		Non-improvers	Improvers	Total
<i>Main analysis</i>				
Original	Not-improved	6 (60.0)	4 (40.0)	10
	Improved	4 (33.3)	8 (66.7)	12
Cross-validation ^b	Not-improved	6 (60.0)	4 (40.0)	10
	Improved	4 (33.3)	8 (66.7)	12
<i>Sensitivity analysis</i>				
Original	Not-improved	7 (70.0)	3 (30.0)	10
	Improved	3 (33.3)	6 (66.7)	9
Cross-validation ^b	Not-improved	7 (70.0)	3 (30.0)	10
	Improved	3 (33.3)	6 (66.7)	9

Note: RCI = reliable change index; Non-improvers = reliable change index of ≤ 1.96 or ≥ -1.96 ; Improvers = reliable change ≥ 1.96 (95% confidence interval) in at least one domain with performance maintained across other domains.

^aPrior probabilities computed from group size. ^bLeave-one-out method; an iterative process of removing then re-classifying a single case at a time based on the discriminant function derived from the remaining sample.

7.6 Discussion

We explored whether intellectual status, cognitive ability and learning potential were predictive of a stringent measure of reliable change following CRT in a cohort diagnosed with schizophrenia-related disorders. Consistent with other studies to calculate RCI (Bryce et al., 2018; Lindenmayer et al., 2017; Murthy et al., 2012; Wykes et al., 1999), a majority of participants realised reliable change in at least one cognitive domain. Improvers achieved significantly better performance on attention/vigilance and cognitive composite compared to Non-improvers.

We found partial support for our hypothesis that a combination of intellectual status and cognitive ability, in conjunction with a measure of learning potential, would be predictive of reliable change. Our results revealed that baseline attention/vigilance and pre-treatment verbal learning potential aided discrimination of Improvers from Non-improvers, explaining a small percentage of the variance in RCI Status. Individuals who, at baseline, scored more poorly on attention/vigilance and who demonstrated greater verbal learning potential, were more likely to realise benefit from CRT.

7.6.1 Predictive role of cognitive ability. The association between baseline cognition and within-domain improvement is one of the more robust associations found in the predictor literature (Biagianti et al., 2016; Bosia, Bechi, et al., 2014; Farreny et al., 2016; Kontis et al., 2013; Penadés et al., 2016). Regarding the association between attention/vigilance and reliable change, Lindenmayer et al. (2017) found that better baseline MCCB attention/vigilance was predictive of within-domain reliable change in a sample of more severely cognitively impaired individuals ($M = 28.11$, $SD = 12.39$). Conversely, Twamley, Burton and Vella (2011) reported a negative association between baseline attention/vigilance and within-domain, post-CRT improvement (on Wechsler Adult Intelligence Scale-III digit span forward). They surmised that there might be greater room for improvement in individuals with poorer initial performance, an interpretation that would, in part, explain our own finding. Attentional processes play a critical role in skills acquisition, underpinning the ability to benefit from repeated practice (Bowie et al., 2008; Chein & Schneider, 2012; M. F. Green, 1996; Kurtz et al., 2009; Kurtz & Wexler, 2006). However, there may be a threshold of performance below which the capacity to benefit from CRT is reduced without additional support (Silverstein et al., 2014). Given the interaction of multiple systems during the learning process (Chein & Schneider, 2012), it is unlikely that any such threshold can be determined through examination of baseline cognition scores alone. Greater insight regarding an individual's capacity to benefit from CRT might be gained through consideration of their baseline learning potential, which is inherently linked to cognition (discussed in Sections 4.9.3 and 7.6.3).

7.6.2 Predictive role of learning potential. Contrary to expectations, training task performance within BrainHQ did not predict response to CRT. However, our exploratory analysis of static measures drawn from the MCCB yielded

a result, with verbal learning potential having prognostic value. This pattern of results was surprising given the stronger support for the prognostic value of training task performance (Biagianti et al., 2016; Fisher et al., 2015, 2009; Fiszdon et al., 2016; Murthy et al., 2012; Surti et al., 2011; Tarasenko et al., 2016) and limited support for static measures of learning potential (M. F. Green et al., 2000; Vaskinn et al., 2008). This clearly needs to be followed up in future work.

7.6.2.1 Training task performance. It is possible our participants spent insufficient time on the Visual Sweeps task (approximately 5 hours) to drive and predict meaningful change. There was minimal overall change in visual processing speed (mean change = -6.62 ms, $SD = 117.57$ ms) and Improvers and Non-improvers did not differ in the degree of change realised ($t[20] = -0.42$, $p = .678$, $d = 0.19$). The lack of predictive effect could also be due to the way we measured task performance. Biagianti et al. (2016), for example, found auditory processing speed at time of performance plateau, not change scores, were predictive of post-intervention cognitive change.

7.6.2.2 Verbal learning potential. While static measures are less predictive than dynamic tests of learning potential (Fiszdon, McClough, et al., 2006; Rempfer et al., 2011; Sergi et al., 2005; Watzke et al., 2009; Weingartz, Wiedl, & Watzke, 2008; Woonings et al., 2002), they are not without prognostic value. Static measures have been found to predict differences in use of semantic clustering techniques (Vaskinn et al., 2008), to explain variance in readiness for psychosocial rehabilitation (Fiszdon, McClough, et al., 2006) and work skills acquisition (Sergi et al., 2005), and have been associated with benefit from rehabilitation (Woonings et al., 2002). It has been argued that learning potential is inherent in tests involving repeated administration as they encourage implementation of strategies to enhance recall (M. F. Green et al., 2000; Vaskinn et al., 2008). Given the parallels between these measures of self-directed learning and the skills that were required for our participants to realise benefit from what was largely unfacilitated CRT training, it is not surprising that a demonstrated ability at baseline to improve on a list learning task corresponded with post-CRT benefit.

7.6.3 The link between baseline cognition, learning potential and response to CRT. When modelling the relationship between basic cognition, learning potential, skills acquisition, and outcome in schizophrenia, Green et al. (2000) characterised learning potential as being dependent on, but distinct from,

baseline cognition, while being closely aligned with external outcome measures. This interconnectedness is manifest in studies that report a relationship between baseline cognition and both learning potential (Kurtz & Wexler, 2006; Rempfer, Hamera, Brown, & Bothwell, 2006; Vaskinn et al., 2009; Wiedl, Wienöbst, Schöttke, Green, & Nuechterlein, 2001) and training task improvement (Biagianti et al., 2016; Davidson et al., 2016; Fiszdon et al., 2005) and, in turn, in studies that report an association between learning potential and outcome (see previous section). Our results support this distinction and highlight the value in assessing both baseline cognition, the profile of which can vary by individual and group, and learning potential when attempting to discern those most likely to benefit from CRT (Boosman et al., 2016). Learning potential proved the stronger measure of whether an individual had the requisite cognitive capacity for reliable change. In a clinical setting, this would have allowed for more informed treatment decisions.

7.6.4 Strengths and limitations. Seeking to identify factors that underpinned variability in individual cognitive response to CRT, our analysis approach addressed some of the limitations inherent in examining group level correlates of pre-post change scores. Reliable change indices accounted for both measurement error and practice effects and revealed individual differences in cognitive response to CRT. In contrast to previous RCI studies, we selected potential predictors that were directly associated with the cognitive domains across which Improvers and Non-improvers realised significantly different levels of change. We extended the predictor field through our exploratory analysis of IQ change and learning potential, providing future direction for larger, confirmatory studies.

It is important to note that these results may not generalise to CRT interventions that incorporate strategy training and/or adjunctive therapies. Moreover, there are limitations to both static and dynamic tests of learning potential that should be taken into account when looking to predict future performance (Boosman et al., 2016; Fiszdon & Johannesen, 2010). Although the measure we selected had more power due to its dimensional properties, it did not account for high achievers, being individuals who scored highly on List 1 of the HVLT-R and thus who had less scope for improvement.

While our results should be interpreted with caution given our small sample size and the large portion of variance unaccounted for, they have face validity and both support, and extend on, previous studies to investigate these factors.

Chapter 8. Patterns and Predictors of Individual Response to CRT

8.1 Chapter Guide

Though presented in publication format, “Exploring Differential Patterns and Predictors of Response to Cognitive Remediation in Individuals Diagnosed with Schizophrenia-Related Disorders” (Reser & Rossell, unpublished) has not yet been submitted. It is recognised that the small study sample size makes publication in top quartile journals unlikely. However, the paper is of clinical interest and may form part of a future commentary or review piece.

The article draws on outcomes from the systematic review presented in Chapter 4. The reader is referred to Section 4.9 of that chapter, which discusses in greater depth the specific variables of interest, to Chapter 5, which sets out the aims and objectives of Study 2, and Chapter 6, which details the study methodology.

There is a marked difference between what was possible in the writing of this article and what had been planned on the basis of a larger study sample size. Having initially anticipated completing the CRT intervention with at least 60 individuals, more traditional analytic methods, such as discriminant analysis or multivariate analysis of variance, had been planned. Additionally, there had been an intention to explore the potential influence of such variables as IQ trajectory and the gene for encoding dysbindin-1 on cognitive response to CRT. However, insufficient variability in IQ trajectory and insufficient power more generally, precluded those planned lines of enquiry and methods of analysis. In their place, in keeping with the theme of identification and exploration of potential predictors of differential cognitive response to CRT, it was decided that a more qualitative approach to the data might reveal patterns of association worthy of future investigation.

This article’s value rests in its exposure of some of the limitations of traditional analytic methods when applied to the complexities of individual variability in response to therapeutic intervention. It rests in the discussion of the implications of such limitations when seeking to translate research outcomes to clinical practice. And it rests in its attempt at something novel: the modelling of techniques that, when applied to larger datasets, might move us closer to understanding what factors influence individual response to, and the efficacy of, CRT in people with schizophrenia.

8.2 Abstract

Background: Heterogeneity is evident in cognitive outcomes following cognitive remediation therapy (CRT) for individuals diagnosed with schizophrenia-related disorders. However, differential patterns of response are infrequently reported, and little is known about potential predictors of differential response. We sought to determine if more granular patterns of cognitive response to CRT could be identified and whether use of an innovative data visualisation technique would help characterise potential patterns and predictors of response.

Method: Twenty-two participants diagnosed with schizophrenia-related disorders completed 24 sessions of CRT. The MATRICS Consensus Cognitive Battery (MCCB) was administered pre- and post-intervention to evaluate cognitive response to CRT. Reliable change indices were calculated across MCCB domains and were examined for distinct patterns of response. Heat maps were generated to aid the investigation of possible subgroup associations between MCCB domain-level change scores and potential predictors of response

Results: Four response patterns were identified: Improved, Declined, Mixed, No Change. When response patterns were analysed as groups, they did not differ across baseline characteristics. The heat maps revealed a possible association between post-intervention symptom severity and cognitive response to CRT in the Mixed response group. Verbal learning potential was the variable that showed the most likelihood of distinguishing between the groups.

Discussion: Heat maps were an effective tool for exploring potential associations between response and variables of interest. This may prove a useful model for future analysis in larger datasets. These preliminary findings suggest that response to CRT extends beyond an improved/not improved dichotomy and that baseline verbal learning potential and clinical presentation at time of post-assessment may be fruitful lines of future enquiry.

8.3 Introduction

When translating research outcomes into clinical practice, information regarding inter-individual variability has the potential to enhance therapeutic decision-making, and to inform the complex process of tailoring interventions to individual needs (Ruberg, Chen, & Wang, 2010). This is especially so where heterogeneity of response is apparent. As Kravitz, Duan, and Braslow (2004, p. 662) explained, in the presence of said heterogeneity, "...the modest benefit ascribed to many treatments in clinical trials can be misleading because modest average effects may reflect a mixture of substantial benefits for some, little benefit for many, and harm for a few." The potential misattribution of group effects to all participants could undermine treatment effectiveness for some and, more generally, reduce the degree to which reported outcomes can be replicated in practice (Kraemer, Frank, & Kupfer, 2006).

Complicating matters further, traditional group-level analysis masks heterogeneity of response (Jacobson et al., 1984). It is not possible to discern inter-individual variability from group-level means and standard deviations, tests of significance, or effect sizes. Moreover, unless underlying moderators of effect are accounted for, the veracity of analytic outcomes can be undermined by potentially biased effect sizes and reduced statistical power (Kraemer et al., 2006). While the limitations of group analysis have long been acknowledged, the adoption of analytic methods that better characterise treatment response variability has been slow (e.g., Jacobson & Truax, 1991; Kraemer, Wilson, Fairburn, & Agras, 2002; Lindhiem, Kolko, & Cheng, 2012).

Although moderately effective in improving cognitive functioning (Grynszpan et al., 2011; Wykes et al., 2011), heterogeneity of response has been reported in a subset of studies investigating cognitive remediation therapy (CRT) for individuals diagnosed with schizophrenia-related disorders (Bryce et al., 2018; Hodge et al., 2010; Lindenmayer et al., 2017; Medalia & Richardson, 2005; Penadés et al., 2006; Vita et al., 2013; Wykes et al., 1999). Estimates from these studies suggest that around 40-50% of participants fail to realise cognitive benefit from CRT. However, echoing Kravitz et al. (2004), it is not clear what proportion of these studies' participants realised substantial versus moderate levels of improvement and, of those who failed to benefit, whether any experienced a clinically significant decline in performance. The data needed to ascertain these more nuanced patterns of

response was either not reported or was limited to an improved/not-improved dichotomy.

Investigation of potential predictors of cognitive response to CRT has primarily focused on group-level outcomes. Of the few CRT studies to examine factors that discriminate improvers from non-improvers (Lindenmayer et al., 2017; Medalia & Richardson, 2005; Vita et al., 2013; Wykes et al., 1999), results are inconsistent. No support has been found for demographics such as age, gender or ethnicity. Vita et al. (2013) found that antipsychotic medication dosage differentiated improvers from non-improvers, a result not replicated by Lindenmayer et al. (2017). Medalia and Richardson (2005) found some support for baseline cognition, an association not found by either Wykes et al. (1999) or Vita et al.. Other potential predictors of differential response have included training type, attendance, and intensity (Medalia & Richardson, 2005), training task progress (Murthy et al., 2012), and intellectual status (Fiszdon, Choi, et al., 2006), though these currently lack replication at a response subgroup level.

We were interested in determining whether different patterns of response existed at a subgroup level and, if so, their association with potential predictor variables of interest. Given the possibility of complex, differential patterns of interaction between multiple predictor variables and multiple response groups, we sought a method of presenting data in a simplified manner that facilitated preliminary, more qualitative exploration of potential associations. Heat maps have a long history of use to highlight characteristics of interest (Wilkinson & Friendly, 2009) and have previously been used to represent “*measures of association between variables*” (Toddenroth, Ganslandt, Castellanos, Prokosch, & Bürkle, 2014, p. 80; italics in original). Heat maps enable the plotting of data irrespective of whether underlying parametric assumptions have been met, allow for the reordering of data so as to optimise the exploration of relationships of interest and, in sufficiently large datasets, can be valuable in exposing the unremarkable as a benchmark for assessing unusual patterns of association (Pleil, Stiegel, Sobus, Liu, & Madden, 2011). As concluded by Pleil et al. (2011, p. 8), “[t]he heat map approach... is an excellent qualitative screening tool for quickly exploring broad hypotheses regarding relationships... before computational efforts are expended.”

8.4 Study Aims

The overarching goal of this preliminary study was to assess whether use of data visualisation techniques would yield additional information regarding potential differential patterns and predictors of response to CRT that might better inform clinical practice, and that could provide direction for future confirmatory studies. Using reliable change index scores as determinates of cognitive response to CRT, we aimed to determine whether: (a) more than two distinct patterns of response were identifiable, (b) resultant subgroups differed in their baseline presentation, and (c) qualitative examination would reveal patterns of association that might represent potential predictors of differential response.

Determination of potential predictors of response was informed by prior research. Select domains of baseline cognition have been found to be predictive of within-domain improvement (Biagianti et al., 2016; Bosia, Zanoletti, et al., 2014; Farreny et al., 2016; Kontis et al., 2013; Wykes et al., 1999). We therefore explored whether potential patterns of association with baseline cognition differed by CRT response group. In previous analysis of this sample, we found that a static measure of verbal learning potential discriminated improvers from non-improvers (Section 7.5.3). We sought to extend on this by examining whether the association differed at a more granular subgroup level. Finally, informed by an apparent change in clinical presentation of some participants across the course of this study, we included measures of pre- and post-intervention clinical functioning to see whether clinical symptoms influenced cognitive response to CRT.

As previous studies have been limited to either group-level or dichotomist (improved/not-improved) analysis, we did not formulate a hypothesis about the number of response groups to emerge. We did not expect participants to differ across demographics or baseline clinical and cognitive presentation but, in keeping with our earlier results, expected that they would differ across verbal learning potential. We further hypothesised that select domains of baseline cognition and learning potential would emerge as possible predictors of differential response. Our examination of the influence of post-intervention clinical presentation was exploratory.

8.5 Methods

Approval for this single arm, pre-post pilot study was obtained from hospital (The Alfred, St Vincent's Hospital Melbourne, Monash Health) and university

(Swinburne University of Technology) human research ethics committees. Study procedures adhered with Declaration of Helsinki principles.

8.5.1 Participants. Participants were recruited through public mental health care services and community sector support groups in the Melbourne Australia region. Eligibility criteria included diagnosed with a schizophrenia-related disorder, aged 18-65 years, stabilised on medication, and fluent in English. Exclusion criteria included an estimated premorbid IQ below 75, reported premorbid condition (e.g., acquired brain injury, neurological disorder) or recent substance abuse that could independently compromise cognitive functioning, and/or electroconvulsive shock therapy in the prior six months.

8.5.2 Assessment.

8.5.2.1 Clinical. Participant's mental health was assessed, and diagnosis confirmed, using the Mini International Neuropsychiatric Interview Screen 5.0.0 (Sheehan & Lecrubier, 2006). Psychotic symptoms (positive, negative and general subscales) were assessed using the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987). The Calgary Depression Scale for Schizophrenia (CDSS; Addington et al., 1990) was used to measure depressive symptoms, selected for its ability to discriminate depressive from negative psychotic symptoms (Kontaxakis et al., 2000). On the PANSS and CDSS, higher scores reflected increased symptomatology over the prior week.

8.5.2.2 Intelligence quotient (IQ). Premorbid IQ was assessed using the Wechsler Test of Adult Reading (WTAR; Wechsler, 2001). Current IQ was assessed using the Wechsler Abbreviated Scale of Intelligence (WASI)-2 subtest version (Wechsler, 1999).

8.5.2.3 Neuropsychological. Cognitive functioning was assessed using the MATRICS Consensus Cognitive Battery (MCCB; Nuechterlein et al., 2008). Age- and gender-adjusted *T*-scores (mean = 50, *SD* = 10; Kern et al., 2008) were calculated for speed of processing, attention/vigilance, working memory, verbal learning, visual learning, reasoning and problem solving, and social cognition domains and for the cognitive composite. Details of measures comprising these domains and their test-retest reliability have been published elsewhere (Georgiades et al., 2017; Nuechterlein et al., 2008).

8.5.3 Reliable change index (RCI). Individual response to CRT was measured by reliable change indices, calculated across MCCB domain- and

composite-level pre-post change scores. The RCI provides a measure of whether clinically meaningful change has occurred and the amount of change beyond that attributable to measurement error (Jacobson & Truax, 1991). To account for practice effects, we used a modified version of Jacobson and Truax's (1991) calculation (see Chelune et al., 1993) using rates published by Gray et al. (2014). MCCB domain level RCIs were assessed at the 90% confidence interval, being ± 1.65 .

8.5.4 Learning potential. Static measures of verbal and visual learning potential were derived from the Hopkins Verbal Learning Test-R (HVLt-R; Benedict et al., 1998) and the Brief Visuospatial Memory Test-R (BVMt-R; Benedict et al., 1996) through calculation of learning scores. Learning scores were calculated using Benedict and colleagues' formula (greater of trial 2 or trial 3 score) – (trial 1 score), standardised by age group using normative data published by the test developers (Benedict et al., 1998, 1996). Higher scores reflected better performance.

8.5.5 Cognitive Remediation Therapy. CRT was undertaken using BrainHQ's (Posit Science™) VISUAL Intensive, a commercially available, web-based tool. Training tasks targeted attention, visual processing speed, and visual working memory. Participants worked with relative independence through up to 40 levels of visual processing training, with each level comprising two of five training tasks: Visual Sweeps, Target Tracker, Double Decision, Eye for Detail, and Hawk Eye. Task difficulty was dynamically responsive to individual performance so as to maintain 80-85% task success rate, with frequent on-screen embellishments used to positively reinforce progress. Detailed task information is available on the BrainHQ website (<https://www.brainhq.com/why-brainhq/brain-training-your-way/brainhq-courses-challenges/visual-intensive>).

8.5.6 Procedure. Potential participants were screened for eligibility before meeting with the first author, who provided a study briefing and obtained written, informed consent. Baseline assessments (demographic, clinical and cognitive) were completed over two, three-hour sessions by trained doctoral-level students and post-doctoral researchers otherwise uninvolved in the study. The senior author regularly performed inter-rater reliability checks. The CRT facilitator remained blind to assessment outcomes until participant completion. Participants attended 1-3 group or individual sessions a week, working independently at their own pace for 45-60 minutes each session. Sessions were supervised by the first author, a Doctor of

Psychology (Clinical) candidate. A single participant worked from home and was monitored remotely. On completion of a minimum 24 sessions, participants attended a single, 3-hour post-intervention assessment session (clinical, cognitive).

Participants were reimbursed for assessment sessions (\$40 per 3-hour session) only.

8.5.7 Response group categorisation. Response group membership was determined based on individual patterns of response across MCCB cognitive domains and the cognitive composite, as measured by the RCI. An $RCI \geq 1.65$ reflected improvement, an $RCI \leq -1.65$ reflected decline, and values within these thresholds equated to no change/maintained performance.

8.5.8 Statistical analysis. Analysis was restricted to participants who completed post-intervention assessments. Due to small subgroup sample sizes it was not possible to determine whether data met assumptions of normality. Median and interquartile values are presented to characterise the sample, with means and standard deviations presented in Appendix J to aid cross-study comparisons. Group differences across continuous baseline variables and MCCB change scores were examined using the Kruskal-Wallis Test, a nonparametric equivalent of one-way analysis of variance. Eta-squared (η^2) was used as a measure of effect size, calculated using Psychometrica's online tool (Lenhard & Lenhard, 2016). Chi-square test for independence (χ^2) was used to examine dichotomous variables. Analysis was limited to main effects; post-hoc analyses were not conducted, minimising the risk of over-interpretation.

8.5.9 Qualitative analysis. Heat maps, generated in Microsoft® Excel with conditional formatting, were used to examine subgroup associations between MCCB domain change scores, i.e., post-intervention score minus baseline score, and potential predictors of response. Measures of baseline cognition, baseline intellectual status, and baseline and post-intervention clinical presentation were standardised using sample group means. Learning potential (HVLt-R and BVMT-R learning) had already been standardised using published normative data. Each heat map cell represents the sum of individual, MCCB domain level change scores multiplied by predictor variable z-scores. For example, in the Declined group, the intersection of baseline CDSS (depressive symptoms) and A/V (MCCB attention/vigilance change score), represents $\text{sum}(\text{sum}(\text{participant}_1 \text{ A/V} * \text{z-CDSS}) + \text{sum}(\text{participant}_2 \text{ A/V} * \text{z-CDSS}) + \text{sum}(\text{participant}_3 \text{ A/V} * \text{z-CDSS}))$. This approach accounts for within-group inter-individual variability. Within each

response group heat map, scores were colour-coded based on within-group percentiles. Purple gradients reflect cell values falling $\leq 10^{\text{th}}$ percentile and teal gradients reflect cell values falling $\geq 90^{\text{th}}$ percentile. Values falling between these were shaded grey to reduce noise.

8.6 Results

Of 30 participants who commenced CRT, 22 completed a minimum 24 sessions and were included in our analysis. Participant flow is presented in Figure 8.1.

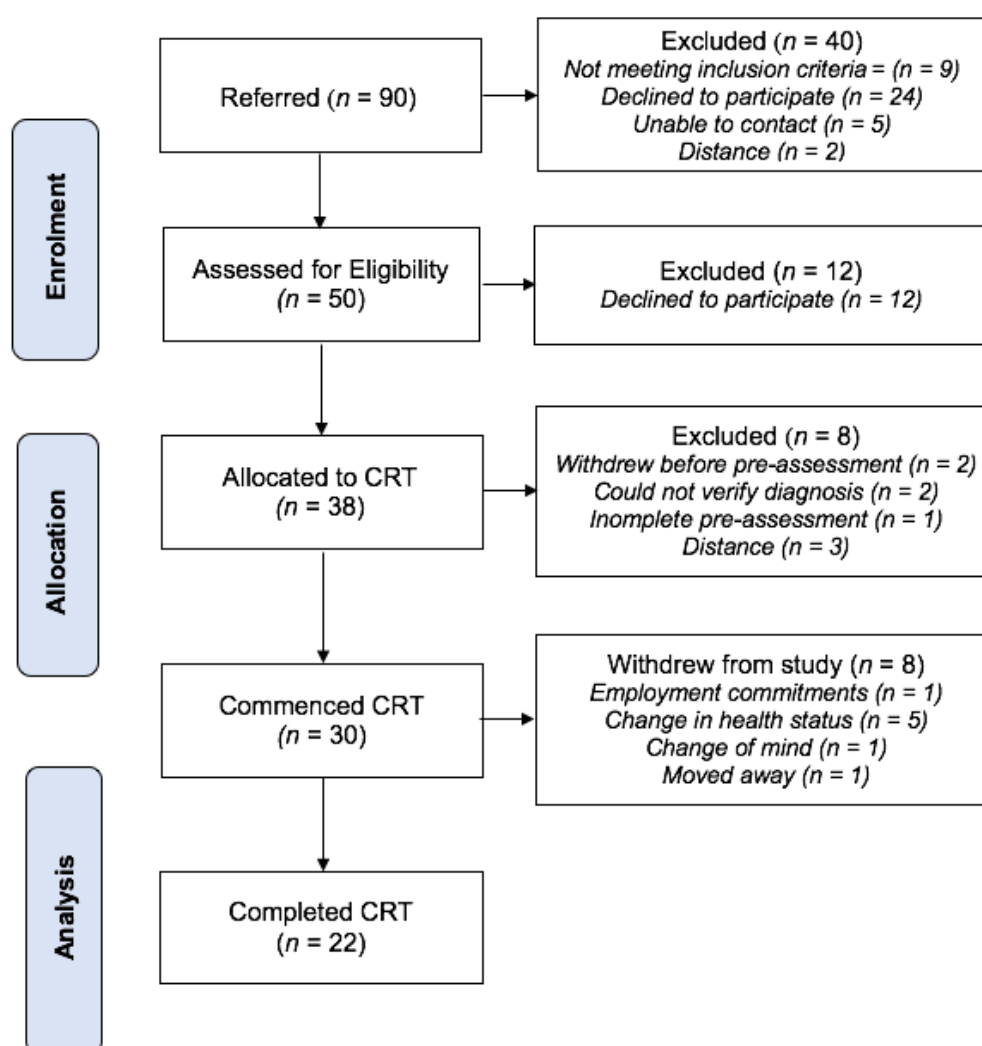


Figure 8.1. CONSORT 2010 Flow Diagram.

8.6.1 Patterns of response. Reliable change was realised across all cognitive domains, with attention/vigilance the most frequently improved domain (Figure 8.2).

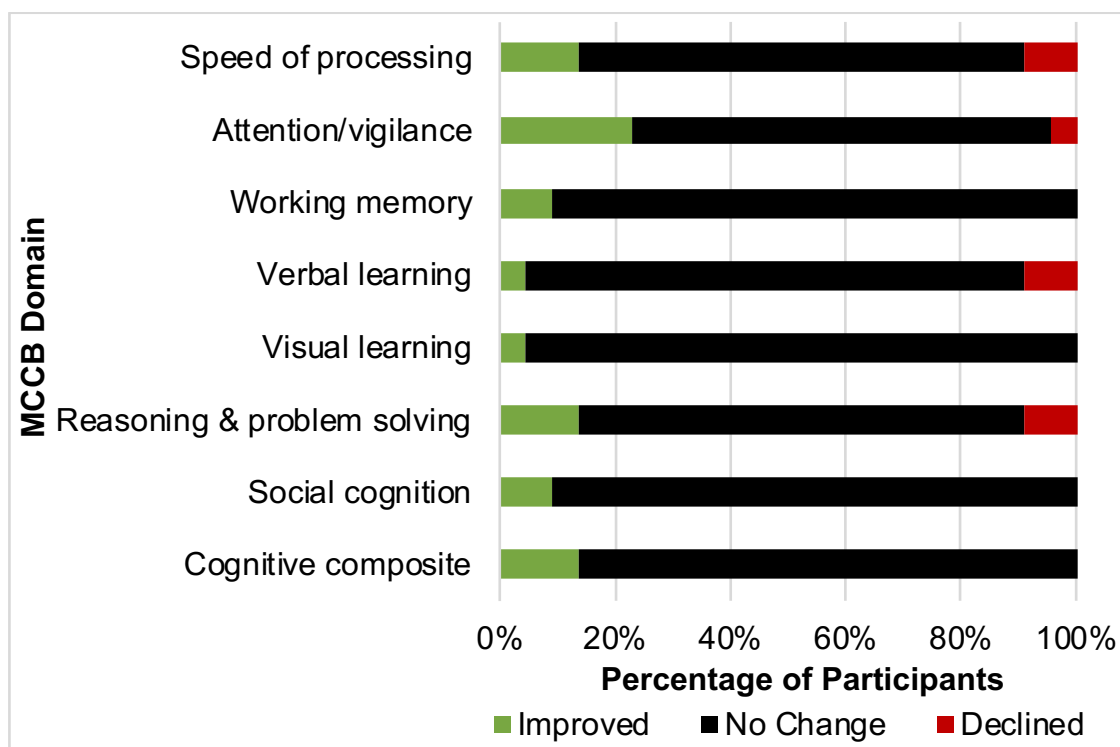


Figure 8.2. Categorisation of individual response to cognitive remediation therapy by MCCB domain (N = 22). Categorisations based on reliable change indices (RCI) at 90% confidence interval, adjusted for practice effects. Improved = $RCI \geq 1.65$; No Change = $RCI < 1.65$ and > -1.65 ; Declined = $RCI \leq -1.65$.

Note: MCCB = MATRICS Consensus Cognitive Battery.

Examination of participant MCCB domain- and composite-level RCI scores revealed four distinct patterns of response:

- Improved ($n = 12$): Individuals who realised improvement in at least one cognitive domain ($RCI \geq 1.65$), with maintained performance across other domains.
- Declined ($n = 3$): Individuals who declined in at least one cognitive domain ($RCI \leq -1.65$), with maintained performance across other domains.

- Mixed ($n = 3$): Individuals who showed a mixture of improvement ($\text{RCI} \geq 1.65$) and decline ($\text{RCI} \leq -1.65$), with maintained performance across other domains.
- No Change ($n = 4$): Individuals who maintained performance across all domains ($\text{RCIs} < 1.65$ and > -1.65).

Differential patterns of cognitive response were most evident on the MCCB cognitive composite, where the Improved group realised significantly greater change compared to the Declined group ($\chi^2[3] = 9.59, p = .022, \eta^2 = 0.40$; see Figure 8.3). Verbal learning was notable for the lack of improvement realised across all but the Improved response group.

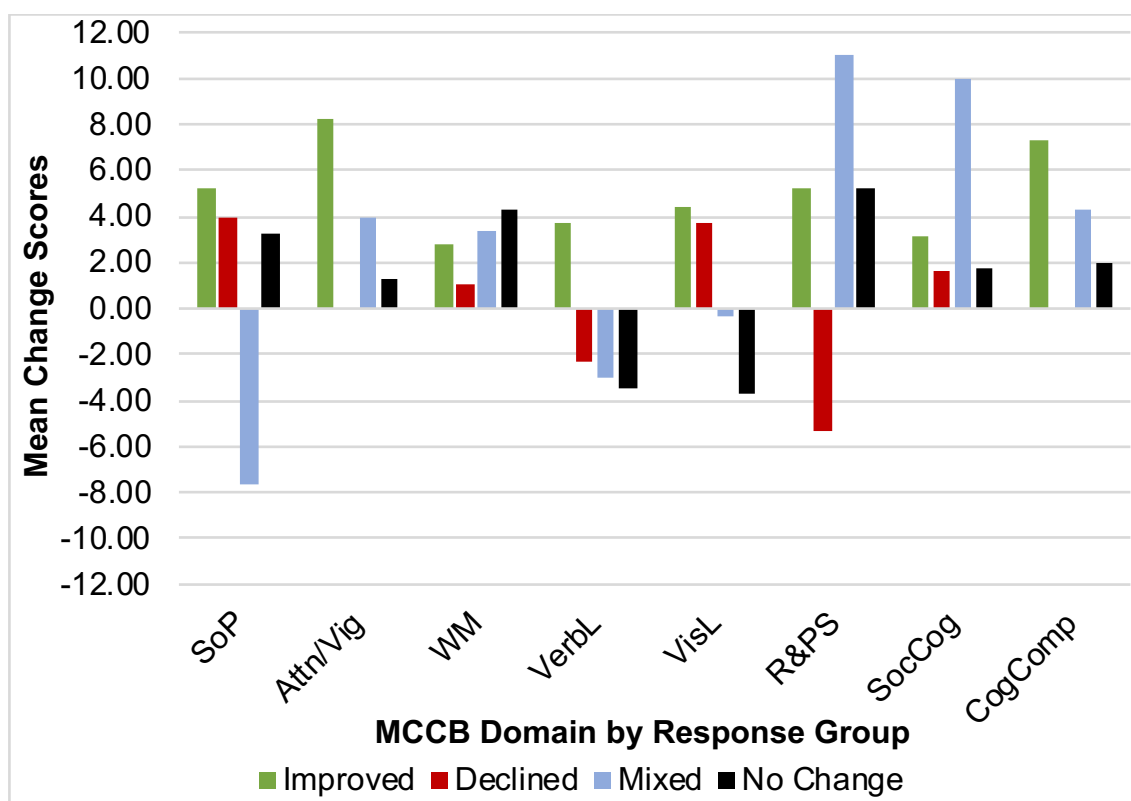


Figure 8.3. Mean change scores by Response Group across MATRICS Consensus Cognitive Battery (MCCB) domains. Response groups: Improved = $\text{RCI} \geq 1.65$ in at least one domain and none ≤ -1.65 ; Declined = $\text{RCI} \leq -1.65$ and none ≥ 1.65 ; Mixed = at least one domain ≥ 1.65 and one domain ≤ -1.65 ; No Change = $\text{RCI} < 1.65$ and > -1.65 . SoP = speed of processing; Attn/Vig = attention/vigilance; WM = working memory; Verbl = verbal learning; VisL = visual learning; R&PS = reasoning & problem solving; SocCog = social cognition CogComp = cognitive composite.

Sample characteristics for study completers by Response Group are presented in Table 8.1. There were no statistically significant differences across Response Group levels. A trend towards significance was found on current IQ; Improved participants had lower current IQ compared to Mixed participants. All groups evidenced a decline in IQ from premorbid levels. Participants with a mixed response to CRT had a younger median age, with a corresponding shorter duration of illness, relative to other groups. They also scored more highly on baseline depressive symptoms and positive and general psychotic symptoms. Across baseline measures of cognition, the Declined group was notable for its stronger cognitive performance, with median scores on four MCCB domains at or above the normative mean.

Table 8.1

Baseline Demographic, Clinical, and Cognitive Characteristics by Response Group^a

Characteristic	Measure	Response Group				χ^2	df	p
		Improved (n = 12)	Declined (n = 3)	Mixed (n = 3)	No Change (n = 4)			
<i>Demographics</i>								
Age (years)	<i>Mdn (IQR)</i>	39.00 (27.75-49.75)	44.00 (43.00-44.00)	27.00 (27.00-37.00)	39.00 (34.00-47.75)	3.06	3	.382
Years of education	<i>Mdn (IQR)</i>	13.50 (13.00-15.00)	14.00 (9.75-16.75)	13.00 (13.00-17.00)	13.50 (13.00-16.25)	0.21	3	.976
Gender (male)	<i>n (%)</i>	8 (66.7)	1 (33.3)	1 (33.3)	2 (50)	1.83	3	.608
Ethnicity	<i>n (%)</i>					11.34	6	.078
Caucasian		12 (100)	2 (66.7)	2 (66.7)	3 (75)			
Asian		0 (0)	1 (33.3)	0 (0)	0 (0)			
Other		0 (0)	0 (0)	1 (33.3)	1 (25)			
<i>Clinical</i>								
Diagnosis	<i>n (%)</i>					5.87	6	.438
Schizophrenia		9 (75)	3 (100)	1 (33.3)	2 (50)			
Schizoaffective		2 (16.7)	0 (0)	2 (66.7)	2 (50)			
Schizophreniform		1 (8.3)	0 (0)	0 (0)	0 (0)			
Years of illness	<i>Mdn (IQR)</i>	11.50 (4.00-18.25)	22.00 (10.00-22.00)	2.00 (1.00-7.00)	9.50 (3.75-26.50)	4.81	3	.186
Medication (CPZ mg/day)	<i>Mdn (IQR)</i>	733.33 (612.50-1100.00)	400.00 (200.00-700.00)	266.66 (200.00-1066.67)	1283.00 (100.00-1483.33)	2.61	3	.456
CDSS	<i>Mdn (IQR)</i>	1.00 (1.00-3.75)	2.00 (0.00-6.00)	8.00 (6.00-16.00)	3.00 (1.25-13.00)	6.40	3	.094
PANSS-positive	<i>Mdn (IQR)</i>	13.00 (12.00-19.75)	13.00 (13.00-22.00)	20.00 (15.00-22.00)	12.50 (8.25-22.00)	2.66	3	.447
PANSS-negative	<i>Mdn (IQR)</i>	13.00 (8.50-14.50)	17.00 (11.00-21.00)	7.00 (7.00-17.00)	11.50 (7.75-21.25)	2.64	3	.451
PANSS-general	<i>Mdn (IQR)</i>	25.50 (21.50-34.00)	29.00 (25.00-35.00)	37.00 (35.00-39.00)	29.00 (23.50-33.75)	4.28	3	.233

<i>Intellectual status</i>								
Premorbid IQ ^b	<i>Mdn (IQR)</i>	104.50 (97.50-110.00)	110.00 (106.00-110.00)	119.00 (108.00-120.00)	111.50 (104.50-117.00)	6.60	3	.086
Current IQ ^c	<i>Mdn (IQR)</i>	90.50 (85.00-97.00)	106.00 (78.00-107.00)	106.00 (105.00-117.00)	101.00 (95.50-110.25)	7.31	3	.063
<i>Learning potential</i>								
HVLT-R learning ^d	<i>Mdn (IQR)</i>	-0.13 (-0.79-1.06)	-0.13 (-2.80-1.20)	-0.79 (-2.21-1.20)	-0.80 (-2.80 -0.30)	3.16	3	.367
BVMT-R learning ^d	<i>Mdn (IQR)</i>	-0.24 (-1.21-1.09)	0.06 (0.06-1.24)	0.22 (-1.12-2.44)	0.06 (-1.27-0.50)	0.96	3	.810
<i>Cognition (MCCB)</i>								
Speed of processing	<i>Mdn (IQR)</i>	39.00 (33.75-44.50)	46.00 (42.00-55.00)	46.00 (44.00-67.00)	43.00 (27.50-45.75)	5.24	3	.155
Attention/vigilance	<i>Mdn (IQR)</i>	36.50 (33.25-44.00)	53.00 (29.00-59.00)	39.00 (30.00-54.00)	43.00 (34.75-52.75)	1.38	3	.709
Working memory	<i>Mdn (IQR)</i>	41.00 (36.50-45.50)	48.00 (31.00-59.00)	39.00 (39.00-49.00)	44.50 (39.00-53.00)	0.96	3	.812
Verbal learning	<i>Mdn (IQR)</i>	34.50 (30.00-44.00)	48.00 (27.00-50.00)	42.00 (39.00-50.00)	34.00 (33.25-43.75)	3.12	3	.373
Visual learning	<i>Mdn (IQR)</i>	33.00 (27.75-39.50)	51.00 (25.00-53.00)	32.00 (18.00-45.00)	46.50 (32.25-56.25)	3.83	3	.280
Reasoning & PS	<i>Mdn (IQR)</i>	42.00 (35.25-50.50)	56.00 (54.00-60.00)	41.00 (28.00-44.00)	39.00 (37.25-49.00)	5.86	3	.119
Social cognition	<i>Mdn (IQR)</i>	40.50 (29.25-48.75)	38.00 (37.00-49.00)	32.00 (24.00-50.00)	40.50 (32.00-48.25)	0.47	3	.926
Cognitive composite	<i>Mdn (IQR)</i>	30.00 (27.00-36.50)	50.00 (26.00-57.00)	35.00 (30.00-38.00)	40.50 (26.50-42.50)	2.22	3	.529

Note. Response Group: Improved = reliable change index of ≥ 1.65 , being the 90% confidence interval, in at least one domain and performance maintained across other domains; Declined = $\text{RCI} \leq -1.65$ and none ≥ 1.65 ; Mixed = at least one domain ≥ 1.65 and one domain ≤ -1.65 ; No change = $\text{RCI} < 1.65$ and > -1.65 . *n* = number; *Mdn* = median; *IQR* = interquartile range; CPZ = Chlorpromazine equivalent; CDSS = Calgary Depression Scale for Schizophrenia; PANSS = Positive and Negative Syndrome Scale; HVLT-R = Hopkins Verbal Learning Test-Revised; BVMT-R = Brief Visual Memory Test-Revised; MCCB = MATRICS Consensus Cognitive Battery; PS = problem solving.

^aContinuous variables analysed with Kruskal-Wallis Test and dichotomous variables with Chi-square test for independence. ^bPremorbid IQ was measured with the Wechsler Test of Adult Reading (WTAR). ^cCurrent IQ was measured with the Wechsler Abbreviated Scale of Intelligence (WASI)-2 subtest version; ^dlearning = greater of Trial 2 or Trial 3 score - Trial 1 score, standardised.

When examining the heat maps (Figure 8.4) there is emerging evidence of cross-group patterns of association between potential predictors of cognitive response (rows) and MCCB domain-level change scores (columns).

8.6.1.1 Baseline cognition. No strong within- or between-group patterns of association were apparent between measures of baseline cognition and MCCB domain-level change scores.

8.6.1.2 Clinical symptomatology. In the Improved group, there was a predominance of post-intervention clinical cells that had values falling in the 10th percentile. The reverse was evident in the Mixed group, with a majority of post-intervention clinical cell values falling in the 90th percentile. This pattern suggests a possible association between post-intervention symptom severity and cognitive response to CRT. Examination of CDSS and PANSS scores (Appendix K), indicates statistical stability in clinical presentation across the course of treatment. However, Mixed group members were more symptomatic at baseline, and experienced more pre- to post-assessment clinical change relative to other groups, which can also be seen when comparing baseline with post-intervention clinical patterns of association in Figure 8.4. Specifically, the Mixed group improved across measures of positive and general psychotic symptoms, but experienced increased depressive and negative psychotic symptomatology by intervention end.

8.6.1.3 Learning potential. A high proportion of verbal learning potential by MCCB domain-level values fell at either end of the percentile rank, suggesting a possible association with cognitive response to CRT. This appears to vary by group, with higher percentiles clustered in the Improved response group and lower percentile values dominating the No Change and, to a lesser extent, the Declined groups.

Without the rigor of statistical analysis to clarify and characterise potential associations, further probing of the data would risk over-interpretation.

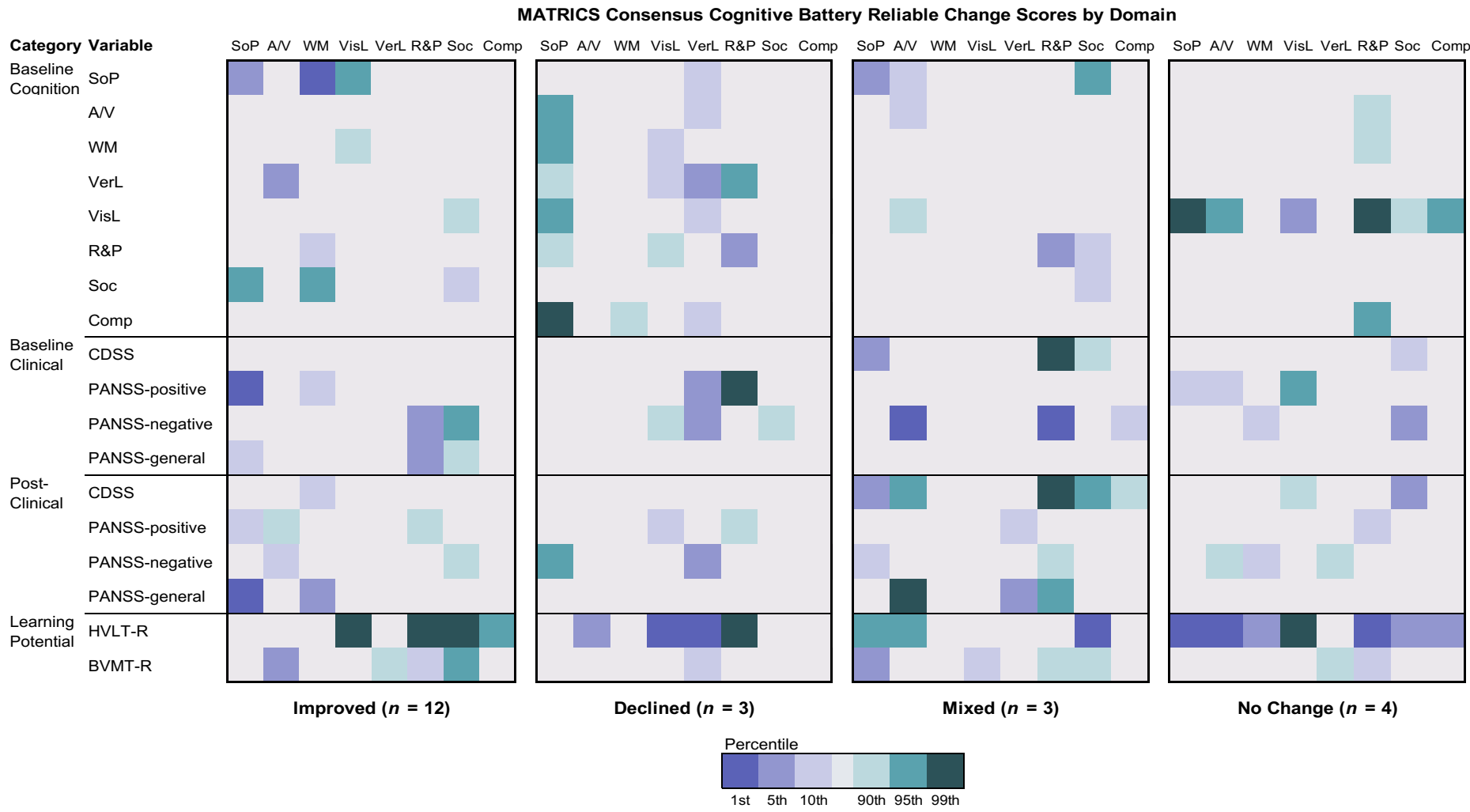


Figure 8.4. Heat maps showing associations between MATRICS Consensus Cognitive Battery change scores (columns) and variables of interest (rows), by Response Group. Colour-coding reflects within group percentiles. Purple gradients reflect values $\leq 10^{\text{th}}$ percentile; teal gradients reflect values $\geq 90^{\text{th}}$ percentile; grey cells reflect values falling within these two percentiles. Response groups: Improved = RCI ≥ 1.65 in at least one domain and none ≤ -1.65 ; Declined = RCI ≤ -1.65 and none ≥ 1.65 ; Mixed = at least one domain ≥ 1.65 and one domain ≤ -1.65 ; No Change = RCI < 1.65 and > -1.65 . SoP = speed of processing; A/V = attention/vigilance; WM = working memory; VisL = visual learning; VerL = verbal learning; R&P = reasoning & problem solving; Soc = social cognition Comp = cognitive composite. CDSS = Calgary Depression Scale for Schizophrenia; PANSS = Positive and Negative Syndrome Scale; HVLN-R = Hopkins Verbal Learning Test-Revised; BVMT-R = Brief Visual Memory Test-Revised; learning = greater of Trial 2 or Trial 3 score - Trial 1 score, standardised.

8.7 Discussion

Heterogeneity is evident in cognitive outcomes following CRT for individuals diagnosed with schizophrenia-related disorders. However, differential patterns of response are infrequently reported and more rarely characterised, and little is known about potential predictors of response variability. This lack of transparency undermines the effectiveness of clinical decision-making and treatment planning. In this preliminary, exploratory study, we sought to determine if more granular patterns of cognitive response to CRT could be identified and, if so, to characterise the patterns and predictors of response using data visualisation techniques.

8.7.1 Patterns of response. Our results are the first, so far as we are aware, to indicate that heterogeneity of cognitive response to CRT may extend beyond the dichotomies of improved/not-improved when considered at a participant level⁷. Examination of reliable change indices revealed four distinct patterns of response. These ranged on a continuum from improved to declined performance, anchored by a group who realised no clinically meaningful cognitive response to CRT. The groups align closely with the range of responses that Kravitz et al. (2004) described as having the potential to confound reported effect sizes, highlighting the importance of making more explicit such inter-individual variability.

Our proportion of improved participants (55%) fell very close to the average of 56% calculated across previous studies to use either a reliable change index, or variant thereof (Bryce et al., 2018; J. Choi & Medalia, 2005; Hodge et al., 2010; Lindenmayer et al., 2017; Medalia et al., 2001; Medalia & Richardson, 2005; Penadés et al., 2006; Vita et al., 2013; Wykes et al., 1999). However, only four individuals realised improvement across more than a single cognitive domain. It is not known how this compares with prior studies. Where previously reported, improvement rates have been provided by cognitive domain rather than by individual participant.

8.7.2 Response group baseline characteristics. There are two caveats to be considered when discussing differences across response group's baseline

⁷ Penadés et al. (2006) determined the number and percentage of participants whose RCI fell below, within, or above a 90% confidence interval. In their sample, no participants were categorised as performing worse than the 90% confidence interval. The improved/not improved dichotomy was not characterised.

presentation. Firstly, as this is the first time cognitive response to CRT has been considered at this level, our discussion is limited to studies that compared improved with not-improved groups. Secondly, our small subgroup sample sizes meant that the analysis was underpowered and at increased risk of type II errors.

As anticipated, response groups did not differ across baseline demographics. This is in keeping with prior studies to compare improved with not-improved groups (Lindenmayer et al., 2017; Medalia & Richardson, 2005; Vita et al., 2013). The hypothesised lack of differentiation across response group's clinical and cognitive presentation is also largely consistent with prior research (Medalia & Richardson, 2005; Vita et al., 2013). Of the few exceptions, Vita et al. (2013) examined psychotic symptoms at a PANSS item level, with differential responses found on positive item delusions and general psychopathology items poor attention and disturbance of volition. Single items on the PANSS, especially the positive and negative subscales, have been found to discriminate well between individual differences in symptom severity (Santor, Ascher-Svanum, Lindenmayer, & Obenchain, 2007), warranting future investigation. Vita et al. also found that having a lower antipsychotic dose differentiated improvers from non-improvers, a result not replicated by Lindenmayer (2017) or in this study. They hypothesised that higher antipsychotic doses could be acting directly on cognition to reduce benefit from CRT, or could be acting indirectly as marker of symptom severity, which Wykes et al. (2011) found to attenuate but not prevent benefit from CRT (Vita et al., 2013). Finally, Medalia and Richardson (2005) found some discriminative evidence for delayed verbal memory, a cognitive function we did not measure.

Contrary to expectations, learning potential did not differ across the four response groups. We had previously found that performance on a static measure of verbal learning potential differed across improved ($M=0.21$, $SD=1.29$) and not-improved ($M=-1.01$, $SD=1.42$) groups ($t[20] = -2.10$, $p = .048$; Reser & Rossell, unpublished). The lack of effect across these current, more exacting, response groups is likely partly due to the adoption of different categorisation rules across the two sets of analyses, which altered group composition. Learning potential has not otherwise been examined in the context of discriminating improved/not-improved response groups.

8.7.3 Use of heat maps to reveal potential predictors of differential response to CRT. The use of heat map visualisations to explore possible

associations between CRT response groups and potential predictors of cognitive response was effective in exposing areas worthy of future consideration. To aid interpretation, we used a divergent colour gradient to expose low and high percentile values, grouped variables of interest in a logical sequence, and presented together cognitive domains that were more specifically targeted in CRT training tasks (i.e., speed of processing through visual learning; Gehlenborg & Wong, 2012). Given our small group sample sizes, we focused only on broad patterns of potential association. To facilitate this, noise was reduced by greying out associations that fell between the 10th and 90th percentiles of each response group.

Investigation of a potential change of clinical presentation in some participants yielded a possible differential association between post-intervention clinical presentation and cognitive response to CRT. This was most apparent in the Mixed group across measures of depressive and psychotic symptomatology and contrasted with associations found in the Improved group. Coupled with observational data from the first author's direct interaction with study participants, we speculate that it was a change in clinical presentation that contributed to the poorer performance of Mixed group participants, who may otherwise have been categorised as Improved. Evidence of an association between baseline symptoms and cognition was found in a systematic review of 58 studies representing 5,009 individuals with a history of non-affective psychosis, whereby higher symptomatology was correlated with poorer cognitive performance (de Gracia Dominguez et al., 2009). And, while evidence suggests that baseline symptom severity does not prevent cognitive gains in response to CRT, benefits can be attenuated with increased symptom severity (Wykes et al., 2011). What is less clear, and could prove a fruitful line of enquiry, is the influence of post-intervention symptomatology on post-intervention assessment performance. It is possible that large scale longitudinal studies that examine the relationship between "current" symptomatology and cognitive response to CRT across multiple time points (e.g., at 20, 40 and 60 sessions of training) could help to tease this relationship out.

The strongest indication of an association with cognitive response to CRT was with verbal learning potential. Opposite patterns of association emerged across Declined/No Change groups and Improved/Mixed groups, albeit more strongly in the Improved and No Change groups. This association is both consistent with our earlier analysis of this sample, where verbal learning potential was found to predict

improved/not-improved group membership, and with previous studies to demonstrate the predictive value of such static measures in assessing participant's capacity to improve across a range of training-dependent activities (Fiszdon, McClough, et al., 2006; Sergi et al., 2005; Vaskinn et al., 2008; Woonings et al., 2002).

8.7.4 Strengths and limitations. Through use of reliable change indices that accounted for both measurement error and practice effects, we were able to characterise heterogeneity of individual response to CRT and present results that could prove more clinically meaningful than traditional group-level analysis. Sensitive to the limitations of statistical analysis involving small samples, heat maps were effective in highlighting potential associations between the variables of interest and response groups. This is a critical first step towards creating a manualised approach to the delivery of CRT in clinical practice. Although we were limited in what definitive conclusions could be drawn, our approach models an alternate method for the examination of CRT predictors over existent, larger datasets, and provides some direction to future investigations regarding potential variables of influence.

It is possible that our findings are an artefact of our small sample, or are specific to our unique group of participants, both potential limitations that can be addressed through more robust, future studies. Further, it is possible that CRT interventions that incorporate strategy training, social cognitive training and/or adjunctive rehabilitation could produce a different set of outcomes to those produced by the methods we employed in this study.

8.7.5 Conclusions. Over thirty years ago, in response to concerns regarding the limitations of traditional group-level analysis, Jacobson, Follette, and Revenstorf (1984, p. 350) suggested that “[s]ome experimentation is in order; the field needs to discover more creative ways of reporting data.” We have attempted a more creative way of exploring data in our effort to better characterise patterns and predictors of cognitive response to CRT to better inform clinical practice. While our approach yielded additional information that would otherwise have been masked by group-level analysis, we encourage a strengthening of this approach across larger, perhaps already completed, CRT trials through use of hierarchical clustering to define response groups and statistical analysis to test the strength of potential associations with predictor variables.

Chapter 9. The Association Between DTNBP1 Genotype and MATRICS Performance

9.1 Chapter Guide

Reser, M. P., Bozaoglu, K., Gurvich, C., Neill, E., Tan, E. J., Rossell, S. L. (in submission). Does the DTNBP1 genotype predict MATRICS Consensus Cognitive Battery performance in schizophrenia and healthy controls?

This chapter comprises the aforementioned article. It has been submitted for publication and reviewer feedback is being responded to by the first author.

Drawing on results from Study 3, this standalone chapter was originally intended as a prelude to exploration of the potential influence of the gene for encoding dysbindin-1 (DTNBP1) on cognitive response to CRT. The small sample size of Study 2 prevented this investigation.

Interest in the potential association between DTNBP1 and cognitive response to CRT spurred this research project over four years ago. Over a dozen studies had reported an association between DTNBP1 and key aspects of cognition (Baek et al., 2012; Zhang, Burdick, Lencz, & Malhotra, 2010). Of the DTNBP1 single-nucleotide polymorphisms (SNPs) associated with schizophrenia and with cognitive impairment, a meta-analysis that considered 10 independent study cohorts representing 7,592 people identified two in particular as having a significant influence on general cognitive ability: P1578 (rs1018381) and P1763 (rs2619522; Zhang et al., 2010). Specifically, minor allele carriers had significantly lower general cognitive ability scores compared to those who were heterozygous on the major allele. It was therefore thought possible that the DTNBP1 genotype might exert an influence on cognitive response to CRT. However, before examining that relationship, I first wanted to establish whether similar associations to those previously reported (reviewed in Chapter 9) could be established in a Melbourne-based schizophrenia and healthy control cohort. In particular, I wanted to determine whether an association between DTNBP1 genotype and performance on the MCCB could be detected. Patterns found cross-sectionally could then be explored in relation to cognitive response to CRT.

9.2 Abstract

Objective: The gene for encoding dysbindin-1, DTNBP1, has been associated with schizophrenia risk, and cognitive ability in healthy controls and individuals with schizophrenia-related disorders. However, previous studies assessing DTNBP1 associations with cognition have yielded inconsistent results, potentially related to methodological differences between studies. We sought to explore the relationship between DTNBP1 genotypes and cognitive performance in schizophrenia and healthy controls using the MATRICS Consensus Cognitive Battery (MCCB), a widely-used, standardised cognitive battery for schizophrenia.

Method: The MCCB performance of 76 participants diagnosed with schizophrenia-related disorders and 160 healthy controls was examined in relation to two DTNBP1 single nucleotide polymorphisms (SNPs), rs1018381 and rs2619522.

Results: Significant diagnostic group by genotype interactions were found in working memory for both SNPs, accounting for 4.9% and 3.9% of the variability respectively. Non-risk group patients (homogenous for major allele) scored lower than risk group patients (minor allele carrier); the reverse was true in the controls. No other interactions or main effects of genotype were found.

Conclusions: The limited associations found between DTNBP1 and cognition, as measured on the MCCB, is consistent with the wider evidence-base. Of the more frequently examined DTNBP1 SNPs, approximately 85% of cognitive associations are not significant. Discrepant results likely reflect the complex interaction of multiple genes implicated in schizophrenia and associated cognitive processes, such that measurable behavioural responses reflect a culmination of influence from otherwise hard to detect single risk variants. The differential sensitivity of the techniques and measures used to assess cognition are also likely contributors to inconsistent results.

9.3 Genes and Cognition in Schizophrenia

Efforts to address the cognitive deficits that characterise schizophrenia-related disorders are hampered by limited pharmacological efficacy (K.-H. Choi, Wykes, & Kurtz, 2013) and by variable individual responses to cognitive enhancement interventions such as cognitive remediation therapy (Bryce et al., 2018; Hodge et al., 2010; Lindenmayer et al., 2017; Medalia & Richardson, 2005; Murthy et al., 2012; Vita et al., 2013; Wykes et al., 1999). Identification of factors that correlate with baseline cognition and, in turn, with treatment response, would aid individualisation of treatment interventions with the aim of optimising cognitive, vocational, and functional gains. Genetic factors may be informative given (a) the high heritability of schizophrenia (Sullivan et al., 2003); (b) heritability of such cognitive domains as attention (heritability [h^2] = 0.48-0.50), processing speed (h^2 = 0.51-0.62) and memory (h^2 = 0.31-0.49; Husted et al., 2009), and (c) evidence of genetic overlap between schizophrenia risk and cognitive ability (Balu & Coyle, 2011; Zai, Robbins, Sahakian, & Kennedy, 2016).

9.4 Dysbindin-1 and Cognition

The gene for encoding dysbindin-1, dystrobrevin binding protein 1 (DTNBP1), has been associated with schizophrenia risk (N. C. Allen et al., 2008; Bray et al., 2005; Funke et al., 2004; Straub et al., 2002) and cognitive ability in both healthy individuals and those diagnosed with schizophrenia-related disorders (Baek et al., 2012; Donohoe et al., 2007; Luciano et al., 2009). The relationship between dysbindin-1 and cognitive impairment is not fully understood; however, reduced levels of dysbindin-1 mRNA and protein in the dorsolateral prefrontal cortex and hippocampal formation of patients with schizophrenia have been implicated in the synaptic pathology found in those brain regions (Talbot et al., 2004; Tang et al., 2009; C. S. Weickert et al., 2004; C. S. Weickert, Rothmond, Hyde, Kleinman, & Straub, 2008). Specifically, such reductions have been associated with reduced glutamate release (Numakawa et al., 2004) and with downregulation of *N*-methyl-*D*-aspartate (Karlsgodt et al., 2011). This in turn has been implicated in the impaired dopaminergic regulation and GABAergic neurotransmission found in schizophrenia (Kantrowitz & Javitt, 2010). Dysbindin-1's association with cognitive functioning is therefore likely indirect, through its contribution to glutamatergic and dopaminergic

dysregulation and to functional disconnection in the cerebral cortex and hippocampal formation (Talbot et al., 2009).

A number of dysbindin-1 SNPs have been examined as potential predictors of cognitive performance in healthy controls and in patients with schizophrenia-related disorders, with further insights offered through dysbindin sandy mice studies (see Appendices L-M, for summary of significant and non-significant associations by cognitive domain). Interpretation of purported associations is complicated by such methodological issues as variability in SNPs, haplotypes, cognitive measures and cognitive domains examined, and by inconsistencies in results obtained.

In a detailed exposition of dysbindin-1 and its protein family, Talbot (2009, p. 216) proposed “direct and indirect evidence for a role of dysbindin-1 in normal learning and memory processes”. This is borne out in a number of studies across verbal and visual memory domains, with positive associations summarised in Table 9.1. Studies involving sandy mice provide the most consistent evidence of deficits in spatial learning and memory (Bhardwaj, Ryan, Wong, & Srivastava, 2015; Cox et al., 2009; Takao et al., 2008) and both short-term (Bhardwaj et al., 2009) and long-term (Feng et al., 2008) object recognition memory. Evidence in human studies is less consistent. Two haplotypes (Hashimoto et al., 2010; Luciano et al., 2009) and four individual SNPs (Alfimova, Monakhov, Abramova, Golubev, & Golimbet, 2010; Hashimoto et al., 2009; Luciano et al., 2009) have been associated with verbal memory, though there has been no cross-study replication of haplotypes or SNPs examined. A single SNP (rs1018381) has been associated with neural correlates of a visual encoding and retrieval task (Thimm, Krug, Markov, et al., 2010), and a nominal association was found between rs2619539 and visual memory (Baek et al., 2012).

Table 9.1

Memory and General Cognitive Ability: Summary of Positive Associations with DTNBP1

Author (year)	Working Memory	Verbal Memory	Visual Memory	Spatial Memory	Cognitive Composite
<i>Human studies</i>					
Burdick et al. (2006)					^a Haplotype rs1018381
Donohoe et al. (2007)	^b Haplotype				
Hashimoto et al. (2009)		rs2619539			
Luciano et al. (2009)	rs1011313	rs1011313			rs742105
		^a Haplotype rs742105			^b Haplotype
Alfimova et al. (2010)		rs2619522			
Hashimoto et al. (2010)		^c Haplotype			
Markov et al. (2010)	rs1018381				
Thimm et al. (2010a)			rs1018381		
Wolf et al. (2011)	rs1047631				
Baek et al. (2012)	<i>rs760761_{LD}</i> <i>rs1018381</i>		<i>rs2619539</i>		<i>rs760761_{LD}</i> <i>rs1018381</i>

Animal studies

Feng et al. (2008)		Sandy mouse	
Takao et al. (2008)	Sandy mouse		Sandy mouse
Bhardwaj et al. (2009)		Sandy mouse	
Cox et al. (2009)		Sandy mouse [#]	Sandy mouse
Jentsch et al. (2009)	Sandy mouse		
Karlsgodt et al. (2011)	Sandy mouse		
Papaleo et al. (2012)	Sandy mouse		
Bhardwaj et al. (2015)	Sandy mouse		Sandy mouse

Note: DTNBP1 = dystrobrevin-binding protein 1 gene. *Italics* = nominally significant after adjustment for multiple comparisons.

^aCTCTAC at SNPs rs909706, rs1018381, rs2619522, rs760761, rs2619528, rs1011313 (Funke et al. 2004); ^bCAT at SNPs rs2619539, rs3213207, rs2619538 (Williams et al. 2004); ^c1-1-1 at SNPs rs3213207, rs1011313, rs760761 (Numakawa et al. 2004).

^{LD}rs760761 was in almost complete linkage disequilibrium with rs2619522 and rs2619528.

[#]marginal deficits in visual learning.

Dysbindin-1 has also been implicated in working memory deficits. The association between DTNBP1 and deficits in working memory found in sandy mice studies (Bhardwaj et al., 2015; Jentsch et al., 2009; Karlsgodt et al., 2011; Papaleo et al., 2012; Takao et al., 2008) has been replicated in schizophrenia patients (Baek et al., 2012; Donohoe et al., 2007) and healthy controls (Luciano et al., 2009; Wolf, Jackson, Kissling, Thome, & Linden, 2011), albeit over different aspects of working memory (Table 9.1). In a majority of instances, minor allele carriers performed more poorly than individuals who were homozygote on the major allele. In the only exception, Wolf et al. (2011) reported that rs1047631 minor allele carriers responded with greater accuracy to a happy versus neutral face working memory condition. This minor allele has previously been identified as part of a protective haplotype (Bray et al., 2005) and has been associated with increased levels of dysbindin-1 mRNA in the prefrontal cortex (C. S. Weickert et al., 2004).

There is evidence that genetic variability in dysbindin-1 is more broadly associated with general cognitive ability (Table 9.1). In a meta-analysis of 8 studies considering 7,592 healthy controls across 10 cohorts, Zhang, Burdick, Lencz and Malhotra (2010) reported that minor allele carriers of rs1018381 and rs2619522 had significantly lower general cognitive ability compared to individuals homozygous on the major allele. The same trend has been found in schizophrenia patient groups, with rs1018381 associated with a measure of general cognitive ability (*g*; Burdick et al., 2006) and with a cognitive composite (Baek et al., 2012). Rs1018381 has previously been identified as a tag SNP for several risk haplotypes (Funke et al., 2004; van den Oord et al., 2003). Evidence on rs2619522 is limited to a single study that found no association with *g* (Peters et al., 2008).

Seeking to address the limitations inherent in use of discrepant cognitive measures, Baek et al. (2012) examined DTNBP1 associations across the cognitive domains identified by the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative (M. F. Green, Nuechterlein, et al., 2004). However, their efforts did not extend to the measures that were actually used in the MATRICS Consensus Cognitive Battery (MCCB). To the best of our knowledge, the association between DTNBP1 and the MCCB has not yet been examined.

9.5 The Current Study

The aim of the present study was to investigate whether DTNBP1 genotype would influence performance across the range of cognitive domains implicated in schizophrenia, as measured on the MCCB. Given evidence of prior associations, we hypothesised that risk allele risk carriers on rs1018381 and rs2619522 would present with poorer performance across working memory, verbal and visual learning domains and on the MCCB cognitive composite. This trend was expected to be strongest on rs1018381 and to be evident in both a patient group and healthy controls. Performance on the remaining MATRICS domains (attention/vigilance, speed of processing, reasoning and problem solving, social cognition) was explored.

9.6 Methods

9.6.1 Participants. Patient ($n = 76$) and healthy control (HC; $n = 160$) data was obtained from the Cognitive and Genetic Explanations of Mental Illnesses (CAGEMIS) bio-databank. Participants had been recruited from the Melbourne, Australia region through multiple feeder studies, and had provided written consent for their de-identified data to be used in this study. Separate ethics approval was obtained through the Alfred Hospital Ethics Committee (project no. 415/17; Appendix N). This study was carried out in accordance with the principles set out by the Australian Government's National Health and Medical Research Council in the National Statement on Ethical Conduct in Human Research (2007; updated May 2007), which complies with the Helsinki Declaration.

Clinical diagnosis was confirmed using the Mini International Neuropsychiatric Interview Screen 5.0.0 (Sheehan & Lecrubier, 2006). Patients met DSM-IV-TR (American Psychiatric Association, 2000) criteria for schizophrenia or schizoaffective disorder; HCs did not meet criteria for DSM-IV-TR assessed disorders. Participants with estimated premorbid IQ below 75 were excluded, as were those with premorbid conditions (e.g., acquired brain injury, neurological disorder) or recent substance abuse that could independently compromise cognitive functioning.

9.6.2 Assessment.

9.6.2.1 Clinical. The Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) was used to assess psychotic symptoms in the patient group.

9.6.2.2 Neuropsychological. Premorbid IQ was assessed using the Wechsler Test of Adult Reading (WTAR; Wechsler, 2001). The MCCB (Nuechterlein et al.,

2008) was used to assess domain level and composite cognitive (CogComp) functioning. Domains included speed of processing (SoP), attention/vigilance (AttnVig), working memory (WM), verbal learning (VerbL), visual learning (VisL), reasoning and problem solving (R-PS), and social cognition (SocCog). Details of measures comprising these domains have been published elsewhere (Nuechterlein et al., 2008). Age- and gender-adjusted MATRICS *T*-scores were used in the analysis.

9.6.3 Genotyping. ⁸DNA from venous blood was extracted using the QIAamp DNA Blood Mini Kit as per manufacturer's instructions (QIAGEN, Hilden Germany). DNA from saliva samples was purified using the PrepIT-L2P DNA purification protocol as per manufacturer's instructions (DNAgenotek, Ottawa, Canada). SNP assays were designed using the Agena Assay Design Suite 1.0 software (Agena, San Diego, CA). Genotyping for two DTNBP1 SNPs of interest (rs1018381, rs2619522) was performed using the MassArray system as per manufacturer's standard protocols (Agena, San Diego, CA). The MassArray platform relies on a primer extension reaction in combination with a mix of mass-tagged dideoxy-nucleotides (iPlex chemistry) to generate a pool of oligo products that are analysed by chip-based matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF). Adherence to Hardy-Weinberg equilibrium (HWE) and allele frequency was examined. For efficiency, the two SNPs were genotyped in a single reaction.

9.6.4 Statistical analysis. Data analysis was undertaken using IBM[®] SPSS[®] Statistics Version 25.0.0. Cognitive measures were screened for normality and univariate outliers. Participants with more than two missing MCCB domain scores were excluded. Univariate outliers were resolved through case exclusion and score adjustment (Tabachnick & Fidell, 2013) to aid meaningful data interpretation. Missing values were resolved using multiple imputation, with sensitivity analysis performed to verify results. Low frequency homozygote minor allele carriers (rs1018381 = 1 patient, 2 HC; rs2619522 = 3 patient) were combined with heterozygote carriers to comprise the risk genotype; the non-risk group comprised participants homozygous on the major allele. Demographic differences between

⁸Methodology for the processing of genetic material was provided by K. Bozaoglu (personal communication, 22 February, 2018).

diagnostic group and, within them, between risk vs non-risk genotypes, were examined using independent-samples t -tests and χ^2 tests. Between diagnostic group differences on MCCB scores were similarly examined.

For the primary hypotheses, two-way between-groups analyses of variance, with diagnostic group (patient, HC) and genotype (risk, non-risk) and diagnostic group by genotype interaction, were used to analyse differences in WM, VerbM, VisM and CogComp performance. To control for multiple comparisons, α was set at .0125 (.05/4) or .0025 (.01/4) where Levene's test was significant. Significant interactions were followed up separately by diagnostic group with independent-samples t -tests. Exploratory analysis was performed separately by diagnostic group using independent-samples t -tests to compare SoP, AttnVig, R-PS and SocCog performance by genotype. Statistical significance was set at .01 for all t -tests.

9.7 Results

Genotype frequencies are presented in Table 9.2. Minor allele frequencies are similar to those reported by Luciano et al. (2009) in an Australian HC cohort. Participant baseline characteristics are summarised in Table 9.3 by SNP, diagnostic group, and genotype. There were no within-diagnostic group differences across genotypes. Patient and HC groups differed significantly on age, years of education and premorbid IQ. Patients were older, had comparatively fewer years of education, and a close to 10-point difference in premorbid IQ. As expected, the patient group performed significantly worse than HCs on all MCCB domains and CogComp. Approximately 84% of the patient group reported Caucasian ethnicity and 8% Asian ethnicity. Approximately 79% of HCs reported Caucasian and 15% Asian ethnicity.

MCCB performance for the patient group were normally distributed. For the HCs, the non-risk group remained negatively skewed on VisL and had a flattened distribution on R-PS; the risk group remained negatively skewed on R-PS. Given the larger sample size and potential impact of transformations on other analysis cells, no further adjustments were made. Failures of homogeneity of variance were evident in WM on rs1018381 and in VisL and CogComp on both SNPs.

Table 9.2

Single Nucleotide Polymorphism (SNP) Frequencies by Diagnostic Group

SNP	Alleles		MAF	Cell Size by Genotype (n)		
	Major	Minor		AA	Aa	aa
rs1018381	C	T				
Healthy control			.091	133	25	2
Patient group ^a			.079	65	10	1
rs2619522	T	G				
Healthy control			.183	91	37	6
Patient group ^a			.179	48	19	3

Note: MAF = minor allele frequency; AA = major allele homozygote; Aa = heterozygote; aa = minor allele homozygote.

^aSchizophrenia-related disorder.

Table 9.3

Diagnostic Group Means (SD) by DTNBP1 SNP and Genotype

Genotype / Sample characteristic	Patient Non-risk	Patient Risk	P-value $/X^2_a$	Control Non-risk	Control Risk	P-value $/X^2_a$
rs1018381	(<i>n</i> = 65)	(<i>n</i> = 11)		(<i>n</i> = 133)	(<i>n</i> = 27)	
Age (years)	40.68 (10.16)	40.09 (11.19)	.862	31.80 (13.17)	28.85 (9.57)	.180
Sex (% female)	36.9%	36.4%	1.00 _a	48.1%	66.7%	0.122 _a
Years of Education	13.49 (3.59)	15.10 (3.51)	.192	16.34 (2.67)	16.38 (1.83)	.931
Premorbid IQ	102.14 (11.03)	104.09 (12.37)	.596	112.44 (9.24)	112.93 (8.62)	.803
Diagnosis (% SZ)	73.80%	54.5%	0.344 _a			
Onset age (years)	24.78 (8.26)	25.56 (6.02)	.788			
Dur. of illness (y)	16.20 (10.91)	17.56 (9.88)	.727			
PANSS positive	15.69 (5.90)	13.27 (4.56)	.201			
PANSS negative	14.52 (5.85)	13.36 (4.84)	.539			
PANSS general	30.28 (9.88)	28.09 (7.64)	.487			
CPZeq (mg/day)	785.49 (1123.70)	552.79 (446.66)	.502			

Genotype / Sample characteristic	Patient Non-risk	Patient Risk	P-value / χ^2_a	Control Non-risk	Control Risk	P-value / χ^2_a
rs2619522	(<i>n</i> = 48)	(<i>n</i> = 22)		(<i>n</i> = 91)	(<i>n</i> = 43)	
Age (years)	40.54 (10.69)	40.91 (9.58)	.891	31.46 (12.64)	32.51 (13.60)	.661
Sex (% female)	39.6%	40.9%	1.00 _a	52.7%	58.1%	0.690 _a
Years of Education	14.36 (3.80)	13.90 (3.21)	.643	16.15 (2.68)	16.36 (2.29)	.708
Premorbid IQ	103.42 (10.28)	102.95 (11.24)	.867	110.54 (9.95)	112.93 (7.96)	.170
Diagnosis (% SZ)	68.8%	59.1%	0.604 _a			
Onset age (years)	24.16 (8.12)	27.11 (7.57)	.185			
Dur. of illness (y)	16.60 (11.55)	15.11 (9.47)	.622			
PANSS positive	14.96 (5.92)	15.45 (5.05)	.735			
PANSS negative	13.74 (5.36)	14.05 (5.77)	.833			
PANSS general	28.89 (9.90)	30.27 (7.09)	.512			
CPZeq (mg/day)	844.68 (1218.26)	492.14 (360.61)	.189			

Note. SD = standard deviation; DTNBP1 = dystrobrevin binding protein 1; *n* = number; SZ = schizophrenia; Dur. = duration; *y* = years; CPZeq (mg/day) = chlorpromazine equivalent. rs1018381 genotype: non-risk = CC, risk = TT,CT. rs2619522 genotype: non-risk = TT, risk = GG,GT.
_aChi-square.

9.7.1 Primary hypotheses. Age- and gender-adjusted MCCB domain and composite *T*-scores are presented in Table 9.4 and Figure 9.1 A-B. Significant diagnostic group by genotype interactions were found in WM for rs1018381, $F(1,232) = 12.05, p = .001$ and rs2619522, $F(1,200) = 8.22, p = .005$, accounting for 4.9% and 3.9% of the variability in WM respectively. The direction of the effect of genotype on WM differed by diagnostic group. For both rs1018381 and rs2619522, patient non-risk carriers performed more poorly than risk carriers ($d = .77$ and $.50$ respectively). In comparison, HC non-risk carriers performed better than risk carriers ($d = .49$ and $.37$ respectively). Although effect sizes were moderate, the differences did not reach significance when adjusted for multiple testing.

Table 9.4

MATRICES Domain and Composite Mean (SD) T-scores and T-test Results by DTNBP1 SNP, Diagnostic Group and Genotype

Genotype / Domain	Patient Non-risk	Patient Risk	Statistics <i>t</i> -value, <i>p</i> -value	Control Non-risk	Control Risk	Statistics <i>t</i> -value, <i>p</i> -value
rs1018381	(<i>n</i> = 65)	(<i>n</i> = 11)		(<i>n</i> = 133)	(<i>n</i> = 27)	
SoP	40.28 (12.19)	47.00 (9.73)	-1.74, .087	56.00 (10.02)	56.22 (10.01)	-0.10, .918
AttnVig	40.17 (13.56)	43.64 (9.70)	-0.81, .420	47.81 (8.81)	46.93 (7.30)	0.49, .625
WM	41.15 (10.01)	48.64 (7.12)	-2.37, .020	55.74 (7.55)	52.04 (7.62)	2.32, .022
VerbL	38.69 (8.73)	40.91 (7.29)	-0.80, .429	50.05 (9.60)	50.07 (7.82)	-0.01, .991
VisL	40.05 (13.60)	50.55 (11.39)	-2.42, .018	53.72 (8.65)	53.59 (8.58)	0.07, .944
R-PS	42.58 (9.48)	43.73 (8.43)	-0.38, .709	52.84 (10.68)	55.11 (8.26)	-1.23, .224
SocCog.	50.51 (11.22)	42.09 (6.89)	-0.45, .652	46.29 (10.58)	47.04 (11.55)	-0.33, .741
CogComp	35.06 (11.37)	42.27 (7.13)	-2.03, .046	52.64 (8.55)	52.22 (8.39)	0.23, .817

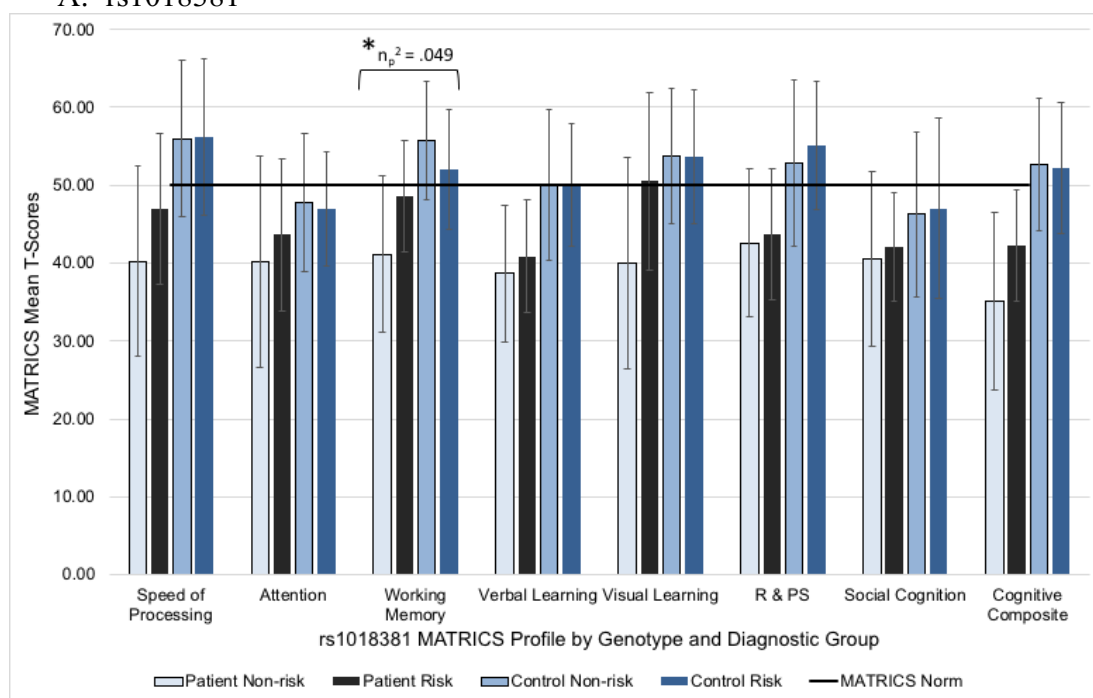
Genotype / Domain	Patient Non-risk	Patient Risk	Statistics <i>t</i> -value, <i>p</i> -value	Control Non-risk	Control Risk	Statistics <i>t</i> -value, <i>p</i> -value
rs2619522	(<i>n</i> = 48)	(<i>n</i> = 22)		(<i>n</i> = 91)	(<i>n</i> = 43)	
SoP	42.00 (12.02)	45.05 (13.15)	-0.96, .343	56.43 (10.03)	54.73 (10.90)	0.89, .376
AttnVig	42.10 (13.01)	40.23 (12.70)	0.56, .574	47.95 (9.49)	47.19 (6.73)	0.53, .596
WM	42.06 (7.86)	46.68 (11.38)	-1.97, .053	55.62 (8.12)	52.67 (7.37)	2.01, .046
VerbL	40.65 (8.18)	38.00 (8.93)	1.22, .226	49.91 (9.93)	49.33 (7.86)	0.34, .734
VisL	40.48 (12.62)	47.27 (15.06)	-1.97, .053	53.75 (8.82)	54.26 (8.10)	-0.32, .750
R-PS	42.58 (8.34)	45.86 (11.06)	-1.38, .174	52.78 (10.85)	52.91 (9.60)	-0.07, .946
SocCog.	41.60 (11.90)	40.27 (7.48)	0.48, .632	45.04 (10.28)	46.63 (12.12)	-0.79, .434
CogComp.	36.58 (9.53)	39.73 (12.46)	-1.16, .250	52.40 (9.30)	51.49 (7.72)	0.56, .580

Note. DTNBP1 = dystrobrevin-binding protein 1 gene; SD = standard deviation; SNP = single nucleotide polymorphism; SoP = speed of processing; AttnVig = attention/vigilance; WM = working memory; VerbL = verbal learning; VisL = visual learning; R-PS = reasoning and problem solving; SocCog. = social cognition; CogComp. = cognitive composite.

rs1018381 genotype: non-risk = CC, risk = TT,CT. rs2619522 genotype: non-risk = TT, risk = GG,GT.

^aAge and gender adjusted.

A. rs1018381



B. rs2619522

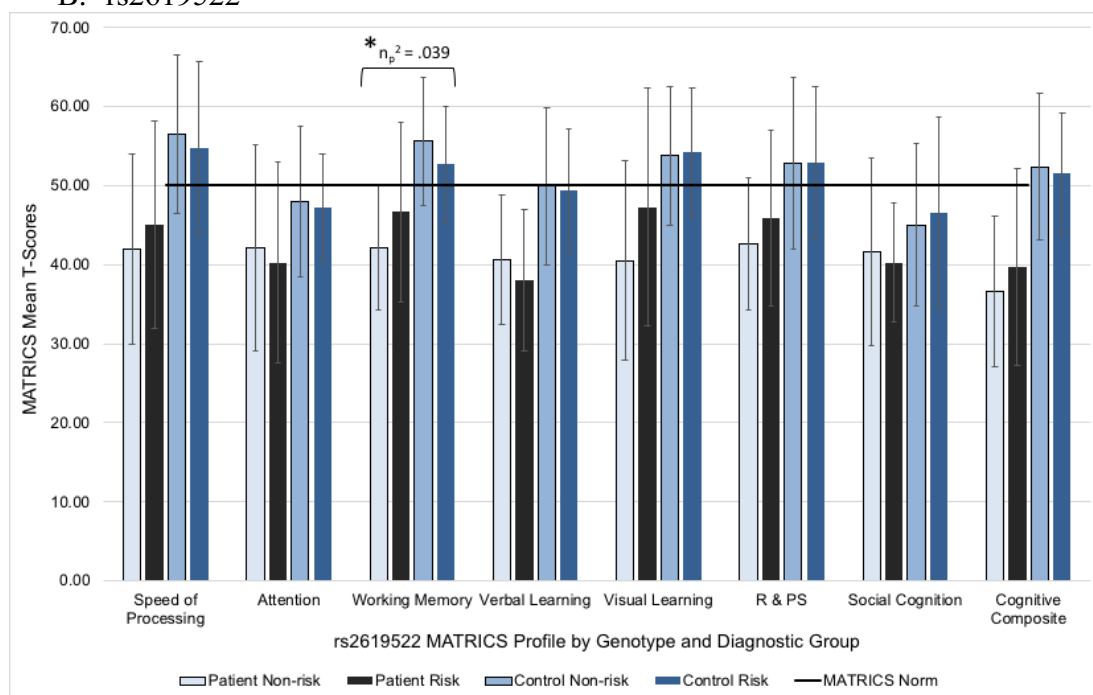


Figure 9.1 A-B. Diagnostic group mean MATRICS domain and composite level T-scores, adjusted for age and gender, by DTNBP1 SNP. Error bars represent standard deviation.

R & PS = Reasoning; Solv. = Solving; Norm = normative mean; n_p^2 = partial eta squared.

There was a nominal interaction in VisL for rs1018381 $F(1,232) = 6.97, p = .009, \eta_p^2 = .029$. Patient non-risk carriers performed more poorly on VisL compared to risk carriers; conversely, there was virtually no difference between non-risk and risk HCs. The same pattern was evident in CogComp for rs1018381, $F(1,232) = 4.42, p = .037, \eta_p^2 = .019$. For VisL and CogComp, neither the interaction or the main effect of genotype reached significance when adjusted for multiple comparisons. No interactions or main effects on genotype were found in Verbl.

9.7.2 Exploratory analysis. No differences were found within diagnostic group when comparing non-risk to risk genotype performances in SoP, AttnVig, R-PS, and SocCog domains.

No significant differences were found when the primary and exploratory analyses were performed on a dataset without imputation of missing values.

9.8 Discussion

As underlying mechanisms continue to be explicated, there is increased evidence of a role for DTNBP1 in the cognitive deficits that manifest in a majority of individuals diagnosed with schizophrenia-related disorders. We investigated whether DTNBP1 genotype would influence performance on the MCCB, a standardised test battery developed to assess the efficacy of cognitive-enhancing treatments for schizophrenia. Participants diagnosed with schizophrenia-related disorders performed significantly worse than healthy controls on all MCCB domains, indicating that the sample is representative.

9.8.1 Working memory and dysbindin-1. We found support for an association between DTNBP1 and WM on the two SNPs examined, rs1018381 and rs2619522. As predicted, the strongest associations were with rs1018381, which has previously been linked to schizophrenia risk and with performance across measures of attention (Baek et al., 2012; Thimm, Krug, Kellermann, et al., 2010), working memory (Baek et al., 2012), semantic verbal fluency (Markov et al., 2009), performance IQ (Luciano et al., 2009), and general cognitive ability (Baek et al., 2012; Burdick et al., 2006), as well as with more sensitive measures of brain functioning (Markov et al., 2009, 2010; Thimm, Krug, Kellermann, et al., 2010; Thimm, Krug, Markov, et al., 2010).

Contrary to expectations, the influence of DTNBP1 genotype on WM differed across patient and HC groups, with rs1018381 and rs2619522 minor alleles appearing to confer a benefit to the patient group not seen in HCs. Specifically, patient group minor allele carriers performed better on WM than individuals homozygous on the major allele. The opposite pattern was found in HCs, with minor allele carriers performing more poorly on WM than individuals homozygous on the major allele. This contrasts with the results of Baek et al. (2012), who reported the same pattern of influence across both Korean schizophrenia patient and HC cohorts; namely, that rs1018381 minor allele carriers performed more poorly on verbal WM. Other studies that examined the influence of these two SNPs on WM performance found no associations (T. A. Greenwood et al., 2011; Kircher et al., 2009; Luciano et al., 2009 Scottish & Australian cohorts; Simons & Van Winkel, 2013; Stefanis et al., 2007).

Looking to other dysbindin-1 SNPs that have been associated with WM, Luciano et al. (2009) found that the rs1011313 minor allele conferred poorer verbal WM performance in a Scottish cohort of HCs, as did Donohoe et al. (2007) on a dysbindin-1 risk haplotype (C-A-T at rs2619539, rs3213207, rs2619538) in an Irish patient cohort. As noted previously, Wolf et al. (2011) found rs1047631, part of a purported protective haplotype, to confer benefit to HC minor allele carriers performing an emotional face WM task.

9.8.2 Other cognitive abilities and dysbindin-1. No significant differences were identified for associations between rs1018381 or rs2619522 on visual or verbal learning domains or on the MATRICS cognitive composite in our sample. Additionally, exploratory analysis performed across speed of processing, attention/vigilance, reasoning and problem-solving, and social cognition MATRICS domains failed to find an effect of DTNBP1 genotype on cognitive performance.

The lack of associations between DTNBP1 and general cognition, as measured on the MCCB, is consistent with the wider evidence-base. When considering the more frequently examined dysbindin-1 SNPs, approximately 85% of associations with cognition are not significant (Supplementary Figure M9 A-C; Appendix M). In an extensive analysis of 38 tag SNPs capturing 150 common variants across DTNBP1, Peters et al. (2008) reported no associations with cognitively-derived schizophrenia subtypes (i.e., cognitive deficit, cognitively spared) in an Australian patient and HC cohort. Several large scale analyses of genes

associated with schizophrenia, including SNPs rs1018381 and rs2619522, have similarly reported no association between DTNBP1 and cognition (T. A. Greenwood et al., 2011; Simons & Van Winkel, 2013).

9.8.3 Biological and methodological considerations. While understanding of the role dysbindin-1 plays in cognitive performance is incomplete, there are likely a number of factors that contribute to the discrepant results. One of the most challenging to unravel is the complex interaction of the various genes that have been implicated in schizophrenia and associated with cognitive processes. As noted by Harrison and Weinberger (2005, p. 55), alongside the specific impact each gene's risk variants has on encoded protein, there are likely "gene-gene, gene-environment and protein-protein" interactions that converge to affect neural mechanisms and processes. With regards to WM, in addition to the purported influence of dysbindin-1 on performance, other associated genes include COMT, DAT/SLC6A3, DRD1/3/4 and SLC18A2 and their influence on dopamine, DISC1, BDNF, ANK3, HEY1, FGF2, NOS1, FKBP5, DNMT38, and MTHFR (Zai et al., 2016). It is possible that measurable behavioural responses result from an accumulation of otherwise subtle risk variants that are either not detectable in isolation or have a stronger association with a SNP or haplotype not examined (Goldberg & Weinberger, 2004; Stefanis et al., 2007). Our unique pattern of results, specific to WM and conferring benefit to the patient group not found in the HCs, might reflect such a culmination of schizophrenia-specific interactions.

Regarding measurable responses, another factor likely contributing to inconsistent results is the differential sensitivity of the techniques and measures used to assess cognition (Goldberg & Weinberger, 2004; Heinrichs, 2005; Rose & Donohoe, 2013). A recent meta-analytic review examining the sensitivity of neuroimaging and cognitive behavioural studies of genetic risk for schizophrenia reported larger effect sizes for imaging (Hedges $g = 0.97$, 95% confidence interval = 0.85–1.08) compared to cognitive behavioural studies (Hedges $g = 0.37$, 95% confidence interval = 0.30–0.45; Rose & Donohoe, 2013). Larger sample sizes found in cognitive behavioural studies did not correspond with larger effect sizes. Accounting for the difference, Rose et al. (2013, p. 525) posited that imaging techniques were more proximal to underlying biological mechanisms and might be less responsive to environmental influence. Similar variability in sensitivity is also apparent across cognitive behavioural measures (Heinrichs, 2005).

Such differences in sensitivity are especially apparent in studies that combine both cognitive behavioural and non-behavioural techniques. Donohoe et al. (2008), for example, used both cognitive behavioural and electrophysiological data to examine the influence of a dysbindin-1 risk haplotype on early visual processing deficits in a schizophrenia patient group. While there was no difference in target hit rates across risk versus non-risk groups on the behavioural measure, P1 amplitudes were significantly smaller in risk compared to non-risk carriers. Two studies have used a combination of behavioural measures and fMRI techniques to examine the influence of rs1018381 genotype on neural activity during memory related tasks. Thimm, Krug, Kellermann et al. (2010) reported no difference in HC performance on a behavioural nonverbal memory task, but a significant group difference in fMRI measured neural activity during nonverbal memory encoding and retrieval processes. Minor allele carriers on rs1018381 evidenced greater activation compared to individuals homozygous on the major allele. Markov and colleagues (Markov et al., 2010) similarly reported no difference in HC performance on a behavioural working memory task, but significantly increased brain activation in the rs1018381 risk allele carriers compared to non-risk carriers. In an earlier study, Markov et al. (2009) reported the same pattern of results when examining the influence of rs1018381 on neural activity during a semantic verbal fluency task. Donohoe et al. attributed the lack of behavioural affect to the simplicity of the task, while Thimm, Krug, Kellermann et al. and Markov et al. suggested that increased neural activity might reflect inefficiency or compensatory efforts. What is not apparent is whether these more proximal indicators of DTNBP1 influence on cognitive processes reflect clinically meaningful deficits, such that they compromise everyday functioning.

Population stratification has also been offered as a potential reason for discrepant results. While this may be true for the handful of studies that have sampled non-Caucasian population groups (Baek et al., 2012; Hashimoto et al., 2009, 2010), a majority of studies have largely comprised participants reporting Caucasian/European-Caucasian ethnicity. This was borne out by Mutsuddi et al. (2006), who re-analysed six DTNBP1-schizophrenia risk association studies comprising participants of European ancestry. Mutsuddi and colleagues concluded that inconsistent cross-study results were not attributable to population stratification, with all reported allele and haplotype frequencies aligned with the HapMap CEU trios.

9.8.4 Limitations and conclusion. Several limitations of this study should be noted. Our examination of the influence of dysbindin-1 on cognition, while conducted with a comprehensive neurocognitive battery, was limited to two of the more frequently examined SNPs in the literature. Although this allowed for cross-study comparison, it has been argued that the influence of single SNPs should be considered within the context of affiliated haplotypes (Harrison & Weinberger, 2005, p. 55). Additionally, our sample size was relatively small for a genetics study and we had insufficient numbers of homozygous minor allele carriers to fully explore the influence of genotype on cognition. Although we corrected for multiple comparisons by applying a more stringent test of main effects and interactions, unequal sample sizes across the ANOVA analysis cells would have increased the risk of type 1 errors.

In conclusion, we found support of an association between DTNBP1 genotype and performance on the MCCB, with an unanticipated but consistent differential response across a patient group and HCs on the working memory domain. It is possible this reflected the interaction of schizophrenia-specific genetic influences that manifest as protective rather than conferring risk in the patient group. It is unclear whether the lack of association with other MCCB cognitive domains is due to the limited number of dysbindin-1 SNPs examined, the sensitivity of the test battery to detect what could be subtle influences on performance, or due to the methodological issues with the use of ANOVA. Larger, more robust replication studies would help address these questions. Given the role of working memory in learning, it remains to be seen whether the influence of dysbindin-1 on working memory extends to individual responses to such cognitive enhancing interventions as cognitive remediation therapy.

Chapter 10. Discussion

10.1 Chapter Guide

The purpose of this final chapter is to draw together and make sense of the multiple lines of enquiry that comprise this body of work. The reader is first presented with a brief synopsis of the underlying impetus for the thesis, after which results from Chapters 4 (Study 1), 7, 8 (Study 2) and 9 (Study 3) are summarised and contextualised. Acknowledgement is given to the more general study limitations, with study specific limitations addressed in the respective chapters. Key implications of the thesis outcomes are discussed. The discussion concludes with consideration of the critical next steps in progressing this essential line of enquiry.

10.2 Impetus for Overarching Thesis Goal

In the introductory chapter, having (a) drawn attention to the poor functional outcomes that are experienced by people diagnosed with schizophrenia and (b) established a link between functional outcome and the cognitive deficits that manifest in schizophrenia, CRT was introduced as a moderately effective tool for ameliorating cognitive deficits with the aim of improving functional outcomes. Evidence regarding the effectiveness of CRT was provided at a neurobiological, cognitive-behavioural and functional level. However, closer examination of the literature revealed that not everyone realised cognitive benefit from CRT. This was apparent in meta-analyses that reported heterogeneity of effect across a number of cognitive domains. It was especially apparent in studies that reported interindividual variability of response to CRT and that quantified the proportion of participants to realise meaningful cognitive change. Reasons for the apparent variability were unclear. There was a lack of transparency in the empirical literature about heterogeneity of response to CRT and a paucity of studies had characterised CRT responder subgroups. A comprehensive synthesis of mediators, moderators and predictors of response to CRT was not available to guide future research efforts or to inform clinical practice. These gaps had the potential to undermine the effectiveness of CRT in real-world settings, in clinical treatment planning, decision-making, and CRT delivery. To address this, the overarching goal of this thesis was to arrive at a better understanding of factors that influence individual cognitive response to, and the efficacy of, CRT in people diagnosed with schizophrenia.

10.3 Summary of Key Outcomes

The goals of this thesis were addressed across three studies. The first, presented in Chapter 4, had the aim of providing an up-to-date synthesis of the CRT predictor literature, making manifest what was known. The second, presented in Chapters 7 and 8, sought through empirical means to consolidate and extend on the review outcomes while presenting clinically meaningful information regarding individual patterns and predictors of cognitive response to CRT. A final, preliminary study presented in Chapter 9 laid the groundwork for examination of a potential genetic correlate of cognitive response to CRT.

10.3.1 Study 1: Systematic review of predictor literature. The systematic review of factors that influence cognitive response to, and the efficacy of, CRT in

schizophrenia represents an important contribution to the CRT literature. The review provides greater transparency of the associated body of research and of the large number of potential predictor variables already examined. For the first time, a profile is available for each of the more frequently examined predictors of cognitive response to CRT. It is now apparent how frequently each predictor has been evaluated and their prognostic value. Premorbid IQ, baseline cognition, and training task engagement/performance emerged as being more strongly predictive of cognitive response to CRT. It was proposed that these might represent markers of an individual's capacity for change. While these have not yet been considered through meta-analysis, baseline cognition and training task performance were previously singled out in review by Keshavan, Vinogradov, Rumsey, Sherrill, and Wagner (2014) as potential predictors of CRT treatment response. The minimal support for other potential demographic, clinical and treatment predictors is consistent with results of earlier meta-analyses to examine mediators and moderators of effect (Grynszpan et al., 2011; McGurk, Twamley, et al., 2007; Wykes et al., 2011).

10.3.2 Study 2: Empirical evaluation of predictors of cognitive response.

The first of two empirical studies involved conducting a CRT intervention with the aim of examining individual patterns and predictors of cognitive response to CRT. Thirty participants diagnosed with schizophrenia were recruited into the study across a two-year period. Twenty-two were included in the final analysis. The study sought to address the limitations of traditional group-level analysis by using RCIs calculated across MCCB change scores to categorise cognitive response subgroups. These were then characterised using baseline data, and cognitive change profiles were generated. Only a few studies have used RCIs to categorise response to CRT; none have characterised resultant responder subgroups. Variables identified through systematic review were subsequently assessed at multiple subgroup levels to evaluate their prognostic value.

In the paper presented in Chapter 7, discriminant analysis was used to identify factors that differentiated CRT responders ($n = 12$) from non-responders ($n = 10$). Baseline AttnVig and a static measure of verbal learning potential emerged as predictors of group membership. It is well known that attentional processes are inherently linked to the learning process (Chein & Schneider, 2012; Leong, Radulescu, Daniel, DeWoskin, & Niv, 2017), and it has previously been demonstrated that the capacity to benefit from instruction is correlated with AttnVig

(M. F. Green, 1996; Wiedl et al., 2001). However, this is the first study to demonstrate that a standard measure of verbal learning from within the MATRICS test battery could have prognostic value. If verified through future studies, this could become an important marker of an individual's capacity to receive cognitive benefit from CRT.

In the spirit of Jacobson, Follette, and Revenstorff's (1984) entreaty for experimentation in pursuit of more creative data reporting methods, the paper presented in Chapter 8 introduced a novel data visualisation technique that was unencumbered by underlying statistical assumptions. Four cognitive responder subgroups were identified and characterised. Through use of heat maps, possible differential associations between MCCB cognitive change scores and predictor variables of interest were explored across the responder subgroups. Even at this more granular level of response, support was found for the prognostic value of verbal learning potential. A potential influence of post-intervention symptomatology on cognitive change scores was also found, a relationship that had not previously been examined. While in need of replication with a larger dataset, the results demonstrate that application of novel analytic techniques has the potential to yield clinically meaningful information about patterns and predictors of individual response to CRT.

10.3.3 Study 3: Dysbindin-1 and working memory. The second empirical study involved secondary data analysis examining the potential influence of the gene for encoding dysbindin-1 (DTNBP1) on MCCB performance across a schizophrenia patient group and a healthy control (HC). While DTNBP1 had previously been associated with both schizophrenia risk and with cognition (N. C. Allen et al., 2008; Baek et al., 2012; Luciano et al., 2009), this preliminary investigation was the first to examine the association between DTNBP1 and performance on the MCCB. A significant diagnostic group by DTNBP1 genotype interaction was found across a measure of WM. Minor allele carriers (i.e., risk carriers) in the patient group performed more strongly on WM compared to major allele carriers; the opposite pattern was evident in the HC group. While the HC results were consistent with those of Baek et al. (2012), results for the patient group were not in the expected direction. The unexpected findings exposed the complexities of genetic association studies. Having demonstrated a possible association between DTNBP1 and MCCB WM performance, results from this study laid the groundwork for future

investigation of potential correlates between DTNBP1 and cognitive response to CRT.

10.4 General Limitations

10.4.1 Barriers to recruitment. The aforementioned studies were not without limitation. The most impactful of these were recruitment challenges which limited the sample size of the CRT intervention study. The small sample size restricted what analysis could be supported in a research project that was primarily interested in examination of subsets of the data. Small group numbers, for example, precluded the use of formal statistical techniques when examining potential associations between purported predictors and cognitive response to CRT in Chapter 8 and prevented the planned examination of genetic correlates (i.e., DTNBP1) of differential response to CRT. It is also possible that with greater power, a wider range of potential predictor variables would have emerged for examination in Chapter 7.

Efforts to recruit through Melbourne's public hospital mental health care services were hampered by (a) university-hospital affiliations that prevented recruitment by the author through a major public hospital network and associated services, (b) a lack of senior psychiatrist support for CRT that manifest in a lack of access to clinicians and referrals to the project across another major public hospital network, and (c) practical limits to the geographic area that the author could support recruitment and CRT training activities across. As a consequence, a majority of participants either self-referred in response to recruitment material or were recruited directly through a number of community service providers.

These issues are not unique to student-researcher led projects. Inadequate organisational support was an issue identified by Cairns, Dark, and Batts (2013) in their review of the lesson to be learnt through implementing CRT across two public hospital mental health services in Queensland, Australia. Further, the barriers posed by senior medical professionals who lack understanding of the scientific principles underpinning CRT, and who are wary of computer-aided medicine, was a concern raised by Merzenich et al. (2014). Future studies of this type would benefit from a collaborative, multisite approach that leveraged affiliations and benefited from greater geographic coverage.

10.4.2 Generalisability. As was demonstrated in Section 3.3, there are a myriad of CRT approaches available, with differences in modality, technique, format, content, duration, and use of adjunctive therapies. Results from meta-analytic studies suggest that differences across methodological and treatment factors do not account for between study heterogeneity of cognitive response to CRT (Grynszpan et al., 2011; McGurk, Twamley, et al., 2007; Wykes et al., 2011). However, that does not presuppose that the factors that are found to influence response to CRT do not vary as a function of approach. For example, on examining predictors of CRT response across a pooled sample of participants who received either CRT alone or CRT combined with social cognition training, Lindenmayer and colleagues (Lindenmayer et al., 2017) reported that stronger baseline WM performance moderated improvements following CRT combined with social cognition training but not CRT alone. Further, it has been suggested that stronger baseline R-PS in particular may facilitate gains from strategy training (Vita et al., 2013). As such, the decisions made in support of the overarching thesis aim will have limited the generalisability of the presented outcomes.

On approaching the systematic review presented in Chapter 4, it was decided to exclude CRT interventions that included social cognition or social skills training or that utilised adjunctive therapies such as work skills training (referred to below as ‘broader CRT approaches’). As a consequence, input from a number of eminent research groups, including, but not limited to, Bell and colleagues (e.g., Bell, Bryson, & Wexler, 2003; Fiszdon et al., 2005) and McGurk and colleagues (e.g., Lindenmayer et al., 2017; McGurk & Mueser, 2008), was not considered. Inclusion of their work may have altered the predictor profiles generated in Chapter 4 and, in turn, the variables selected for evaluation in Chapters 7 and 8. Conversely, the outcomes of the systematic review may not generalise to those broader CRT approaches.

A series of decisions were also made regarding the CRT intervention underpinning Chapters 7 and 8 that defined the scope of the investigation and, in turn, the generalisability of study outcomes. It is possible, for example, that a different set of predictors of response might have emerged from an acute inpatient population or from a sample that was more severely cognitively impaired at baseline. It is also possible that a different set of predictors would have emerged in response to strategy or social skills training. However, the approach selected, and predictors

examined, emerged from, confirmed and extended on an evidence base that represented 15 different core treatment/training programs delivered across a range of modalities, durations, and levels of intensity.

A final consideration regarding the generalisability of reported outcomes relates to differences in international standards and systems of healthcare which, more generally, can result in markedly different levels of performance across such domains as access, equity, and health care outcomes (Schneider, Sarnak, Squires, Shah, & Doty, 2017). A recent international comparison of healthcare systems ranked the United Kingdom, Australia and the Netherlands as top performers, while the United States ranked poorly on four of five outcome domains and last on overall performance (Schneider et al., 2017). The potential participant base in Australia and the United Kingdom benefits from universal healthcare systems that, in Australia at least, is characterised by high levels of engagement with specialised public and community mental health services by people diagnosed with schizophrenia (V. A. Morgan et al., 2010). It is possible that the influence of non-specific treatment effects, such as engagement in a regular, goal-directed activity guided by supportive clinicians (Kurtz et al., 2007; Wykes & Spaulding, 2011), is greater in CRT trials that engage participants who have not previously had regular access to public and/or community supports. By extension, results from Study 2 might not generalise to individuals treated under different healthcare models. Moreover, differences in the relative influence of specific versus non-specific treatment effects could manifest in different predictors of response (Wykes & Spaulding, 2011).

10.4.3 Subgroup analysis and multiplicity. The examination of mediators, moderators, and predictors of cognitive response to CRT presented in Chapters 7 and 8 involved subgroup analyses. In addition to the responder subgroups that were identified, sample data was further dissected through consideration of a number of potential predictor variables. Each of these intersections represented a subgroup. Though an important aspect of evaluating the efficacy of an intervention, subgroup analysis carries with it an increased risk of spurious findings and of over interpretation (Alosh et al., 2015; Dmitrienko, Millen, & Lipkovich, 2017; Lagakos, 2006). Indeed, the odds of identifying a subgroup that has an opposite effect to the overall group effect increases as a function of the number of factors used to classify subgroups (e.g., cognitive outcome, symptomatic outcome, functional outcome) and the number of levels each factor has (Alosh et al., 2015). By extension, an inherent

issue of subgroup analysis is that of multiplicity, or the increased risk of making Type I errors due to the multiple comparisons made (Lagakos, 2006; Wang et al., 2007). While there are statistical methods of controlling for multiplicity issues, such as applying a Bonferroni adjustment to the level of alpha, studies are often underpowered to detect meaningful subgroup associations to explain heterogeneity of response (Alosh et al., 2015).

Efforts were made in the studies reported in Chapters 7, 8, and 9 to mitigate the risk of spurious findings and of overinterpretation of the results. All investigations were defined a priori, were informed by prior research, and results were discussed in light of prior findings. In Chapter 7, cognitive outcome domains were reduced to a single outcome factor (responder group) with 2 levels (improved, not improved). Correlations were used to aid selection of the most appropriate predictor variables and use of discriminant analysis reduced their examination to the test of a single linear equation. In Chapter 8, no formal statistical methods were employed when examining the potential relationship between purported predictor variables and cognitive response to CRT. While the risk of spurious findings remained high, the data visualisation approach introduced was framed as exploratory and interpretation of the heat map was cautious. In Chapter 9, which benefited from a larger sample size, a test of interaction was used to evaluate the influence of DTNBP1 risk status on MCCB performance and a Bonferroni adjustment was applied.

10.5 Implications of Thesis Outcomes

To aid discussion of the implications of the thesis outcomes, key contributions are reiterated in brief:

- i. Increased transparency of the CRT predictor literature, providing both visibility of the 81 predictors of cognitive response already examined and a comprehensive review of the 20 that had been examined a minimum three times.
- ii. Evaluation of the prognostic value of the more frequently examined predictors of cognitive response to CRT, making explicit what proportion of examined associations were statistically significant.
- iii. Identification of premorbid IQ, baseline cognition, and training task engagement/performance as potential markers of an individual's capacity

to realise cognitive change following CRT, providing an important focal point for future research.

- iv. Through a synthesis of prior research and through the results of Study 2, the fact that not everyone receives cognitive benefit from CRT was demonstrated. Further, through the use of a more clinically meaningful measure of response, several differential patterns of cognitive response to CRT were identifiable.
- v. Provided preliminary evidence that a standard measure of verbal learning from within the MATRICS test battery, which could easily be administered in clinical settings, could have prognostic value in determining who is more likely to receive cognitive benefit from CRT.
- vi. Provided preliminary evidence of a possible influence of post-intervention symptomatology on post-intervention assessments, a relationship not previously explored.
- vii. Provided preliminary evidence of an association between the gene for encoding dysbindin-1 and WM performance on the MCCB.
- viii. Demonstrated that application of novel analytic techniques has the potential to yield clinically meaningful information about patterns and predictors of individual response to CRT.

10.5.1 Are we measuring the “right stuff?”: Implications to-date. In 2000, Green and colleagues asked the question, “Are we measuring the ‘right stuff?’” (p. 119). This, of course, was in relation to the association between neurocognitive deficits and functional outcome in schizophrenia. However, it is as pertinent to the examination of predictors of cognitive response to, and the efficacy of, CRT in schizophrenia. To answer that question, one first needs to have accumulated and analysed a reasonably sized body of data, as was presented in Chapter 4.

Outcomes from the systematic review indicate that too many potential predictor variables have been examined too few times to determine their prognostic value ($n = 61$). This could be indicative of a less than systematic approach to this aspect of CRT efficacy research, which benefits from a controlled program of exploratory investigations followed by adequately sized, multi-site confirmatory studies to verify potential moderators and mediators of effect (see Kraemer, 2016).

Conversely, it could indicate that no effect was found to justify further investigation. That was true for 33 of the infrequently examined potential predictors. Significant associations that were reported across another 22 remain unverified, while evidence for the remainder potential predictors was equivocal (refer to Appendix D).

Of the 25% of potential predictors that had been examined a minimum three times, outcomes from the systematic review challenge some of the broad generalisations made about possible factors to influence cognitive response to CRT. Age, in particular, has been proposed as a potential moderator of treatment effect (e.g., Cellard et al., 2011; Wykes & Spaulding, 2011). Origins of this generalisation can be traced to outcomes of studies that used dichotomised age groups to explore potential differential responses to CRT (McGurk & Mueser, 2008; Wykes et al., 2009). However, these findings have not been borne out in meta-analyses or in the large number of studies to examine age as a continuous variable. It would seem though that efforts to find an association using questionable techniques continues (Kontis et al., 2013; Seccomandi et al., 2018). Similarly, little evidence was found of the potential influence of baseline symptom severity on cognitive response to CRT. This was a factor identified in the Wykes et al. (2011) meta-analysis as having a potential (non-significant) effect on a measure of global cognition. Indeed, evidence that has been presented suggests that neither baseline demographic or clinical factors exert sufficient influence to act as barriers to receiving cognitive benefit from CRT.

Outcomes from the systematic review presented in this thesis indicate that we might be getting closer to the “right stuff”. Ironically, close to 20 years after the seminal paper by Green et al. (2000), concepts around learning potential and a patient’s neurocognitive strengths and weaknesses as guides for treatment intervention have re-emerged. The stronger evidence found for such factors as premorbid IQ, baseline cognition, and training task engagement/performance, being potential markers of an individual’s capacity to realise cognitive change following CRT, provide an important focal point for future investigation.

10.5.2 Implications of methodological approach. Outcomes from this thesis have highlighted the importance of shifting our consideration from average treatment effects (i.e., group-level analysis) to individual and subgroup levels of treatment response to better understand the factors that influence the efficacy of CRT. However, the aforementioned limitations posed by traditional approaches to subgroup analysis are common to the CRT predictor literature and potentially

undermine the veracity of what conclusions can be drawn. To recap, of the CRT predictor studies reported in Chapter 4, an average 4.8 predictor variables were examined across an average 3.95 cognitive domains (Section 4.62.). That equates to an average 19 subgroup analyses and, if multiple comparisons are not accounted for, a greater than 50% risk of making at least one Type I error and around a 20% risk of making at least two Type I errors (derived from figure presented on page 1669; Lagakos, 2006). Of note, only 8 of the 40 articles reviewed reported controlling for multiple comparisons.

There remains a tension between the rigours of empirical research, which allows for reproducibility, and the more exploratory analysis needed to better understand individual variability in response to interventions that are ultimately intended for clinical use (Ruberg et al., 2010). In clinical neuropsychology, for example, more qualitative single case study (see Caramazza & Coltheart, 2006) or case series (see Schwartz & Dell, 2010) methods are applied. In defence of this approach, McCloskey argued, “given the acknowledged need to consider individual patients' performance patterns, what function would be served by aggregating the data over subjects...?” (1993, p. 275). The same challenge could be made in reference to CRT predictor analysis, where traditional approaches have left us with broad generalisations that make it difficult to determine ‘who benefits’.

Outcomes from this thesis have demonstrated that the application of novel analytic techniques has the potential to yield clinically meaningful information about patterns and predictors of individual response to CRT. With adequate sample sizes, data visualisation techniques such as the heat maps presented in Chapter 8 can be augmented with hierarchical clustering techniques (Wilkinson & Friendly, 2009). Another modelling technique that can be supported with larger datasets is that of classification trees. Ruberg, Chen, and Wang (2010) demonstrated the technique using a pooled sample of schizophrenia patients involved in antipsychotic drug trials; they identified specific items on the PANSS that, two weeks after treatment commencement, were predictive of treatment response. Machine learning techniques have also been used with effect to identify predictors of treatment outcome. For example, Armañanzas et al. (2013) used machine learning to identify a set of predictors that could classify with 90% accuracy outcome (full versus partial recovery) following temporal lobe epilepsy surgery. Hettige and colleagues (Hettige et al., 2017) were similarly able to classify with 67% accuracy those at future risk of

suicide attempt in schizophrenia. Each of these represent hypothesis generating approaches that require confirmatory studies to validate the outcomes.

10.5.3 Clinical implications. CRT is currently the only moderately effective intervention for ameliorating characteristic cognitive deficits that have been associated with poor functional outcomes following a diagnosis of schizophrenia. The economic impact of poor functional outcomes in such areas as educational and vocational pursuits, and the support required in the face of poor community functioning and social relations, is considerable. While the estimated economic cost of schizophrenia varies greatly by country (Jin & Mosweu, 2017), in Australia alone, schizophrenia had an estimated annual societal cost of \$1.44 billion (Carr, Neil, Halpin, Holmes, & Lewin, 2003). When considered at an individual level, the Australian lifetime societal cost, adjusted to 2015 values, was recently estimated at \$US988,264 (Jin & Mosweu, 2017). In line with global trends (Chong et al., 2016), lost productivity, both on the part of the diagnosed individual and on the part of their carers, accounted for a significant portion of the total cost (60.3%; Jin & Mosweu, 2017; Langley-Hawthorne, 1997). Indeed, around 90% of Australian's diagnosed with schizophrenia aged 30-64 are neither employed or engaged in study (Waghorn, Chant, Lloyd, & Harris, 2011). While less quantifiable, the burden on family members often extends beyond financial concerns to impact their physical and mental wellbeing, social networks, quality of life, and aspirations for the future (Millier et al., 2014).

CRT is a relatively low-cost intervention (Wykes, Reeder, et al., 2007) that, in addition to improving functional outcomes (refer to Section 3.4.3), has the potential to improve gains from other therapeutic interventions (Drake et al., 2013) and to reduce hospital readmission rates (Garrido et al., 2017). However, outcomes from this thesis have demonstrated that we still do not know why a large proportion of people diagnosed with schizophrenia fail to realise cognitive benefit from CRT. Nor do we know how to identify those who are most likely to benefit. As CRT becomes more widely endorsed in clinical treatment guidelines, such as its recent inclusion in the "Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the management of schizophrenia and related disorders" (Galletly et al., 2015), the consequences of not knowing the predictors of response are significant. Treatment guidelines are currently limited to a more general recommendation that CRT be used in response to evidence of cognitive impairment.

Unintentionally, such broad recommendations serve to mask evidence of heterogeneity of cognitive response to CRT, fostering the false impression that the moderate benefits reported in clinical trials are applicable to all (discussed in Section 8.3; Kraemer et al., 2006; Kravitz et al., 2004). Due to a lack of evidence, clinical guidelines are currently unable to prescribe how best to match individual need with CRT approach. Based on current estimates, that potentially means that for every 10 people referred to CRT, on average, 4 are not likely to experience a cognitive benefit. Poor rates of response could in turn undermine clinician confidence in the effectiveness of CRT, reinforce the mistrust in medical professional of non-pharmacological interventions, and demoralise further individuals who already experience significant burden.

Public healthcare services in Australia are overburdened and under resourced and, in the face of acute need, fail to adequately address the ongoing needs of chronic schizophrenia patients (Nielssen, McGorry, Castle, & Galletly, 2017). With appropriate supports, CRT has the potential to ease some of that burden. However, to ensure that limited resources are directed to those most likely to benefit, there is a critical need to better understand the differential patterns and predictors of cognitive response to CRT.

10.6 Future Directions

Better understanding of differential patterns and predictors of cognitive response to CRT will only come about through further research. However, there are number of more immediate steps that can be taken that capitalise on existing datasets before looking to new, longer-term research projects.

10.6.1 Immediate steps. With minimal effort or financial cost, where ethical approvals have been obtained to re-analyse existing datasets, research groups should seek to replicate the key outcomes presented in this body of work. In the first instance, the retrospective calculation of reliable change indices across cognitive outcome domains would (a) make explicit what proportion of CRT participants received cognitive benefit from CRT and (b) help determine whether more than an improved/not improved dichotomy can be identified. In the second instance, for research groups whose neurocognitive assessment pack included a measure of verbal (e.g., the HVLIT-R, CVLT, Rey Auditory Verbal Learning Test) or visual (e.g., BVMT-R) learning, the prognostic value of static measures of verbal and visual

learning could be examined. Similarly, where symptoms were measured post-intervention, correlations between post-intervention symptom dimensions and domain-level cognitive change scores could be examined. Finally, for those with larger datasets, or who, through collaborative efforts, are able to combine multiple datasets from equivalent or similar CRT approaches, it might be possible to use hierarchical clustering techniques paired with heat map visualisations to examine the prognostic value of such variables as premorbid IQ, baseline cognition, and learning potential across responder subgroups. Each of these steps, either singularly or in combination, would lend weight to the veracity of the thesis outcomes and help to consolidate evidence in support of the purported markers of an individual's capacity to receive cognitive benefit from CRT.

10.6.2 Longer-term steps. Longer-term, a significant shift in approach is required to further our understanding of factors that influence cognitive response to, and the efficacy of, CRT. While there is evident heterogeneity in response to CRT, we are still without definitive answers regarding factors that influence its efficacy. This body of work has exposed a range of issues that have served to undermine efforts to-date. A majority of CRT mediator and moderator analysis has been performed using data obtained from RCTs designed and powered to evaluate efficacy. A majority are underpowered to detect interaction effects, i.e., subgroup analysis, and a majority do not control for multiplicity. As previously pointed out (Section 4.8.7), no study has investigated all predictors with the same data set and there might be cross cultural, education, or socioeconomic differences that influence CRT outcomes differently internationally. It is also unclear to what extent different CRT approaches exert a differential influence on cognitive response, or to what extent predictors of response differ by CRT approach.

There is a need for an updated meta-analysis of the efficacy of CRT across cognitive and functional outcomes. With the proliferation of CRT efficacy studies since 2009, and the introduction of a number of new CRT programs, it would benefit knowing whether there had been a shift in effect size. Where sufficient RCTs have been conducted, it might also be possible to compare efficacy across a lower level of CRT approach, for example, directly comparing Delahunty and Morice's cognitive remediation therapy, CogPack and Posit Science outcomes. Further, to compliment results of the systematic review presented in Chapter 4, it would be of value to undertake a similar review of studies that did not meet criteria, i.e., broader CRT

approaches that included social cognition training or that utilized adjunctive therapies. It would then be possible to see whether a similar pattern emerged regarding the prognostic value of demographic, clinical, cognitive, treatment, and other variables of interest.

Outputs from the respective systematic reviews could in turn inform wider exploratory efforts to identify a consensus suite of potential predictors of cognitive response to CRT. With appropriate ethical approval, a change in approach might involve an international data pooling initiative to develop a de-identified database of sufficient size to support exploratory analysis using machine learning, classification trees, or other modelling approaches. Notwithstanding differences in study design and CRT approach, meta-analyses of CRT efficacy draw on such pooled data, albeit at a summary level. Excepting the requirement for participant level data, there is no reason why a similar approach could not be applied to the examination of predictors of cognitive response to CRT. As has been done in meta-analytic studies, the influence of such variables as study country, CRT approach, use of adjunctive therapies, and type of control, could be included as potential predictors of response.

Following these exploratory initiatives, there is a requirement for the consensus suite of potential predictors to be verified through adequately powered (i.e., powered for subgroup analysis), multi-site randomized controlled trials informed by a priori hypotheses, ideally involving cross-research group collaboration or further international data pooling initiatives. Stratified randomization techniques should be used to ensure adequate representation of expected responder subgroups (Alosh et al., 2015). To better inform clinical practice, cognitive outcome should be measured using tests of both statistical significance and clinically meaningful change, and predictors of response should ideally be examined over the latter.

There are encouraging indications that some of these steps are already being implemented. For example, a number of the articles included in the systematic review presented in Chapter 4 involved the analysis of pooled CRT cohorts, increasing sample size and power (e.g., Biagianti et al., 2016; K. Greenwood et al., 2011). Of greater importance, a collaboration involving Professor Wykes of Kings College London and Dr Morris of the National Institute of Mental Health resulted in the establishment of the Database of Cognitive Training and Remediation Studies (DoCTRS). This is beginning to yield results with several recent publications and poster abstracts drawing on this growing database (e.g., Cella et al., 2017;

Seccomandi et al., 2018). However, to yield the results required to inform clinical practice, research groups need to let go of old lines and methods of enquiry to embrace, as a new starting point, widescale exploration of patterns and predictors of differential cognitive response to CRT.

10.7 Conclusion

The outcomes of this thesis have consolidated and made transparent what was known but not manifest about factors that influence individual response to, and the efficacy of, CRT in people diagnosed with schizophrenia. Moreover, the outcomes have extended the knowledge base through identification of a number of new lines of enquiry that require further exploratory (post-intervention symptoms, static measures of learning potential, genetic correlates) or confirmatory (baseline AttnVig) study. Finally, the outcomes have challenged traditional methods of analysis in the field, modelling but one of a range of novel, alternate approaches that could be employed to aid a better formulation to influence treatment guidelines and, in turn, clinical practice. While a step has been taken towards better understanding the source of differences in response to CRT (Kurtz, 2012), we have not yet arrived at the place where we can match an individual to the CRT program they are most likely to receive benefit from (Kaneko & Keshavan, 2012). Further steps are needed to progress this critical line of enquiry.

References

- Adcock, R. A., Dale, C., Fisher, M., Aldebot, S., Genevsky, A., Simpson, G. V., ... Vinogradov, S. (2009). When top-down meets bottom-up: auditory training enhances verbal memory in schizophrenia. *Schizophrenia Bulletin*, 35(6), 1132–1141. <http://doi.org/10.1093/schbul/sbp068>
- Addington, D., Addington, J., Maticka-Tyndale, E., & Joyce, J. (1992). Reliability and validity of a depression rating scale for schizophrenics. *Schizophrenia Research*, 6, 201–208. [http://doi.org/http://dx.doi.org/10.1016/0920-9964\(92\)90003-N](http://doi.org/http://dx.doi.org/10.1016/0920-9964(92)90003-N)
- Addington, D., Addington, J., & Schissel, B. (1990). A depression rating scale for schizophrenics. *Schizophrenia Research*, 3, 247–251. [http://doi.org/http://dx.doi.org/10.1016/0920-9964\(90\)90005-R](http://doi.org/http://dx.doi.org/10.1016/0920-9964(90)90005-R)
- Ahmed, A. O., Hunter, K. M., Goodrum, N. M., Batten, N.-J., Birgenheir, D., Hardison, E., ... Buckley, P. F. (2015). A randomized study of cognitive remediation for forensic and mental health patients with schizophrenia. *Journal of Psychiatric Research*, 68, 8–18. <http://doi.org/10.1016/j.jpsychires.2015.05.013>
- Alfimova, M. V, Monakhov, M. V, Abramova, L. I., Golubev, S. a, & Golimbet, V. E. (2010). Polymorphism of serotonin receptor genes (5-HTR2A) and Dysbindin (DTNBP1) and individual components of short-term verbal memory processes in Schizophrenia. *Neuroscience and Behavioral Physiology*, 40(8), 934–940. <http://doi.org/10.1007/s11055-010-9348-7>
- Allen, D. N., Goldstein, G., & Warnick, E. (2003). A consideration of neuropsychologically normal schizophrenia. *Journal of the International Neuropsychological Society*, 9(1), 56–63. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/12570358>
- Allen, N. C., Bagade, S., McQueen, M. B., Ioannidis, J. P. A., Kavvoura, F. K., Khoury, M. J., ... Bertram, L. (2008). Systematic meta-analyses and field synopsis of genetic association studies in schizophrenia: the SzGene database. *Nature Genetics*, 40(7), 827–834. <http://doi.org/10.1038/ng.171>
- Alosh, M., Fritsch, K., Huque, M., Mahjoob, K., Pennello, G., Rothmann, M., ... Yue, L. (2015). Statistical Considerations on Subgroup Analysis in Clinical Trials. *Statistics in Biopharmaceutical Research*, 7(4), 286–303. <http://doi.org/10.1080/19466315.2015.1077726>

- American Psychiatric Association. (2000). *Diagnostic and Statistical Manual of Mental Disorders (4th ed., text. rev.)*. Washington, DC: Author.
<http://doi.org/10.1176/appi.books.9780890423349>
- American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (5th ed.)*. Washington, DC: American Psychiatric Association.
- Ammari, N., Heinrichs, R. W., Pinnock, F., Miles, A. A., Muharib, E., & McDermid Vaz, S. (2014). Preserved, deteriorated, and premorbidly impaired patterns of intellectual ability in schizophrenia. *Neuropsychology*, 28(3), 353–358.
<http://doi.org/10.1037/neu0000026>
- Andreasen, N. C. (1981). *Scale for Assessment of Negative Symptoms (SANS)*. Iowa City, IA: University of Iowa.
- Andreasen, N. C. (1984). *Scale for Assessment of Positive Symptoms (SAPS)*. Iowa City, IA: University of Iowa.
- Armañanzas, R., Alonso-Nanclares, L., DeFelipe-Oroquieta, J., Kastanauskaite, A., de Sola, R. G., DeFelipe, J., ... Larrañaga, P. (2013). Machine Learning Approach for the Outcome Prediction of Temporal Lobe Epilepsy Surgery. *PLoS ONE*, 8(4), 1–9. <http://doi.org/10.1371/journal.pone.0062819>
- August, S. M., Kiwanuka, J. N., McMahon, R. P., & Gold, J. M. (2012). The MATRICS Consensus Cognitive Battery (MCCB): Clinical and Cognitive Correlates. *Schizophrenia Research*, 134(1), 76–82.
<http://doi.org/10.1016/j.schres.2011.10.015>
- Baek, J. H., Kim, J. S., Ryu, S., Oh, S., Noh, J., Lee, W. K., ... Hong, K. S. (2012). Association of genetic variations in DTNBP1 with cognitive function in schizophrenia patients and healthy subjects. *American Journal of Medical Genetics.*, 159B(7), 841–849. <http://doi.org/10.1002/ajmg.b.32091>
- Bakkour, N., Samp, J., Akhras, K., El Hammi, E., Soussi, I., Zahra, F., ... Toumi, M. (2014). Systematic review of appropriate cognitive assessment instruments used in clinical trials of schizophrenia, major depressive disorder and bipolar disorder. *Psychiatry Research*, 216(3), 291–302.
<http://doi.org/10.1016/j.psychres.2014.02.014>
- Balu, D. T., & Coyle, J. T. (2011). Neuroplasticity signaling pathways linked to the pathophysiology of schizophrenia. *Neuroscience and Biobehavioral Reviews*, 35(3), 848–870. <http://doi.org/10.1016/j.neubiorev.2010.10.005>

- Bark, N., Revheim, N., Huq, F., Khalderov, V., Ganz, Z. W., & Medalia, A. (2003). The impact of cognitive remediation on psychiatric symptoms of schizophrenia. *Schizophrenia Research*, 63(3), 229–235. [http://doi.org/10.1016/S0920-9964\(02\)00374-2](http://doi.org/10.1016/S0920-9964(02)00374-2)
- Bell, M. D., Bryson, G. J., & Wexler, B. E. (2003). Cognitive remediation of working memory deficits: durability of training effects in severely impaired and less severely impaired schizophrenia. *Acta Psychiatrica Scandinavica*, 108(2), 101–109. <http://doi.org/http://dx.doi.org/10.1034/j.1600-0447.2003.00090.x>
- Bender, R., Bunce, C., Clarke, M., Gates, S., Lange, S., Pace, N. L., & Thorlund, K. (2008). Attention should be given to multiplicity issues in systematic reviews. *Journal of Clinical Epidemiology*, 61(9), 857–865. <http://doi.org/10.1016/j.jclinepi.2008.03.004>
- Benedict, R. H. B., Schretlen, D., Groninger, L., & Brandt, J. (1998). Hopkins Verbal Learning Test - Revised: Normative Data and Analysis of Inter-Form and Test-Retest Reliability. *The Clinical Neuropsychologist (Neuropsychology, Development and Cognition: Section D)*, 12(1), 43–55. <http://doi.org/10.1076/clin.12.1.43.1726>
- Benedict, R. H. B., Schretlen, D., Groninger, L., Dobraski, M., & Shpritz, B. (1996). Revision of the Brief Visuospatial Memory Test: Studies of Normal Performance, Reliability, and Validity. *Psychological Assessment*, 8(2), 145–153. <http://doi.org/10.1037/1040-3590.8.2.145>
- Benoit, A., Harvey, P.-O., Bherer, L., & Lepage, M. (2016). Does the Beck Cognitive Insight Scale Predict Response to Cognitive Remediation in Schizophrenia? *Schizophrenia Research and Treatment*, 2016, 1–6. <http://doi.org/10.1155/2016/6371856>
- Bhardwaj, S. K., Baharnoori, M., Sharif-Askari, B., Kamath, A., Williams, S., & Srivastava, L. K. (2009). Behavioral characterization of dysbindin-1 deficient sandy mice. *Behavioural Brain Research*, 197(2), 435–441. <http://doi.org/10.1016/j.bbr.2008.10.011>
- Bhardwaj, S. K., Ryan, R. T., Wong, T. P., & Srivastava, L. K. (2015). Loss of dysbindin-1, a risk gene for schizophrenia, leads to impaired group 1 metabotropic glutamate receptor function in mice. *Frontiers in Behavioral Neuroscience*, 9(March), 1–11. <http://doi.org/10.3389/fnbeh.2015.00072>
- Biagiante, B., Fisher, M., Neilands, T. B., Loewy, R., & Vinogradov, S. (2016).

- Engagement with the auditory processing system during targeted auditory cognitive training mediates changes in cognitive outcomes in individuals with schizophrenia. *Neuropsychology*, 30(8), 998–1008.
<http://doi.org/10.1037/neu0000311>
- Boosman, H., Bovend'Eerdt, T. J. H., Visser-Meily, J. M. A., Nijboer, T. C. W., & van Heugten, C. M. (2016). Dynamic testing of learning potential in adults with cognitive impairments: A systematic review of methodology and predictive value. *Journal of Neuropsychology*, 10(2), 186–210.
<http://doi.org/10.1111/jnp.12063>
- Bor, J., Brunelin, J., D'Amato, T., Costes, N., Suaud-Chagny, M.-F., Saoud, M., & Poulet, E. (2011). How can cognitive remediation therapy modulate brain activations in schizophrenia? An fMRI study. *Psychiatry Research*, 192(3), 160–166. <http://doi.org/10.1016/j.psychres.2010.12.004>
- Bosia, M., Bechi, M., Marino, E., Anselmetti, S., Poletti, S., Cocchi, F., ... Cavallaro, R. (2007). Influence of catechol-O-methyltransferase Val158Met polymorphism on neuropsychological and functional outcomes of classical rehabilitation and cognitive remediation in schizophrenia. *Neuroscience Letters*, 417(3), 271–274. <http://doi.org/10.1016/j.neulet.2007.02.076>
- Bosia, M., Bechi, M., Pirovano, A., Buonocore, M., Lorenzi, C., Cocchi, F., ... Cavallaro, R. (2014). COMT and 5-HT1A-receptor genotypes potentially affect executive functions improvement after cognitive remediation in schizophrenia. *Health Psychology and Behavioral Medicine*, 2(1), 509–516.
<http://doi.org/10.1080/21642850.2014.905206>
- Bosia, M., Buonocore, M., Bechi, M., Spangaro, M., Pigoni, A., Croci, M., ... Cavallaro, R. (2017). Cognitive remediation and functional improvement in schizophrenia: Is it a matter of size? *European Psychiatry*, 40, 26–32.
<http://doi.org/10.1016/j.eurpsy.2016.06.007>
- Bosia, M., Zanoletti, A., Spangaro, M., Buonocore, M., Bechi, M., Cocchi, F., ... Cavallaro, R. (2014). Factors affecting cognitive remediation response in schizophrenia: the role of COMT gene and antipsychotic treatment. *Psychiatry Research*, 217(1–2), 9–14. <http://doi.org/10.1016/j.psychres.2014.02.015>
- Bottlender, R., Strauss, A., & Möller, H.-J. (2010). Social disability in schizophrenic, schizoaffective and affective disorders 15 years after first admission. *Schizophrenia Research*, 116(1), 9–15.

<http://doi.org/10.1016/j.schres.2009.10.008>

- Bowie, C. R., Grossman, M., Gupta, M., Holshausen, K., & Best, M. W. (2017). Action-based cognitive remediation for individuals with serious mental illnesses: Effects of real-world simulations and goal setting on functional and vocational outcomes. *Psychiatric Rehabilitation Journal*, 40(1), 53–60. <http://doi.org/10.1037/prj0000189>
- Bowie, C. R., Grossman, M., Gupta, M., Oyewumi, L. K., & Harvey, P. D. (2014). Cognitive remediation in schizophrenia: efficacy and effectiveness in patients with early versus long-term course of illness. *Early Intervention in Psychiatry*, 8(1), 32–38. <http://doi.org/10.1111/eip.12029>
- Bowie, C. R., Leung, W. W., Reichenberg, A., McClure, M. M., Patterson, T. L., Heaton, R. K., & Harvey, P. D. (2008). Predicting schizophrenia patients' real-world behavior with specific neuropsychological and functional capacity measures. *Biological Psychiatry*, 63(5), 505–11. <http://doi.org/10.1016/j.biopsych.2007.05.022>
- Bowie, C. R., Reichenberg, A., Patterson, T. L., Heaton, R. K., & Harvey, P. D. (2006). Determinants of Real-World Functional Performance in Schizophrenia Subjects: Correlations With Cognition, Functional Capacity, and Symptoms. *The American Journal of Psychiatry*, 163(3), 418–425. <http://doi.org/http://dx.doi.org/10.1176/appi.ajp.163.3.418>
- Bozikas, V. P., & Andreou, C. (2011). Longitudinal studies of cognition in first episode psychosis: a systematic review of the literature. *The Australian and New Zealand Journal of Psychiatry*, 45(2), 93–108. <http://doi.org/10.3109/00048674.2010.541418>
- Bray, N. J., Preece, A., Williams, N. M., Moskvina, V., Buckland, P. R., Owen, M. J., & O'Donovan, M. C. (2005). Haplotypes at the dystrobrevin binding protein 1 (DTNBP1) gene locus mediate risk for schizophrenia through reduced DTNBP1 expression. *Human Molecular Genetics*, 14(14), 1947–1954. <http://doi.org/10.1093/hmg/ddi199>
- Brewer-Mixon, K. K., & Cullum, C. M. (2013). Historical principles and foundations of neuropsychological rehabilitation. In C. A. Noggle, R. S. Dean, & M. T. Barisa (Eds.), *Neuropsychological Rehabilitation* (pp. 1–11). New York, NY: Springer.
- Bryce, S. D., Rossell, S. L., Lee, S. J., Lawrence, R. J., Tan, E. J., Carruthers, S. P.,

- & Ponsford, J. L. (2018). Neurocognitive and Self-efficacy Benefits of Cognitive Remediation in Schizophrenia: A Randomized Controlled Trial. *Journal of the International Neuropsychological Society*, 1–14.
<http://doi.org/10.1017/S1355617717001369>
- Buckley, P. F., Miller, B. J., Lehrer, D. S., & Castle, D. J. (2009). Psychiatric comorbidities and schizophrenia. *Schizophrenia Bulletin*, 35(2), 383–402.
<http://doi.org/10.1093/schbul/sbn135>
- Buonocore, M., Bosia, M., Bechi, M., Spangaro, M., Cavedoni, S., Cocchi, F., ... Cavallaro, R. (2017). Is Longer Treatment Better? A Comparison Study of 3 Versus 6 Months Cognitive Remediation in Schizophrenia. *Neuropsychology*, 31(4), 467–473. <http://doi.org/10.1037/neu0000347>
- Burdick, K. E., Lencz, T., Funke, B., Finn, C. T., Szeszko, P. R., Kane, J. M., ... Malhotra, A. K. (2006). Genetic variation in DTNBP1 influences general cognitive ability. *Human Molecular Genetics*, 15(10), 1563–1568.
<http://doi.org/10.1093/hmg/ddi481>
- Burton, C. Z., Vella, L., Kelsoe, J. R., Bilder, R. M., & Twamley, E. W. (2015). Catechol-O-methyltransferase genotype and response to Compensatory Cognitive Training in outpatients with schizophrenia. *Psychiatric Genetics*, 25, 131–134.
- Burton, C. Z., Vella, L., & Twamley, E. W. (2011). Clinical and Cognitive Insight in a Compensatory Cognitive Training Intervention. *American Journal of Psychiatric Rehabilitation*, 14(4), 307–326.
<http://doi.org/10.1080/15487768.2011.622159>
- Cairns, A., Dark, F., & Batts, M. (2013). Implementing cognitive remediation therapy: Lessons from two public mental health services. *Australasian Psychiatry*, 21(5), 476–480. <http://doi.org/10.1177/1039856213497808>
- Caramazza, A., & Coltheart, M. (2006). Cognitive neuropsychology twenty years on. *Cognitive Neuropsychology*, 23(1), 3–12.
<http://doi.org/10.1080/02643290500443250>
- Carr, V. J., Neil, A. L., Halpin, S. a, Holmes, S., & Lewin, T. J. (2003). Costs of schizophrenia and other psychoses in urban Australia: findings from the Low Prevalence (Psychotic) Disorders Study. *The Australian and New Zealand Journal of Psychiatry*, 37(1), 31–40.
<http://doi.org/http://dx.doi.org/10.1046/j.1440-1614.2003.01092.x>

- Cella, M., Stahl, D., Morris, S., Keefe, R. S. E., Bell, M. D., & Wykes, T. (2017). Effects of cognitive remediation on negative symptoms dimensions: exploring the role of working memory. *Psychological Medicine*, (2017), 1–9. <http://doi.org/10.1017/S0033291717000757>
- Cella, M., & Wykes, T. (2017). The nuts and bolts of Cognitive Remediation: Exploring how different training components relate to cognitive and functional gains. *Schizophrenia Research*, 5–9. <http://doi.org/10.1016/j.schres.2017.09.012>
- Cellard, C., Whaley, S., & Wykes, T. (2011). Revisiting Cognitive Remediation for Schizophrenia: Facing the Challenges of the Future. In M. S. Ritsner (Ed.), *Handbook of Schizophrenia Spectrum Disorders, Volume III* (Vol. III, pp. 209–223). Dordrecht: Springer. <http://doi.org/10.1007/978-94-007-0834-1>
- Chein, J. M., & Schneider, W. (2012). The Brain's Learning and Control Architecture. *Current Directions in Psychological Science*, 21(2), 78–84. <http://doi.org/10.1177/0963721411434977>
- Chelune, G. J., Naugle, R. I., Lüders, H., Sedlak, J., & Awad, I. A. (1993). Individual change after epilepsy surgery: Practice effects and base-rate information. *Neuropsychology*, 7(I), 41–52. <http://doi.org/10.1037/0894-4105.7.1.41>
- Choi, J., Fiszdon, J. M., & Medalia, A. (2010). Expectancy-value theory in persistence of learning effects in schizophrenia: role of task value and perceived competency. *Schizophrenia Bulletin*, 36(5), 957–965. <http://doi.org/10.1093/schbul/sbq078>
- Choi, J., & Medalia, A. (2005). Factors associated with a positive response to cognitive remediation in a community psychiatric sample. *Psychiatric Services*, 56(5), 602–604. <http://doi.org/10.1176/appi.ps.56.5.602>
- Choi, J., & Medalia, A. (2010). Intrinsic motivation and learning in a schizophrenia spectrum sample. *Schizophrenia Research*, 118(1–3), 12–19. <http://doi.org/10.1016/j.schres.2009.08.001>
- Choi, K.-H., Wykes, T., & Kurtz, M. M. (2013). Adjunctive pharmacotherapy for cognitive deficits in schizophrenia: meta-analytical investigation of efficacy. *The British Journal of Psychiatry*, 203(3), 172–8. <http://doi.org/10.1192/bjp.bp.111.107359>
- Chong, H. Y., Teoh, S. L., Wu, D. B.-C., Kotirum, S., Chiou, C.-F., & Chaiyakunapruk, N. (2016). Global economic burden of schizophrenia: a systematic review. *Neuropsychiatric Disease and Treatment*, 12, 357–373.

- <http://doi.org/10.2147/NDT.S96649>
- Corbera, S., Wexler, B. E., Poltorak, A., Thime, W. R., & Kurtz, M. M. (2017). Cognitive remediation for adults with schizophrenia: Does age matter? *Psychiatry Research*, 247(April 2016), 21–27.
<http://doi.org/10.1016/j.psychres.2016.10.084>
- Cox, M. M., Tucker, A. M., Tang, J., Talbot, K., Richer, D. C., Yeh, L., & Arnold, S. E. (2009). Neurobehavioral abnormalities in the dysbindin-1 mutant, sandy, on a C57BL/6J genetic background. *Genes, Brain and Behavior*, 8(4), 390–397.
<http://doi.org/10.1111/j.1601-183X.2009.00477.x>
- Daskalakis, Z. J., Christensen, B. K., Fitzgerald, P. B., & Chen, R. (2008). Dysfunctional neural plasticity in patients with schizophrenia. *Arch.Gen.Psychiatry*, 65(1538–3636 (Electronic)), 378–385.
<http://doi.org/http://dx.doi.org/10.1001/archpsyc.65.4.378>
- Davidson, C. A., Johannesen, J. K., & Fiszdon, J. M. (2016). Role of learning potential in cognitive remediation: Construct and predictive validity. *Schizophrenia Research*, 171(1–3), 117–124.
<http://doi.org/10.1016/j.schres.2016.01.044>
- de Gracia Dominguez, M., Viechtbauer, W., Simons, C. J. P., van Os, J., & Krabbendam, L. (2009). Are Psychotic Psychopathology and Neurocognition Orthogonal? A Systematic Review of Their Associations. *Psychological Bulletin*, 135(1), 157–171. <http://doi.org/10.1037/a0014415>
- Delahunty, A., & Morice, R. (1993). *The Frontal Executive Program. A Neurocognitive Rehabilitation Program for Schizophrenia, revised 2nd edn.* Albury, NSW, NSW.
- Dickinson, D., Ramsey, M. E., & Gold, J. M. (2007). Overlooking the Obvious: A Meta-analytic Comparison of Digit Symbol Coding Tasks and Other Cognitive Measures in Schizophrenia. *Archives of General Psychiatry*, 64, 532–542.
<http://doi.org/http://dx.doi.org/10.1001/archpsyc.64.5.532>
- Dickinson, D., Tenhula, W., Morris, S., Brown, C., Peer, J., Spencer, K., ... Bellack, A. S. (2010). A Randomized, Controlled Trial of Computer-Assisted Cognitive Remediation for Schizophrenia. *American Journal of Psychiatry*, 167, 170–180.
<http://doi.org/http://dx.doi.org/10.1176/appi.ajp.2009.09020264>
- Dickson, H., Laurens, K. R., Cullen, A. E., & Hodgins, S. (2012). Meta-analyses of cognitive and motor function in youth aged 16 years and younger who

- subsequently develop schizophrenia. *Psychological Medicine*, 42(4), 743–55.
<http://doi.org/10.1017/S0033291711001693>
- Dmitrienko, A., Millen, B., & Lipkovich, I. (2017). Multiplicity considerations in subgroup analysis. *Statistics in Medicine*, 36(28), 4446–4454.
<http://doi.org/10.1002/sim.7416>
- Donohoe, G., Morris, D. W., Clarke, S., McGhee, K. a, Schwaiger, S., Nangle, J.-M., ... Corvin, A. (2007). Variance in neurocognitive performance is associated with dysbindin-1 in schizophrenia: a preliminary study. *Neuropsychologia*, 45(2), 454–8. <http://doi.org/10.1016/j.neuropsychologia.2006.06.016>
- Donohoe, G., Morris, D. W., De Sanctis, P., Magno, E., Montesi, J. L., Garavan, H. P., ... Foxe, J. J. (2008). Early visual processing deficits in dysbindin-associated schizophrenia. *Biological Psychiatry*, 63(5), 484–489.
<http://doi.org/10.1016/j.biopsych.2007.07.022>
- Drake, R. J., Day, C. J., Picucci, R., Warburton, J., Larkin, W., Husain, N., ... Marshall, M. (2013). A naturalistic, randomized, controlled trial combining cognitive remediation with cognitive-behavioural therapy after first-episode non-affective psychosis. *Psychological Medicine*, 44, 1889–1899.
<http://doi.org/10.1017/S0033291713002559>
- Eack, S. M., Hogarty, G. E., Cho, R. Y., Prasad, K. M. R., Greenwald, D. P., Hogarty, S. S., & Keshavan, M. S. (2010). Neuroprotective Effects of Cognitive Enhancement Therapy Against Gray Matter Loss in Early Schizophrenia. *Archives of General Psychiatry*, 67(7), 674–682.
<http://doi.org/http://dx.doi.org/10.1001/archgenpsychiatry.2010.63>
- Eranti, S. V., MacCabe, J. H., Bundy, H., & Murray, R. M. (2013). Gender difference in age at onset of schizophrenia: A meta-analysis. *Psychological Medicine*, 43(1), 155–167. <http://doi.org/10.1017/S003329171200089X>
- Evans, S. R. (2013). Clinical trial structures. *Journal of Experimental Stroke & Translational Medicine*, 31(9), 1713–1723.
<http://doi.org/10.1109/TMI.2012.2196707>. Separate
- Farreny, A., Aguado, J., Corbera, S., Ochoa, S., Huerta-Ramos, E., & Usall, J. (2016). Baseline Predictors for Success Following Strategy-Based Cognitive Remediation Group Training in Schizophrenia. *The Journal of Nervous and Mental Disease*, 204(8), 585–589.
<http://doi.org/10.1097/NMD.0000000000000509>

- Farreny, A., Aguado, J., Ochoa, S., Haro, J. M., & Usall, J. (2013). The role of negative symptoms in the context of cognitive remediation for schizophrenia. *Schizophrenia Research*, 150(1), 58–63.
<http://doi.org/10.1016/j.schres.2013.08.008>
- Feng, Y. Q., Zhou, Z. Y., He, X., Wang, H., Guo, X. L., Hao, C. J., ... Li, W. (2008). Dysbindin deficiency in sandy mice causes reduction of snapin and displays behaviors related to schizophrenia. *Schizophrenia Research*, 106(2–3), 218–228. <http://doi.org/10.1016/j.schres.2008.07.018>
- Fett, A.-K. J., Velthorst, E., Reichenberg, A., Ruggero, C., Callahan, J., Bromet, E. J., & Kotov, R. (2018). Eighteen-year course of cognitive functioning in psychotic disorders: findings from the Suffolk County mental health longitudinal study. *Schizophrenia Bulletin*, 44(Supp1), S40.
- Fett, A.-K. J., Viechtbauer, W., Dominguez, M.-G., Penn, D. L., van Os, J., & Krabbendam, L. (2011). The relationship between neurocognition and social cognition with functional outcomes in schizophrenia: a meta-analysis. *Neuroscience and Biobehavioral Reviews*, 35(3), 573–588.
<http://doi.org/10.1016/j.neubiorev.2010.07.001>
- Fisher, M., Herman, A., Stephens, D. B., & Vinogradov, S. (2016). Neuroscience-informed computer-assisted cognitive training in schizophrenia. *Annals of the New York Academy of Sciences*, 1366(1), 90–114.
<http://doi.org/10.1111/nyas.13042>
- Fisher, M., Holland, C., Merzenich, M. M., & Vinogradov, S. (2009). Using neuroplasticity-based auditory training to improve verbal memory in schizophrenia. *The American Journal of Psychiatry*, 166(7), 805–811.
<http://doi.org/10.1176/appi.ajp.2009.08050757>
- Fisher, M., Holland, C., Subramaniam, K., & Vinogradov, S. (2010). Neuroplasticity-based cognitive training in schizophrenia: an interim report on the effects 6 months later. *Schizophrenia Bulletin*, 36(4), 869–879.
<http://doi.org/10.1093/schbul/sbn170>
- Fisher, M., Loewy, R., Carter, C., Lee, A., Ragland, J. D., Niendam, T., ... Vinogradov, S. (2015). Neuroplasticity-Based Auditory Training Via Laptop Computer Improves Cognition in Young Individuals With Recent Onset Schizophrenia. *Schizophrenia Bulletin*, 41(1), 1–9.
<http://doi.org/10.1093/schbul/sbt232>

- Fisher, M., Mellon, S. H., Wolkowitz, O., & Vinogradov, S. (2016). Neuroscience-informed auditory training in schizophrenia: A final report of the effects on cognition and serum brain-derived neurotrophic factor. *Schizophrenia Research: Cognition*, 3, 1–7. <http://doi.org/10.1016/j.scog.2015.10.006>
- Fiszdon, J. M., Cardenas, A. S., Bryson, G. J., & Bell, M. D. (2005). Predictors of Remediation Success on a Trained Memory Task. *The Journal of Nervous and Mental Disease*, 193(9), 602–608.
<http://doi.org/10.1097/01.nmd.0000177790.23311.ba>
- Fiszdon, J. M., Choi, J., Bryson, G. J., & Bell, M. D. (2006). Impact of intellectual status on response to cognitive task training in patients with schizophrenia. *Schizophrenia Research*, 87(1–3), 261–269.
<http://doi.org/10.1016/j.schres.2006.04.011>
- Fiszdon, J. M., Choi, K. H., Bell, M. D., Choi, J., & Silverstein, S. M. (2016). Cognitive remediation for individuals with psychosis: efficacy and mechanisms of treatment effects. *Psychological Medicine*, (2016), 1–15.
<http://doi.org/10.1017/S0033291716001951>
- Fiszdon, J. M., & Johannesen, J. K. (2010). Comparison of computational methods for the evaluation of learning potential in schizophrenia. *Journal of the International Neuropsychological Society : JINS*, 16(2010), 613–620.
<http://doi.org/10.1017/S1355617710000317>
- Fiszdon, J. M., McClough, J. F., Silverstein, S. M., Bell, M. D., Jaramillo, J. R., & Smith, T. E. (2006). Learning potential as a predictor of readiness for psychosocial rehabilitation in schizophrenia. *Psychiatry Research*, 143(2–3), 159–166. <http://doi.org/10.1016/j.psychres.2005.09.012>
- Franck, N., Duboc, C., Sundby, C., Amado, I., Wykes, T., Demily, C., ... Vianin, P. (2013). Specific vs general cognitive remediation for executive functioning in schizophrenia: A multicenter randomized trial. *Schizophrenia Research*, 147(1), 68–74. <http://doi.org/10.1016/j.schres.2013.03.009>
- Franzen, M. D., Burgess, E. J., & Smith-Seemiller, L. (1997). Methods of estimating premorbid functioning. *Archives of Clinical Neuropsychology*, 12(8), 711–38.
Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/14590649>
- Friedman, J. I., Harvey, P. D., McGurk, S. R., White, L., Parrella, M., Raykov, T., ... Davis, K. L. (2002). Correlates of Change in Functional Status of Institutionalized Geriatric Schizophrenic Patients: Focus on Medical

- Comorbidity. *American Journal of Psychiatry*, 159(August), 1388–1394.
<http://doi.org/http://dx.doi.org/10.1176/appi.ajp.159.8.1388>
- Funke, B., Finn, C. T., Plocik, A. M., Lake, S., Derosse, P., Kane, J. M., ...
 Malhotra, A. K. (2004). Association of the DTNBP1 Locus with Schizophrenia
 in a U.S. Population. *American Journal of Human Genetics*, 75(5), 891–898.
<http://doi.org/http://dx.doi.org/10.1086/425279>
- Furberg, C. D., & Friedman, L. M. (2012). Approaches to data analyses of clinical
 trials. *Progress in Cardiovascular Diseases*, 54(4), 330–334.
<http://doi.org/10.1016/j.pcad.2011.07.002>
- Fusar-Poli, P., Deste, G., Smieskova, R., Barlati, S., Yung, A. R., Howes, O., ...
 Borgwardt, S. (2012). Cognitive Functioning in Prodromal Psychosis. *Archives
 of General Psychiatry*, 69(6), 562–571.
<http://doi.org/http://dx.doi.org/10.1001/archgenpsychiatry.2011.1592>
- Galderisi, S., Rossi, A., Rocca, P., Bertolino, A., Mucci, A., Bucci, P., ... Psychoses,
 I. N. for R. on. (2014). The influence of illness-related variables, personal
 resources and context-related factors on real-life functioning of people with
 schizophrenia. *World Psychiatry*, 13, 275–287.
<http://doi.org/http://dx.doi.org/10.1002/wps.20167>
- Galletly, C., Castle, D., Dark, F., Humberstone, V., Jablensky, A., Killackey, E., ...
 Tran, N. (2015). *Royal Australian and New Zealand College of Psychiatrists
 clinical practice guidelines for the management of schizophrenia and related
 disorders. Australian and New Zealand Journal of Psychiatry* (Vol. 50).
<http://doi.org/10.1177/0004867416641195>
- Garrido, G., Penadés, R., Barrios, M., Aragay, N., Ramos, I., Vallès, V., ... Vendrell,
 J. M. (2017). Computer-assisted cognitive remediation therapy in
 schizophrenia: Durability of the effects and cost-utility analysis. *Psychiatry
 Research*, 254(February), 198–204.
<http://doi.org/10.1016/j.psychres.2017.04.065>
- Gehlenborg, N., & Wong, B. (2012). Heat maps. *Nature Methods*, 9(3), 213.
<http://doi.org/http://dx.doi.org/10.1038/nmeth.1902>
- Georgiades, A., Davis, V. G., Atkins, A. S., Khan, A., Walker, T. W., Loebel, A., ...
 Keefe, R. S. E. (2017). Psychometric characteristics of the MATRICS
 Consensus Cognitive Battery in a large pooled cohort of stable schizophrenia
 patients. *Schizophrenia Research*, 190, 172–179.

<http://doi.org/10.1016/j.schres.2017.03.040>

- Gilbert, E., Mérette, C., Jomphe, V., Emond, C., Rouleau, N., Bouchard, R.-H. H., ... Maziade, M. (2014). Cluster analysis of cognitive deficits may mark heterogeneity in schizophrenia in terms of outcome and response to treatment. *European Archives of Psychiatry and Clinical Neuroscience*, 264(4), 333–343. <http://doi.org/10.1007/s00406-013-0463-7>
- Goff, D. C., Falkai, P., Fleischhacker, W. W., Girgis, R. R., Kahn, R. M., Uchida, H., ... Lieberman, J. A. (2017). The Long-Term Effects of Antipsychotic Medication on Clinical Course in Schizophrenia. *American Journal of Psychiatry*, 174, 840–849. <http://doi.org/10.1176/appi.ajp.2017.16091016>
- Goff, D. C., Hill, M., & Barch, D. M. (2011). The treatment of cognitive impairment in schizophrenia. *Pharmacology, Biochemistry, and Behavior*, 99(2), 245–53. <http://doi.org/10.1016/j.pbb.2010.11.009>
- Goldberg, T. E., Goldman, R. S., Burdick, K. E., Malhotra, A. K., Lencz, T., Patel, R. C., ... Robinson, D. G. (2007). Cognitive improvement after treatment with second-generation antipsychotic medications in first-episode schizophrenia: is it a practice effect? *Archives of General Psychiatry*, 64(10), 1115–1122. <http://doi.org/10.1001/archpsyc.64.10.1115>
- Goldberg, T. E., & Weinberger, D. R. (2004). Genes and the parsing of cognitive processes. *Trends in Cognitive Sciences*, 8(7), 325–335. <http://doi.org/10.1016/j.tics.2004.05.011>
- Goldstein, G. (1990). Neuropsychological heterogeneity in schizophrenia: a consideration of abstraction and problem-solving abilities. *Archives of Clinical Neuropsychology*, 5(3), 251–64. <http://doi.org/http://dx.doi.org/10.1093/arclin/5.3.251>
- Goldstein, G., Allen, D. N., & Seaton, B. E. (1998). A comparison of clustering solutions for cognitive heterogeneity in schizophrenia. *Journal of the International Neuropsychological Society*, 4(4), 353–62. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/9656609>
- Goldstein, G., & Shemansky, W. J. (1995). Influences on cognitive heterogeneity in schizophrenia. *Schizophrenia Research*, 18(1), 59–69. [http://doi.org/http://dx.doi.org/10.1016/0920-9964\(95\)00040-2](http://doi.org/http://dx.doi.org/10.1016/0920-9964(95)00040-2)
- Gomar, J. J., Valls, E., Radua, J., Mareca, C., Tristany, J., del Olmo, F., ... McKenna, P. J. (2015). A Multisite, Randomized Controlled Clinical Trial of

- Computerized Cognitive Remediation Therapy for Schizophrenia. *Schizophrenia Bulletin*, 41(6), 1–10. <http://doi.org/10.1093/schbul/sbv059>
- Gray, B. E., McMahon, R. P., Green, M. F., Seidman, L. J., Mesholam-Gately, R. I., Kern, R. S., ... Gold, J. M. (2014). Detecting reliable cognitive change in individual patients with the MATRICS Consensus Cognitive Battery. *Schizophrenia Research*, 159(1), 182–187. <http://doi.org/10.1016/j.schres.2014.07.032>
- Green, B. F., & Hall, J. A. (1984). Quantitative Methods for Literature Reviews. *Annual Review of Psychology*, 35(1), 37–54. <http://doi.org/10.1146/annurev.ps.35.020184.000345>
- Green, M. F. (1996). What are the functional consequences of neurocognitive deficits in schizophrenia? *The American Journal of Psychiatry*, 153(3), 321–30. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/8610818>
- Green, M. F., Kern, R. S., Braff, D. L., & Mintz, J. (2000). Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the “right stuff”? *Schizophrenia Bulletin*, 26(1), 119–36. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/10755673>
- Green, M. F., Kern, R. S., & Heaton, R. K. (2004). Longitudinal studies of cognition and functional outcome in schizophrenia: implications for MATRICS. *Schizophrenia Research*, 72(1), 41–51. <http://doi.org/10.1016/j.schres.2004.09.009>
- Green, M. F., & Nuechterlein, K. H. (1999). Should schizophrenia be treated as a neurocognitive disorder? *Schizophrenia Bulletin*, 25(2), 309–19. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/10416733>
- Green, M. F., Nuechterlein, K. H., Gold, J. M., Barch, D. M., Cohen, J., Essock, S., ... Marder, S. R. (2004). Approaching a consensus cognitive battery for clinical trials in schizophrenia: the NIMH-MATRICES conference to select cognitive domains and test criteria. *Biological Psychiatry*, 56(5), 301–307. <http://doi.org/10.1016/j.biopsych.2004.06.023>
- Green, R. E. A., Melo, B., Christensen, B., Ngo, L.-A., Monette, G., & Bradbury, C. (2008). Measuring premorbid IQ in traumatic brain injury: an examination of the validity of the Wechsler Test of Adult Reading (WTAR). *Journal of Clinical and Experimental Neuropsychology*, 30(2), 163–172. <http://doi.org/10.1080/13803390701300524>

- Greenwood, K., Hung, C.-F. F., Tropeano, M., McGuffin, P., & Wykes, T. (2011). No association between the Catechol-O-Methyltransferase (COMT) val158met polymorphism and cognitive improvement following cognitive remediation therapy (CRT) in schizophrenia. *Neuroscience Letters*, 496(2), 65–69. <http://doi.org/10.1016/j.neulet.2011.03.075>
- Greenwood, T. A., Lazzeroni, L. C., Murray, S. S., Cadenhead, K. S., Calkins, M. E., Dobie, D. J., ... Braff, D. L. (2011). Analysis of 94 candidate genes and 12 endophenotypes for schizophrenia from the Consortium on the Genetics of Schizophrenia. *American Journal of Psychiatry*, 168, 930–946.
- Greenwood, T. A., Light, G. A., Swerdlow, N. R., Radant, A. D., & Braff, D. L. (2012). Association analysis of 94 candidate genes and schizophrenia-related endophenotypes. *PloS One*, 7(1), e29630. <http://doi.org/10.1371/journal.pone.0029630>
- Grynszpan, O., Perbal, S., Pelissolo, A., Fossati, P., Jouvent, R., Dubal, S., & Perez-Diaz, F. (2011). Efficacy and specificity of computer-assisted cognitive remediation in schizophrenia: a meta-analytical study. *Psychological Medicine*, 41(1), 163–173. <http://doi.org/10.1017/S0033291710000607>
- Harada, C. N., Love, M. C. N., & Triebel, K. (2013). Normal Cognitive Aging. *Clinical Geriatric Medicine*, 29(4), 737–752. <http://doi.org/10.1016/j.cger.2013.07.002>.Normal
- Harrison, P. J., & Weinberger, D. R. (2005). Schizophrenia genes, gene expression, and neuropathology: on the matter of their convergence. *Molecular Psychiatry*, 10, 40–68; image 5. <http://doi.org/10.1038/sj.mp.4001686>
- Harrow, M., Grossman, L. S., Herbener, E. S., & Davies, E. W. (2000). Ten-year outcome: patients with schizoaffective disorders, schizophrenia, affective disorders and mood-incongruent psychotic symptoms. *The British Journal of Psychiatry*, 177(5), 421–426. <http://doi.org/10.1192/bjp.177.5.421>
- Harvey, P. D., Bertisch, H., Friedman, J. I., Marcus, S., Parrella, M., White, L., & Davis, K. (2003). The course of functional decline in geriatric patients with schizophrenia. *The American Journal of Geriatric Psychiatry*, 11(6), 610–619. <http://doi.org/http://dx.doi.org/10.1097/00019442-200311000-00005>
- Harvey, P. D., Parrella, M., White, L., Mohs, R. C., Davidson, M., & Davis, K. L. (1999). Convergence of cognitive and adaptive decline in late-life schizophrenia. *Schizophrenia Research*, 35, 77–84.

- [http://doi.org/http://dx.doi.org/10.1016/S0920-9964\(98\)00109-1](http://doi.org/http://dx.doi.org/10.1016/S0920-9964(98)00109-1)
- Hashimoto, R., Noguchi, H., Hori, H., Nakabayashi, T., Suzuki, T., Iwata, N., ... Kunugi, H. (2010). A genetic variation in the dysbindin gene (DTNBP1) is associated with memory performance in healthy controls. *World Journal of Biological Psychiatry*, 11(2_2), 431–438.
<http://doi.org/10.3109/15622970902736503>
- Hashimoto, R., Noguchi, H., Hori, H., Ohi, K., Yasuda, Y., Takeda, M., & Kunugi, H. (2009). Association between the dysbindin gene (DTNBP1) and cognitive functions in Japanese subjects. *Psychiatry and Clinical Neurosciences*, 63(4), 550–556. <http://doi.org/10.1111/j.1440-1819.2009.01985.x>
- Haut, K. M., Lim, K. O., & MacDonald, A. (2010). Prefrontal cortical changes following cognitive training in patients with chronic schizophrenia: effects of practice, generalization, and specificity. *Neuropsychopharmacology*, 35(9), 1850–9. <http://doi.org/10.1038/npp.2010.52>
- Heaton, R. K., Temkin, N., Dikmen, S., Avitable, N., Taylor, M. J., Marcotte, T. D., & Grant, I. (2001). Detecting change: A comparison of three neuropsychological methods, using normal and clinical samples. *Archives of Clinical Neuropsychology*, 16(1), 75–91. [http://doi.org/10.1016/S0887-6177\(99\)00062-1](http://doi.org/10.1016/S0887-6177(99)00062-1)
- Heinrichs, R. W. (2005). The primacy of cognition in schizophrenia. *The American Psychologist*, 60(3), 229–42. <http://doi.org/10.1037/0003-066X.60.3.229>
- Heinrichs, R. W., & Awad, A. G. (1993). Neurocognitive subtypes of chronic schizophrenia. *Schizophrenia Research*, 9(1), 49–58.
[http://doi.org/http://dx.doi.org/10.1016/0920-9964\(93\)90009-8](http://doi.org/http://dx.doi.org/10.1016/0920-9964(93)90009-8)
- Heinrichs, R. W., Miles, A. A., Ammari, N., & Muharib, E. (2013). Cognition as a central illness feature in schizophrenia. In P. Harvey (Ed.), *Cognitive Impairment in Schizophrenia: Characteristics, Assessment, and Treatment* (pp. 1–23). Cambridge, UK: Cambridge University Press.
<http://doi.org/http://dx.doi.org/10.1017/CBO9781139003872.002>
- Heinrichs, R. W., & Zakzanis, K. K. (1998). Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. *Neuropsychology*, 12(3), 426–45.
Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/9673998>
- Hettige, N. C., Nguyen, T. B., Yuan, C., Rajakulendran, T., Baddour, J., Bhagwat, N., ... De Luca, V. (2017). Classification of suicide attempters in schizophrenia

- using sociocultural and clinical features: A machine learning approach. *General Hospital Psychiatry*, 47, 20–28.
<http://doi.org/10.1016/j.genhosppsych.2017.03.001>
- Hill, N. T. M., Mowszowski, L., Naismith, S. L., Chadwick, V. L., Valenzuela, M., & Lampit, A. (2017). Computerized cognitive training in older adults with mild cognitive impairment or dementia: A systematic review and meta-analysis. *American Journal of Psychiatry*, 174(4), 329–340.
<http://doi.org/10.1176/appi.ajp.2016.16030360>
- Hill, S. K., Bishop, J. R., Palumbo, D., & Sweeney, J. a. (2010). Effect of second-generation antipsychotics on cognition: current issues and future challenges. *Expert Review of Neurotherapeutics*, 10(1), 43–57.
<http://doi.org/10.1586/ern.09.143.Effect>
- Hill, S. K., Ragland, J. D., Gur, R. C., & Raquel, E. (2002). Neuropsychological Profiles Delineate Distinct Profiles of Schizophrenia, an Interaction Between Memory and Executive Function, and Uneven Distribution of Clinical Subtypes. *Journal of Clinical and Experimental Neuropsychology*, 24(6), 765–780. <http://doi.org/http://dx.doi.org/10.1076/jcen.24.6.765.8402>
- Hodge, M. A. R., Siciliano, D., Withey, P., Moss, B., Moore, G., Judd, G., ... Harris, A. (2010). A randomized controlled trial of cognitive remediation in schizophrenia. *Schizophrenia Bulletin*, 36(2), 419–27.
<http://doi.org/10.1093/schbul/sbn102>
- Hogarty, G. E., & Flesher, S. (1999). Practice Principles of Cognitive Enhancement Therapy for Schizophrenia. *Schizophrenia Bulletin*, 25(4), 693–708.
<http://doi.org/10.1093/oxfordjournals.schbul.a033411>
- Holthausen, E. A. E., Wiersma, D., Sitskoorn, M. M., Hijman, R., Dingemans, P. M., Schene, A. H., & van den Bosch, R. J. (2002). Schizophrenic patients without neuropsychological deficits: subgroup, disease severity or cognitive compensation? *Psychiatry Research*, 112(1), 1–11. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/12379446>
- Homack, S. R., & Reynolds, C. R. (2007). Wechsler Abbreviated Scale of Intelligence (WASI). In S. R. Homack & C. R. Reynolds (Eds.), *Essentials of Assessment with Brief Intelligence Tests* (pp. 77–115). Hoboken, NJ: Wiley & Sons.
- Horswill, M. (n.d.). Reliable Change Index (RC or RCI). Brisbane, QLD, Australia.

Retrieved from

<https://teaching.psy.uq.edu.au/tools/statsrepo/?download=927%0A%0A>

- Hoti, F., Tuulio-Henriksson, A., Haukka, J., Partonen, T., Holmström, L., & Lönnqvist, J. (2004). Family-based clusters of cognitive test performance in familial schizophrenia. *BMC Psychiatry*, 4, 20. <http://doi.org/10.1186/1471-244X-4-20>
- Husted, J. A., Lim, S., Chow, E. W. C., Greenwood, C., & Bassett, A. S. (2009). Heritability of Neurocognitive Traits in Familial Schizophrenia. *American Journal of Medical Genetics*, 150B(6), 845–853. <http://doi.org/10.1002/ajmg.b.30907>
- Isaac, C., & Januel, D. (2016). Neural correlates of cognitive improvements following cognitive remediation in schizophrenia: a systematic review of randomized trials. *Socioaffective Neuroscience & Psychology*, 6(1), 30054. <http://doi.org/10.3402/snp.v6.30054>
- Jääskeläinen, E., Juola, P., Hirvonen, N., Mcgrath, J. J., Saha, S., Isohanni, M., ... Miettunen, J. (2013). A Systematic Review and Meta-Analysis of Recovery in Schizophrenia. *Schizophrenia Bulletin*, 39(6), 1296–1306. <http://doi.org/10.1093/schbul/sbs130>
- Jablensky, A. (2006). Subtyping schizophrenia: implications for genetic research. *Molecular Psychiatry*, 11(9), 815–836. <http://doi.org/10.1038/sj.mp.4001857>
- Jacobson, N. S., Follette, W. C., & Revenstorf, D. (1984). Psychotherapy outcome research: methods for reporting variability and evaluating clinical significance. *Psychotherapy Research*, 15, 336–352.
- Jacobson, N. S., & Truax, P. (1991). Clinical significance: A statistical approach to defining meaningful change in psychotherapy research. *Journal of Consulting and Clinical Psychology*, 59(1), 12–19. <http://doi.org/10.1037/0022-006X.59.1.12>
- Javitt, D. C. (2009a). Sensory processing in schizophrenia: neither simple nor intact. *Schizophrenia Bulletin*, 35(6), 1059–1064. <http://doi.org/10.1093/schbul/sbp110>
- Javitt, D. C. (2009b). When doors of perception close: bottom-up models of disrupted cognition in schizophrenia. *Annual Review of Clinical Psychology*, 5, 249–275. <http://doi.org/10.1146/annurev.clinpsy.032408.153502>
- Jentsch, J. D., Trantham-Davidson, H., Jairl, C., Tinsley, M., Cannon, T. D., & Lavin, A. (2009). Dysbindin modulates prefrontal cortical glutamatergic circuits

- and working memory function in mice. *Neuropsychopharmacology*, 34(12), 2601–2608. <http://doi.org/10.1038/npp.2009.90>
- Jin, H., & Mosweu, I. (2017). The Societal Cost of Schizophrenia: A Systematic Review. *PharmacoEconomics*, 35(1), 25–42. <http://doi.org/10.1007/s40273-016-0444-6>
- Kaneko, Y., & Keshavan, M. S. (2012). Cognitive remediation in schizophrenia. *Clinical Psychopharmacology and Neuroscience*, 10(3), 125–135. <http://doi.org/http://dx.doi.org/10.9758/cpn.2012.10.3.125>
- Kantrowitz, J. T., & Javitt, D. C. (2010). Thinking glutamatergically: changing concepts of schizophrenia based upon changing neurochemical models. *Clinical Schizophrenia & Related Psychoses*, 4(3), 189–200. <http://doi.org/10.3371/CSRP.4.3.6>
- Karlsgodt, K. H., Robleto, K., Trantham-Davidson, H., Jairl, C., Cannon, T. D., Lavin, A., & Jentsch, J. D. (2011). Reduced dysbindin expression mediates N-methyl-D-aspartate receptor hypofunction and impaired working memory performance. *Biological Psychiatry*, 69(1), 28–34. <http://doi.org/10.1016/j.biopsych.2010.09.012>
- Kay, S. R., Fiszbein, A., & Opler, L. A. (1987). The Positive and Negative Syndrome Scale (PANSS) for Schizophrenia. *Schizophrenia Bulletin*, 13(2), 261–276. <http://doi.org/http://dx.doi.org/10.1093/schbul/13.2.261>
- Kay, S. R., Opler, L. A., & Lindenmayer, J. P. (1988). Reliability and validity of the positive and negative syndrome scale for schizophrenics. *Psychiatry Research*, 23(1), 99–110. [http://doi.org/http://dx.doi.org/10.1016/0165-1781\(88\)90038-8](http://doi.org/http://dx.doi.org/10.1016/0165-1781(88)90038-8)
- Keefe, R. S. E., Bilder, R. M., Davis, S. M., Harvey, P. D., Palmer, B. W., Gold, J. M., ... Lieberman, J. A. (2007). Neurocognitive effects of antipsychotic medications in patients with chronic schizophrenia in the CATIE trial. *Archives of General Psychiatry*, 64(6), 633–647. <http://doi.org/10.1001/archpsyc.64.6.633>
- Keefe, R. S. E., Eesley, C. E., & Poe, M. P. (2005). Defining a cognitive function decrement in schizophrenia. *Biological Psychiatry*, 57(6), 688–91. <http://doi.org/10.1016/j.biopsych.2005.01.003>
- Keefe, R. S. E., & Fenton, W. S. (2007). How should DSM-V criteria for schizophrenia include cognitive impairment? *Schizophrenia Bulletin*, 33(4), 912–20. <http://doi.org/10.1093/schbul/sbm046>

- Kelly, A. M. C., & Garavan, H. (2005). Human functional neuroimaging of brain changes associated with practice. *Cerebral Cortex*, 15(8), 1089–1102. <http://doi.org/10.1093/cercor/bhi005>
- Kendler, K. S., Ohlsson, H., Sundquist, J., & Sundquist, K. (2015). IQ and schizophrenia in a Swedish national sample: Their causal relationship and the interaction of IQ with genetic risk. *American Journal of Psychiatry*, 172(3), 259–265. <http://doi.org/10.1176/appi.ajp.2014.14040516>
- Kern, R. S., Gold, J. M., Dickinson, D., Green, M. F., Nuechterlein, K. H., Baade, L. E., ... Marder, S. R. (2011). The MCCB impairment profile for schizophrenia outpatients: Results from the MATRICS psychometric and standardization study. *Schizophrenia Research*, 126(1–3), 124–131. <http://doi.org/10.1016/j.schres.2010.11.008>
- Kern, R. S., Nuechterlein, K. H., Green, M. F., Baade, L. E., Fenton, W. S., Gold, J. M., ... Marder, S. R. (2008). The MATRICS Consensus Cognitive Battery, part 2: co-norming and standardization. *The American Journal of Psychiatry*, 165(2), 214–220. <http://doi.org/10.1176/appi.ajp.2007.07010043>
- Keshavan, M. S., Vinogradov, S., Rumsey, J., Sherrill, J., & Wagner, A. (2014). Cognitive training in mental disorders: update and future directions. *The American Journal of Psychiatry*, 171(5), 510–22. <http://doi.org/10.1176/appi.ajp.2013.13081075>
- Khandaker, G. M., Barnett, J. H., White, I. R., & Jones, P. B. (2011). A quantitative meta-analysis of population-based studies of premorbid intelligence and schizophrenia. *Schizophrenia Research*, 132(2–3), 220–7. <http://doi.org/10.1016/j.schres.2011.06.017>
- Kircher, T., Markov, V., Krug, A., Eggermann, T., Zerres, K., Nöthen, M. M., ... Rietschel, M. (2009). Association of the DTNBP1 genotype with cognition and personality traits in healthy subjects. *Psychological Medicine*, 39(10), 1657–1665. <http://doi.org/10.1017/S0033291709005388>
- Kontaxakis, V. P., Havaki-Kontaxaki, B. J., Stamouli, S. S., Margariti, M. M., Collias, C. T., & Christodoulou, G. N. (2000). Comparison of four scales measuring depression in schizophrenic inpatients. *European Psychiatry*, 15(4), 274–277. [http://doi.org/10.1016/S0924-9338\(00\)00232-7](http://doi.org/10.1016/S0924-9338(00)00232-7)
- Kontis, D., Huddy, V., Reeder, C., Landau, S., & Wykes, T. (2013). Effects of age and cognitive reserve on cognitive remediation therapy outcome in patients with

- schizophrenia. *The American Journal of Geriatric Psychiatry*, 21(3), 218–230.
<http://doi.org/http://dx.doi.org/10.1016/j.jagp.2012.12.013>
- Krabbendam, L., & Aleman, A. (2003). Cognitive rehabilitation in schizophrenia: a quantitative analysis of controlled studies. *Psychopharmacology (Berl)*, 169(3–4), 376–382. <http://doi.org/10.1007/s00213-002-1326-5>
- Kraemer, H. C. (2016). Messages for clinicians: Moderators and mediators of treatment outcome in randomized clinical trials. *American Journal of Psychiatry*, 173(7), 672–679. <http://doi.org/10.1176/appi.ajp.2016.15101333>
- Kraemer, H. C., Frank, E., & Kupfer, D. J. (2006). Moderators of Treatment Outcomes. *Jama*, 296(10), 1286. <http://doi.org/10.1001/jama.296.10.1286>
- Kraemer, H. C., Wilson, G. T., Fairburn, C. G., & Agras, W. S. (2002). Mediators and moderators of treatment effects in randomized clinical trials. *Archives of General Psychiatry*, 59(10), 877–883.
<http://doi.org/http://dx.doi.org/10.1001/archpsyc.59.10.877>
- Kravitz, R. L., Duan, N., & Braslow, J. (2004). Evidence-based medicine, heterogeneity of treatment effects, and the trouble with averages. *Milbank Quarterly*, 82(4), 661–687. <http://doi.org/10.1111/j.0887-378X.2004.00327.x>
- Kremen, W. S., Seidman, L. J., Faraone, S. V., Toomey, R., & Tsuang, M. T. (2000). The Paradox of Normal Neuropsychological Function in Schizophrenia. *Journal of Abnormal Psychology*, 109, 743–752. <http://doi.org/10.1037//0021-843X.109.4.743>
- Kremen, W. S., Seidman, L. J., Faraone, S. V., & Tsuang, M. T. (2008). IQ decline in cross-sectional studies of schizophrenia: methodology and interpretation. *Psychiatry Research*, 158(2), 181–94.
<http://doi.org/10.1016/j.psychres.2006.01.022>
- Kueider, A. M., Parisi, J. M., Gross, A. L., & Rebok, G. W. (2012). Computerized cognitive training with older adults: A systematic review. *PLoS ONE*, 7(7).
<http://doi.org/10.1371/journal.pone.0040588>
- Kurtz, M. M. (2012). Cognitive remediation for schizophrenia: current status, biological correlates and predictors of response. *Expert Review of Neurotherapeutics*, 12.7, 813–821.
<http://doi.org/http://dx.doi.org/10.1586/ern.12.71>
- Kurtz, M. M., Jeffrey, S. B., & Rose, J. (2010). Elementary neurocognitive function, learning potential and everyday life skills in schizophrenia: what is their

- relationship? *Schizophrenia Research*, 116(2–3), 280–8.
<http://doi.org/10.1016/j.schres.2009.08.011>
- Kurtz, M. M., Moberg, P. J., Gur, R. C., & Gur, R. E. (2001). Approaches to cognitive remediation of neuropsychological deficits in schizophrenia: a review and meta-analysis. *Neuropsychol Rev*, 11(4), 197–210.
<http://doi.org/10.1023/a:1012953108158>
- Kurtz, M. M., Seltzer, J. C., Fujimoto, M., Shagan, D. S., & Wexler, B. E. (2009). Predictors of change in life skills in schizophrenia after cognitive remediation. *Schizophrenia Research*, 107(2–3), 267–274.
<http://doi.org/10.1016/j.schres.2008.10.014>
- Kurtz, M. M., Seltzer, J. C., Shagan, D. S., Thime, W. R., & Wexler, B. E. (2007). Computer-assisted cognitive remediation in schizophrenia: what is the active ingredient? *Schizophrenia Research*, 89(1–3), 251–260.
<http://doi.org/10.1016/j.schres.2006.09.001>
- Kurtz, M. M., & Wexler, B. E. (2006). Differences in performance and learning proficiency on the Wisconsin Card Sorting Test in schizophrenia: Do they reflect distinct neurocognitive subtypes with distinct functional profiles? *Schizophrenia Research*, 81(2–3), 167–171.
<http://doi.org/10.1016/j.schres.2005.09.003>
- Lagakos, S. W. (2006). The Challenge of Subgroup Analyses — Reporting without Distorting. *New England Journal of Medicine*, 354(16), 1667–1669.
<http://doi.org/10.1056/NEJMp068070>
- Lance, R. F., Kennedy, M. L., & Leberg, P. L. (2000). Classification bias in discriminant function analyses used to evaluate putatively different taxa. *Journal of Mammalogy*, 81(1), 245–249. [http://doi.org/10.1644/1545-1542\(2000\)081<0245:CBIDFA>2.0.CO;2](http://doi.org/10.1644/1545-1542(2000)081<0245:CBIDFA>2.0.CO;2)
- Langley-Hawthorne, C. (1997). Modeling the lifetime costs of treating schizophrenia in Australia. *Clinical Therapeutics*, 19(6), 1470–1495.
[http://doi.org/10.1016/S0149-2918\(97\)80020-3](http://doi.org/10.1016/S0149-2918(97)80020-3)
- Lecrubier, Y., Sheehan, D. V., Weiller, E., Amorim, P., Bonora, I., Harnett Sheehan, K., ... Dunbar, G. C. (1997). The Mini International Neuropsychiatric Interview (MINI). A short diagnostic structured interview: reliability and validity according to the CIDI. *European Psychiatry*, 12(5), 224–231.
[http://doi.org/10.1016/S0924-9338\(97\)83296-8](http://doi.org/10.1016/S0924-9338(97)83296-8)

- Leeson, V. C., Barnes, T. R. E., Harrison, M., Matheson, E., Harrison, I., Mutsatsa, S. H., ... Joyce, E. M. (2010). The relationship between IQ, memory, executive function, and processing speed in recent-onset psychosis: 1-year stability and clinical outcome. *Schizophrenia Bulletin*, 36(2), 400–9.
<http://doi.org/10.1093/schbul/sbn100>
- Leeson, V. C., Sharma, P., Harrison, M., Ron, M. A., Barnes, T. R. E., & Joyce, E. M. (2011). IQ trajectory, cognitive reserve, and clinical outcome following a first episode of psychosis: a 3-year longitudinal study. *Schizophrenia Bulletin*, 37(4), 768–77. <http://doi.org/10.1093/schbul/sbp143>
- Lenhard, W., & Lenhard, A. (2016). Calculation of Effect Sizes.
<http://doi.org/10.13140/RG.2.1.3478.4245>
- Leong, Y. C., Radulescu, A., Daniel, R., DeWoskin, V., & Niv, Y. (2017). Dynamic Interaction between Reinforcement Learning and Attention in Multidimensional Environments. *Neuron*, 93(2), 451–463.
<http://doi.org/10.1016/j.neuron.2016.12.040>
- Levine, S. Z., Lurie, I., Kohn, R., & Levav, I. (2011). Trajectories of the course of schizophrenia: From progressive deterioration to amelioration over three decades. *Schizophrenia Research*, 126(1–3), 184–191.
<http://doi.org/10.1016/j.schres.2010.10.026>
- Lewandowski, K. E., Sperry, S. H., Cohen, B. M., & Ongür, D. (2014). Cognitive variability in psychotic disorders: a cross-diagnostic cluster analysis. *Psychological Medicine*, 44(15), 3239–3248.
<http://doi.org/10.1017/S0033291714000774>
- Liberati, A., Altman, D. G., Tetzlaff, J., Mulrow, C., Gøtzsche, P. C., Ioannidis, J. P. a, ... Moher, D. (2009). The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Medicine*, 6(7), e1000100.
<http://doi.org/10.1371/journal.pmed.1000100>
- Lindenmayer, J.-P., Ozog, V. A., Khan, A., Ljuri, I., Fregenti, S., & McGurk, S. R. (2017). Predictors of response to cognitive remediation in service recipients with severe mental illness. *Psychiatric Rehabilitation Journal*, 40(1), 61–69.
<http://doi.org/10.1037/prj0000252>
- Lindhiem, O., Kolko, D. J., & Cheng, Y. (2012). Predicting Psychotherapy Benefit: A Probabilistic and Individualized Approach. *Behavior Therapy*, 43(2), 381–

392. <http://doi.org/10.1016/j.beth.2011.08.004>
- López-Luengo, B., & Vázquez, C. (2003). Effects of Attention Process Training on cognitive functioning of schizophrenic patients. *Psychiatry Research*, 119(1–2), 41–53. [http://doi.org/10.1016/S0165-1781\(03\)00102-1](http://doi.org/10.1016/S0165-1781(03)00102-1)
- Luciano, M., Miyajima, F., Lind, P. A., Bates, T. C., Horan, M., Harris, S. E., ... Payton, A. (2009). Variation in the dysbindin gene and normal cognitive function in three independent population samples. *Genes, Brain, and Behavior*, 8(2), 218–227. <http://doi.org/10.1111/j.1601-183X.2008.00462.x>
- MacKinnon, D. P. (2011). Integrating Mediators and Moderators in Research Design. *Research on Social Work Practice*, 21(6), 675–681. <http://doi.org/10.1177/1049731511414148>
- Mak, M., Samochowiec, J., Tybura, P., Bieńkowski, P., Karakiewicz, B., Zaremba Pechmann, L., & Mroczek, B. (2013). The efficacy of cognitive rehabilitation with RehaCom programme in schizophrenia patients. The role of selected genetic polymorphisms in successful cognitive rehabilitation. *Annals of Agricultural and Environmental Medicine*, 20(1), 77–81. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/23540216>
- Markov, V., Krug, A., Krach, S., Jansen, A., Eggermann, T., Zerres, K., ... Kircher, T. (2010). Impact of schizophrenia-risk gene dysbindin 1 on brain activation in bilateral middle frontal gyrus during a working memory task in healthy individuals. *Human Brain Mapping*, 31(2), 266–275. <http://doi.org/10.1002/hbm.20862>
- Markov, V., Krug, A., Krach, S., Whitney, C., Eggermann, T., Zerres, K., ... Kircher, T. (2009). Genetic variation in schizophrenia-risk-gene dysbindin 1 modulates brain activation in anterior cingulate cortex and right temporal gyrus during language production in healthy individuals. *NeuroImage*, 47(4), 2016–22. <http://doi.org/10.1016/j.neuroimage.2009.05.067>
- Marsden, E., & Torgerson, C. J. (2012). Single group, pre- and post-test research designs: Some methodological concerns. *Oxford Review of Education*, 38(5), 583–616. <http://doi.org/10.1080/03054985.2012.731208>
- McCloskey, M. (1993). Theory and Evidence in Cognitive Neuropsychology: A “Radical” Response to Robertson, Knight, Rafal, and Shimamura (1993). *Journal of Experimental Psychology: Learning, Memory, and Ognition*, 19(3), 718–734. <http://doi.org/http://dx.doi.org/10.1037/0278-7393.19.3.718>

- McGrath, J., Saha, S., Chant, D., & Welham, J. (2008). Schizophrenia: A concise overview of incidence, prevalence, and mortality. *Epidemiologic Reviews*, 30, 67–76. <http://doi.org/10.1093/epirev/mxn001>
- McGurk, S. R., & Mueser, K. T. (2008). Response to Cognitive Rehabilitation in Older Versus Younger Persons with Severe Mental Illness. *American Journal of Psychiatric Rehabilitation*, 11, 90–105. <http://doi.org/10.1080/15487760701853136>
- McGurk, S. R., Mueser, K. T., Covell, N. H., Cicerone, K. D., Drake, R. E., Silverstein, S. M., ... Essock, S. M. (2013). Mental health system funding of cognitive enhancement interventions for schizophrenia: Summary and update of the New York Office of Mental Health expert panel and stakeholder meeting. *Psychiatric Rehabilitation Journal*, 36(3), 133–45. <http://doi.org/10.1037/prj0000020>
- McGurk, S. R., Mueser, K. T., Feldman, K., Wolfe, R., & Pascaris, A. (2007). Cognitive training for supported employment: 2-3 year outcomes of a randomized controlled trial. *The American Journal of Psychiatry*, 164(3), 437–441. <http://doi.org/10.1176/appi.ajp.164.3.437>
- McGurk, S. R., Mueser, K. T., & Pascaris, A. (2005). Cognitive training and supported employment for persons with severe mental illness: one-year results from a randomized controlled trial. *Schizophrenia Bulletin*, 31(4), 898–909. <http://doi.org/10.1093/schbul/sbi037>
- McGurk, S. R., Twamley, E. W., Sitzler, D. I., McHugo, G. J., & Mueser, K. T. (2007). A meta-analysis of cognitive remediation in schizophrenia. *The American Journal of Psychiatry*, 164(12), 1791–1802. <http://doi.org/10.1176/appi.ajp.2007.07060906.A>
- Medalia, A., & Choi, J. (2009). Cognitive Remediation in Schizophrenia. *Neuropsychology Review*, 19, 353–364. <http://doi.org/http://dx.doi.org/10.1007/s11065-009-9097-y>
- Medalia, A., Revheim, N., & Casey, M. (2000). Remediation of memory disorders in schizophrenia. *Psychological Medicine*, 30(6), 1451–1459. <http://doi.org/http://dx.doi.org/10.1017/S0033291799002913>
- Medalia, A., Revheim, N., & Casey, M. (2001). The remediation of problem-solving skills in schizophrenia. *Schizophrenia Bulletin*, 27(2), 259–67. <http://doi.org/http://dx.doi.org/10.1093/oxfordjournals.schbul.a006872>

- Medalia, A., & Richardson, R. (2005). What predicts a good response to cognitive remediation interventions? *Schizophrenia Bulletin*, 31(4), 942–53.
<http://doi.org/10.1093/schbul/sbi045>
- Medalia, A., & Saperstein, A. M. (2013). Does cognitive remediation for schizophrenia improve functional outcomes? *Current Opinion Psychiatry*, 26, 151–157. <http://doi.org/10.1097/YCO.0b013e32835dcbd4>
- Mehta, U. M., Thirthalli, J., Subbakrishna, D. K., Gangadhar, B. N., Eack, S. M., & Keshavan, M. S. (2013). Social and neuro-cognition as distinct cognitive factors in schizophrenia: A systematic review. *Schizophrenia Research*, 148(1–3), 3–11. <http://doi.org/10.1016/j.schres.2013.05.009>
- Meier, M. H., Ph, D., Keefe, R. S. E., Ph, D., Fisher, H. L., Ph, D., ... Ph, D. (2014). Neuropsychological Decline in Schizophrenia From the Premorbid to the Postonset Period : Evidence From a Population-Representative Longitudinal Study Ne ., *American Journal of Psychiatry*, 171(1)(Table 1), 91–102.
<http://doi.org/10.1176/appi.ajp.2013.12111438>
- Merzenich, M. M., Van Vleet, T. M., & Nahum, M. (2014). Brain plasticity-based therapeutics. *Frontiers in Human Neuroscience*, 8(June), 1–16.
<http://doi.org/10.3389/fnhum.2014.00385>
- Mesholam-Gately, R. I., Giuliano, A. J., Goff, K. P., Faraone, S. V., & Seidman, L. J. (2009). Neurocognition in first-episode schizophrenia: a meta-analytic review. *Neuropsychology*, 23(3), 315–36. <http://doi.org/10.1037/a0014708>
- Miles, A. A., Heinrichs, R. W., Ammari, N., Hartman, L., McDermid Vaz, S., & Muharib, E. (2014). Stability and change in symptoms, cognition, and community outcome in schizophrenia. *Schizophrenia Research*, 152(2–3), 435–439. <http://doi.org/10.1016/j.schres.2013.09.006>
- Milev, P., Ho, B.-C., Arndt, S., & Andreasen, N. C. (2005). Predictive values of neurocognition and negative symptoms on functional outcome in schizophrenia: a longitudinal first-episode study with 7-year follow-up. *The American Journal of Psychiatry*, 162(3), 495–506. <http://doi.org/10.1176/appi.ajp.162.3.495>
- Millier, A., Schmidt, U., Angermeyer, M. C., Chauhan, D., Murthy, V., Toumi, M., & Cadi-Soussi, N. (2014). Humanistic burden in schizophrenia: A literature review. *Journal of Psychiatric Research*, 54(1), 85–93.
<http://doi.org/10.1016/j.jpsychires.2014.03.021>
- Mohamed, S., Rosenheck, R., Swartz, M., Stroup, S., Lieberman, J. A., & Keefe, R.

- S. E. (2008). Relationship of Cognition and Psychopathology to Functional Impairment in Schizophrenia. *American Journal of Psychiatry*, 2008(August), 1–10. <http://doi.org/10.1176/appi.ajp.2008.07111713>
- Möller, H. J., Jäger, M., Riedel, M., Obermeier, M., Strauss, A., & Bottlender, R. (2011). The Munich 15-year follow-up study (MUFUSSAD) on first-hospitalized patients with schizophrenic or affective disorders: assessing courses, types and time stability of diagnostic classification. *European Psychiatry*, 26(4), 231–43. <http://doi.org/10.1016/j.eurpsy.2010.04.012>
- Morgan, C., Lappin, J., Heslin, M., Donoghue, K., Lomas, B., Reininghaus, U., ... Dazzan, P. (2014). Reappraising the long-term course and outcome of psychotic disorders: The AESOP-10 study. *Psychological Medicine*, 44(13), 2713–2726. <http://doi.org/10.1017/S0033291714000282>
- Morgan, V. A., Waterreus, A., Jablensky, A., Mackinnon, A., McGrath, J. J., Carr, V. J., ... Saw, W. (2010). *People living with psychotic illness 2010 second Australian national survey*.
- Murthy, N. V., Mahncke, H., Wexler, B. E., Maruff, P., Inamdar, A., Zucchetto, M., ... Alexander, R. (2012). Computerized cognitive remediation training for schizophrenia: an open label, multi-site, multinational methodology study. *Schizophrenia Research*, 139(1–3), 87–91. <http://doi.org/10.1016/j.schres.2012.01.042>
- Mutsuddi, M., Morris, D. W., Waggoner, S. G., Daly, M. J., Scolnick, E. M., & Sklar, P. (2006). Analysis of high-resolution HapMap of DTNBP1 (Dysbindin) suggests no consistency between reported common variant associations and schizophrenia. *American Journal of Human Genetics*, 79(5), 903–909. <http://doi.org/10.1086/508942>
- National Center for Biotechnology Information. (2014a). rs1018381. Retrieved July 8, 2014, from https://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=1018381
- National Center for Biotechnology Information. (2014b). rs2619522. Retrieved July 8, 2014, from http://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=2619522
- National Health and Medical Research Council, the A. R. C. and the A. V.-C. C. (2007). *National Statement on Ethical Conduct in Human Research 2007 (Updated May 2015)*. Canberra, Australia. Retrieved from

- <https://www.nhmrc.gov.au/print/book/export/html/51613>
- Nielssen, O., McGorry, P., Castle, D., & Galletly, C. (2017). The RANZCP guidelines for Schizophrenia: Why is our practice so far short of our recommendations, and what can we do about it? *Australian and New Zealand Journal of Psychiatry*, 51(7), 670–674.
<http://doi.org/10.1177/0004867417708868>
- Niendam, T. a, Jalbrzikowski, M., & Bearden, C. E. (2009). Exploring predictors of outcome in the psychosis prodrome: implications for early identification and intervention. *Neuropsychology Review*, 19(3), 280–93.
<http://doi.org/10.1007/s11065-009-9108-z>
- Nuechterlein, K. H., Barch, D. M., Gold, J. M., Goldberg, T. E., Green, M. F., & Heaton, R. K. (2004). Identification of separable cognitive factors in schizophrenia. *Schizophrenia Research*, 72(1), 29–39.
<http://doi.org/10.1016/j.schres.2004.09.007>
- Nuechterlein, K. H., & Green, M. F. (2006). *MCCB MATRICS Consensus Cognitive Battery Manual*. USA.
- Nuechterlein, K. H., Green, M. F., Kern, R. S., Baade, L. E., Barch, D. M., Cohen, J. D., ... Marder, S. R. (2008). The MATRICS Consensus Cognitive Battery, part 1: test selection, reliability, and validity. *The American Journal of Psychiatry*, 165(2), 203–13. <http://doi.org/10.1176/appi.ajp.2007.07010042>
- Numakawa, T., Yagasaki, Y., Ishimoto, T., Okada, T., Suzuki, T., Iwata, N., ... Hashimoto, R. (2004). Evidence of novel neuronal functions of dysbindin, a susceptibility gene for schizophrenia. *Human Molecular Genetics*, 13(21), 2699–708. <http://doi.org/10.1093/hmg/ddh280>
- O’Leary, D. S., Flaum, M., Kesler, M. L., Flashman, L. a, Arndt, S., & Andreasen, N. C. (2000). Cognitive correlates of the negative, disorganized, and psychotic symptom dimensions of schizophrenia. *The Journal of Neuropsychiatry and Clinical Neurosciences*, 12(1), 4–15. <http://doi.org/10.1176/jnp.12.1.4>
- O’Reilly, K., O’Connell, P., Donohoe, G., Coyle, C., O’Sullivan, D., Azvee, Z., ... Kennedy, H. G. (2016). Anticholinergic burden in schizophrenia and ability to benefit from psychosocial treatment programmes: a 3-year prospective cohort study. *Psychological Medicine*, 46(15), 3199–3211.
<http://doi.org/10.1017/S0033291716002154>
- Opler, L. A., Medalia, A., Opler, M. G., & Stahl, S. M. (2014). Pharmacotherapy of

- cognitive deficits in schizophrenia. *CNS Spectrums*, 19(2), 142–56.
<http://doi.org/10.1017/S1092852913000771>
- Overall, J. E., & Gorham, D. R. (1962). The Brief Psychiatric Rating Scale. *Psychiatric Reports*, 10, 799–812. <http://doi.org/doi.org/10.2466/PRO.10.3.799-812>
- Palmer, B. W., Heaton, R. K., Paulsen, J. S., Kuck, J., Braff, D. L., Harris, M. J., ... Jeste, D. V. (1997). Is it possible to be schizophrenic yet neuropsychologically normal? *Neuropsychology*, 11(3), 437–46. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/9223148>
- Panizzutti, R., Hamilton, S. P., & Vinogradov, S. (2013). Genetic correlate of cognitive training response in schizophrenia. *Neuropharmacology*, 64, 264–267. <http://doi.org/10.1016/j.neuropharm.2012.07.048>
- Papaleo, F., Yang, F., Garcia, S., Chen, J., Lu, B., Crawley, J. N., & Weinberger, D. R. (2012). Dysbindin-1 modulates prefrontal cortical activity and schizophrenia-like behaviors via dopamine/D2 pathways. *Molecular Psychiatry*, 17(1), 85–98. <http://doi.org/10.1038/mp.2010.106>
- Patel, R., Spreng, R. N., & Turner, G. R. (2013). Functional brain changes following cognitive and motor skills training: A quantitative meta-analysis. *Neurorehabilitation and Neural Repair*, 27(3), 187–199. <http://doi.org/10.1177/1545968312461718>
- Penadés, R., Catalán, R., Salamero, M., Boget, T., Puig, O., Guarch, J., & Gastó, C. (2006). Cognitive remediation therapy for outpatients with chronic schizophrenia: a controlled and randomized study. *Schizophrenia Research*, 87(1–3), 323–331. <http://doi.org/10.1016/j.schres.2006.04.019>
- Penadés, R., González-Rodríguez, A., Catalán, R., Segura, B., Bernardo, M., & Junqué, C. (2017). Neuroimaging studies of cognitive remediation in schizophrenia: A systematic and critical review. *World Journal of Psychiatry*, 7(1), 34. <http://doi.org/10.5498/wjp.v7.i1.34>
- Penadés, R., Pujol, N., Catalán, R., Masana, G., García-Rizo, C., Bargalló, N., ... Junqué, C. (2016). Cortical thickness in regions of frontal and temporal lobes is associated with responsiveness to cognitive remediation therapy in schizophrenia. *Schizophrenia Research*, 171(1–3), 110–116. <http://doi.org/10.1016/j.schres.2016.01.006>
- Penadés, R., Pujol, N., Catalán, R., Massana, G., Rametti, G., García-Rizo, C., ...

- Junqué, C. (2013). Brain effects of cognitive remediation therapy in schizophrenia: A structural and functional neuroimaging study. *Biological Psychiatry*, 73(10), 1015–1023. <http://doi.org/10.1016/j.biopsych.2013.01.017>
- Perälä, J., Suvisaari, J., Saarni, S. I., Kuoppasalmi, K., Isometsä, E., Pirkola, S., ... Lönnqvist, J. (2007). Lifetime prevalence of psychotic and bipolar I disorders in a general population. *Archives of General Psychiatry*, 64(1), 19–28. <http://doi.org/10.1001/archpsyc.64.1.19>
- Peters, K., Wiltshire, S., Henders, A. K., Dragović, M., Badcock, J. C., Chandler, D., ... Jablensky, A. (2008). Comprehensive analysis of tagging sequence variants in DTNBP1 shows no association with schizophrenia or with its composite neurocognitive endophenotypes. *American Journal of Medical Genetics*, 147B(7), 1159–1166. <http://doi.org/10.1002/ajmg.b.30741>
- Pilling, S., Bebbington, P., Kuipers, E., Garety, P., Geddes, J., Martindale, B., ... Morgan, C. (2002). Psychological treatments in schizophrenia: II. Meta-analyses of randomized controlled trials of social skills training and cognitive remediation. *Psychological Medicine*, 32(5), 783–791. <http://doi.org/http://dx.doi.org/10.1017/S0033291702005640>
- Pincus, T., Miles, C., Froud, R., Underwood, M., Carnes, D., & Taylor, S. J. (2011). Methodological criteria for the assessment of moderators in systematic reviews of randomised controlled trials: a consensus study. *BMC Medical Research Methodology*, 11(1), 14. <http://doi.org/10.1186/1471-2288-11-14>
- Pleil, J. D., Stiegel, M. A., Sobus, J. R., Liu, Q., & Madden, M. C. (2011). Observing the human exposome as reflected in breath biomarkers: Heat map data interpretation for environmental and intelligence research. *Journal of Breath Research*, 5(3), 1–9. <http://doi.org/10.1088/1752-7155/5/3/037104>
- Popov, T., Jordanov, T., Rockstroh, B., Elbert, T., Merzenich, M. M., & Miller, G. a. (2011). Specific cognitive training normalizes auditory sensory gating in schizophrenia: a randomized trial. *Biological Psychiatry*, 69(5), 465–471. <http://doi.org/10.1016/j.biopsych.2010.09.028>
- Posit Science. (2018). Visual Sweeps. Retrieved February 8, 2018, from <https://www.brainhq.com/why-brainhq/about-the-brainhq-exercises/brainspeed/visual-sweeps>
- Rabinowitz, J., Levine, S. Z., & Häfner, H. (2006). A population based elaboration of the role of age of onset on the course of schizophrenia. *Schizophrenia*

- Research*, 88(1–3), 96–101. <http://doi.org/10.1016/j.schres.2006.07.007>
- Radhakrishnan, R., Kiluk, B. D., & Tsai, J. (2016). A Meta-analytic Review of Non-specific Effects in Randomized Controlled Trials of Cognitive Remediation for Schizophrenia. *Psychiatric Quarterly*, 87(1), 57–62. <http://doi.org/10.1007/s11126-015-9362-6>
- Ramsay, I. S., & Macdonald, A. W. (2015). Brain Correlates of Cognitive Remediation in Schizophrenia: Activation Likelihood Analysis Shows Preliminary Evidence of Neural Target Engagement. *Schizophrenia Bulletin*, 41(6), 1276–1284. <http://doi.org/10.1093/schbul/sbv025>
- Ramsay, I. S., Nienow, T. M., & MacDonald, A. W. (2017). Increases in Intrinsic Thalamocortical Connectivity and Overall Cognition Following Cognitive Remediation in Chronic Schizophrenia. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, 2(4), 355–362. <http://doi.org/10.1016/j.bpsc.2016.11.001>
- Reddy, L. F., Horan, W. P., Jahshan, C., & Green, M. F. (2014). Cognitive Remediation for Schizophrenia: A Review of Recent Findings. *Current Treatment Options in Psychiatry*, 1(2), 121–133. <http://doi.org/10.1007/s40501-014-0011-8>
- Reeder, C., Huddy, V., Cella, M., Taylor, R., Greenwood, K., Landau, S., & Wykes, T. (2017). A new generation computerised metacognitive cognitive remediation programme for schizophrenia (CIRCuiTS): A randomised controlled trial. *Psychological Medicine*, 47(15), 2720–2730. <http://doi.org/10.1017/S0033291717001234>
- Rempfer, M., Brown, C., & Hamera, E. (2011). Learning potential as a predictor of skill acquisition in people with serious mental illness. *Psychiatry Research*, 185(1–2), 293–295. <http://doi.org/10.1016/j.psychres.2009.12.009>
- Rempfer, M., Hamera, E., Brown, C., & Bothwell, R. J. (2006). Learning proficiency on the Wisconsin Card Sorting Test in people with serious mental illness: What are the cognitive characteristics of good learners? *Schizophrenia Research*, 87(1–3), 316–322. <http://doi.org/10.1016/j.schres.2006.05.012>
- Remschmidt, H., & Theisen, F. (2012). Early-onset schizophrenia1. *Neuropsychobiology*, 66(1), 63–69. <http://doi.org/10.1159/000338548>
- Reser, M. P., Slikboer, R., & Rossell, S. L. (2018). Predictors of Response to Cognitive Remediation Therapy: Systematic Review of Literature. In

Schizophrenia International Research Society 6th Biennial Conference.

- Revell, E. R., Neill, J. C., Harte, M., Khan, Z., & Drake, R. J. (2015). A systematic review and meta-analysis of cognitive remediation in early schizophrenia. *Schizophrenia Research*, 168(1–2), 213–222. <http://doi.org/10.1016/j.schres.2015.08.017>
- Revier, C. J., Reininghaus, U., Dutta, R., Fearon, P., Murray, R. M., Doody, G. A., ... Jones, P. B. (2015). Ten-year outcomes of first-episode psychoses in the MRC AEsOP-10 study. *Journal of Nervous and Mental Disease*, 203(5), 379–386. <http://doi.org/10.1097/NMD.0000000000000295>
- Rodewald, K., Holt, D. V., Rentrop, M., Roesch-ely, D., Liebreinz, M., Funke, J., ... Kaiser, S. (2014). Predictors for Improvement of Problem-Solving during Cognitive Remediation for Patients with Schizophrenia. *Journal of the International Neuropsychological Society*, 20(4), 455–460. <http://doi.org/10.1017/S1355617714000162>
- Rose, E. J., & Donohoe, G. (2013). Brain vs behavior: an effect size comparison of neuroimaging and cognitive studies of genetic risk for schizophrenia. *Schizophrenia Bulletin*, 39(3), 518–526. <http://doi.org/10.1093/schbul/sbs056>
- Royston, P., Altman, D. G., & Sauerbrei, W. (2006). Dichotomizing continuous predictors in multiple regression: A bad idea. *Statistics in Medicine*, 25(1), 127–141. <http://doi.org/10.1002/sim.2331>
- Ruberg, S. J., Chen, L., & Wang, Y. (2010). The mean does not mean as much anymore: Finding sub-groups for tailored therapeutics. *Clinical Trials*, 7(5), 574–583. <http://doi.org/10.1177/1740774510369350>
- Sánchez, P., Peña, J., Bengoetxea, E., Ojeda, N., Elizagárate, E., Ezcurra, J., & Gutiérrez, M. (2014). Improvements in negative symptoms and functional outcome after a new generation cognitive remediation program: a randomized controlled trial. *Schizophrenia Bulletin*, 40(3), 707–715. <http://doi.org/10.1093/schbul/sbt057>
- Santen, G., Danhof, M., & Della Pasqua, O. (2009). Sensitivity of the Montgomery Asberg Depression Rating Scale to response and its consequences for the assessment of efficacy. *Journal of Psychiatric Research*, 43(12), 1049–1056. <http://doi.org/10.1016/j.jpsychires.2009.02.001>
- Santor, D. A., Ascher-Svanum, H., Lindenmayer, J. P., & Obenchain, R. L. (2007). Item response analysis of the Positive and Negative Syndrome Scale. *BMC*

- Psychiatry*, 7, 1–10. <http://doi.org/10.1186/1471-244X-7-66>
- Schaefer, J., Giangrande, E., Weinberger, D. R., & Dickinson, D. (2013). The global cognitive impairment in schizophrenia: Consistent over decades and around the world. *Schizophrenia Research*, 150(1), 42–50.
<http://doi.org/10.1016/j.schres.2013.07.009>
- Schneider, E. C., Sarnak, D. O., Squires, D., Shah, A., & Doty, M. M. (2017). *Mirror, Mirror 2017: International comparison reflects flaws and opportunities for better U.S. health care*. New York, NY. Retrieved from <https://www.commonwealthfund.org/publications/fund-reports/2017/jul/mirror-mirror-2017-international-comparison-reflects-flaws-and>
- Schwartz, M. F., & Dell, G. S. (2010). Case Series Investigations in Cognitive Neuropsychology. *Cognitive Neuropsychology*, 27(6), 477–494.
<http://doi.org/10.1080/02643294.2011.574111>.Case
- Seccomandi, B., Agbedjro, D., Bell, M., Keefe, R., Keshavan, M., Galderisi, S., ... Cella, M. (2018). Does age influence response to cognitive remediation. *Schizophrenia Bulletin*, 44, S196–S197.
<http://doi.org/https://doi.org/10.1093/schbul/sby016>.482
- Sergi, M. J., Kern, R. S., Mintz, J., & Green, M. F. (2005). Learning potential and the prediction of work skill acquisition in schizophrenia. *Schizophrenia Bulletin*, 31(1), 67–72. <http://doi.org/10.1093/schbul/sbi007>
- Sharip, S., Michie, P., Schall, U., Drysdale, K., Case, V., Sankaranarayanan, A., ... Das, S. (2013). Generalization of cognitive training in an Australian sample of schizophrenia patients. *Comprehensive Psychiatry*, 54(7), 865–72.
<http://doi.org/10.1016/j.comppsy.2013.03.015>
- Sheehan, D. V., & Lecrubier, Y. (2006). Mini International Neuropsychiatric Interview (M.I.N.I).
- Sheehan, D. V., Lecrubier, Y., Harnett Sheehan, K., Janavs, J., Weiller, E., Keskiner, A., ... Dunbar, G. (1997). The validity of the Mini International Neuropsychiatric Interview (MINI) according to the SCID-P and its reliability. *European Psychiatry*, 12(5), 232–241. [http://doi.org/10.1016/S0924-9338\(97\)83297-X](http://doi.org/10.1016/S0924-9338(97)83297-X)
- Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., ... Dunbar, G. C. (1998). The mini-international neuropsychiatric interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric

- interview for DSM-IV and ICD-10. *Clinical Journal of Psychiatry*, 59(Suppl 20), 22–33. Retrieved from <http://www.psychiatrist.com/>
- Silverstein, S. M., Roché, M. W. ., Khan, Z. ., Carson, S. J. ., Malinovsky, I. ., Newbill, W. A. ., ... Wilkniss, S. M. . (2014). Enhancing and promoting recovery in attentionally impaired people diagnosed with schizophrenia: Results from a randomized controlled trial of attention shaping in a partial hospital program. *American Journal of Psychiatric Rehabilitation*, 17(3), 272–305. <http://doi.org/10.1080/15487768.2014.935681>
- Silverstein, S. M., Spaulding, W. D., Menditto, A. A., Savitz, A., Liberman, R. P., Berten, S., & Starobin, H. (2009). Attention shaping: a reward-based learning method to enhance skills training outcomes in schizophrenia. *Schizophrenia Bulletin*, 35(1), 222–32. <http://doi.org/10.1093/schbul/sbm150>
- Simons, C. J. P., & Van Winkel, R. (2013). Intermediate phenotype analysis of patients, unaffected siblings, and healthy controls identifies VMAT2 as a candidate gene for psychotic disorder and neurocognition. *Schizophrenia Bulletin*, 39(4), 848–856. <http://doi.org/10.1093/schbul/sbs067>
- Sponheim, S. R., Jung, R. E., Seidman, L. J., Mesholam-Gately, R. I., Manoach, D. S., O’Leary, D. S., ... Schulz, S. C. (2010). Cognitive deficits in recent-onset and chronic schizophrenia. *Journal of Psychiatric Research*, 44(7), 421–428. <http://doi.org/10.1016/j.jpsychires.2009.09.010>
- Stefanis, N. C., Trikalinos, T. A., Avramopoulos, D., Smyrnis, N., Evdokimidis, I., Ntzani, E. E., ... Stefanis, C. N. (2007). Impact of schizophrenia candidate genes on schizotypy and cognitive endophenotypes at the population level. *Biological Psychiatry*, 62(7), 784–792. <http://doi.org/10.1016/j.biopsych.2006.11.015>
- Stephan, K. E., Friston, K. J., & Frith, C. D. (2009). Dysconnection in Schizophrenia: From abnormal synaptic plasticity to failures of self-monitoring. *Schizophrenia Bulletin*, 35(3), 509–527. <http://doi.org/10.1093/schbul/sbn176>
- Stirling, J. (2003). Neurocognitive function and outcome in first-episode schizophrenia: a 10-year follow-up of an epidemiological cohort. *Schizophrenia Research*, 65(2–3), 75–86. [http://doi.org/10.1016/S0920-9964\(03\)00014-8](http://doi.org/10.1016/S0920-9964(03)00014-8)
- Strassnig, M. T., Raykov, T., O’Gorman, C., Bowie, C. R., Sabbag, S., Durand, D., ... Harvey, P. D. (2015). Determinants of different aspects of everyday outcome in schizophrenia: The roles of negative symptoms, cognition, and

- functional capacity. *Schizophrenia Research*, 165(1), 76–82.
<http://doi.org/10.1016/j.schres.2015.03.033>
- Straub, R. E., MacLean, C. J., Ma, Y., Webb, B. T., Myakishev, M. V., Harris-Kerr, C., ... Kendler, K. S. (2002). Genome-wide scans of three independent sets of 90 Irish multiplex schizophrenia families and follow-up of selected regions in all families provides evidence for multiple susceptibility genes. *Molecular Psychiatry*, 7(6), 542–559. <http://doi.org/10.1038/sj.mp.4001051>
- Subramaniam, K., Luks, T. L., Fisher, M., Simpson, G. V, Nagarajan, S., & Vinogradov, S. (2012). Computerized cognitive training restores neural activity within the reality monitoring network in schizophrenia. *Neuron*, 73(4), 842–853. <http://doi.org/10.1016/j.neuron.2011.12.024>
- Sullivan, P. F., Kendler, K. S., & Neale, M. C. (2003). Schizophrenia as a Complex Trait: Evidence from a meta-analysis of twin studies. *Archives of General Psychiatry*, 60(12), 1187–1192.
<http://doi.org/http://dx.doi.org/10.1001/archpsyc.60.12.1187>
- Surti, T. S., Corbera, S., Bell, M. D., & Wexler, B. E. (2011). Successful computer-based visual training specifically predicts visual memory enhancement over verbal memory improvement in schizophrenia. *Schizophrenia Research*, 132(2–3), 131–134. <http://doi.org/10.1016/j.schres.2011.06.031>
- Tabachnick, B. G., & Fidell, L. S. (2013). *Using Multivariate Statistics* (6th, Inter ed.). Boston, MA: Pearson Education.
- Takao, K., Toyama, K., Nakanishi, K., Hattori, S., Takamura, H., Takeda, M., ... Hashimoto, R. (2008). Impaired long-term memory retention and working memory in *sd* mutant mice with a deletion in *Dtnbp1*, a susceptibility gene for schizophrenia. *Molecular Brain*, 1, 11. <http://doi.org/10.1186/1756-6606-1-11>
- Talbot, K., Eidem, W. L., Tinsley, C. L., Benson, M. A., Thompson, E. W., Smith, R. J., ... Arnold, S. E. (2004). Dysbindin-1 is reduced in intrinsic , glutamatergic terminals of the hippocampal formation in schizophrenia, 113(9), 1353–1363. <http://doi.org/10.1172/JCI200420425>.The
- Talbot, K., Ong, W.-Y., Blake, D. J., Tang, J., Louneva, N., Carlson, G. C., & Arnold, S. E. (2009). Dysbindin-1 and Its Protein Family. In A. Lajtha, D. Javitt, & J. Kantrowitz (Eds.), *Handbook of Neurochemistry and Molecular Neurobiology: Schizophrenia* (pp. 107–241). Boston, MA: Springer US.
<http://doi.org/10.1007/978-0-387-30410-6>

- Tandon, R. (2013). Schizophrenia and other Psychotic Disorders in DSM-5: Clinical Implications of Revisions from DSM-IV. *Clinical Schizophrenia & Related Psychoses*, 7(1), 16–20.
<http://doi.org/http://dx.doi.org/10.3371/CSRP.TA.032513>
- Tang, J., LeGros, R. P., Louneva, N., Yeh, L., Cohen, J. W., Hahn, C.-G., ... Talbot, K. (2009). Dysbindin-1 in dorsolateral prefrontal cortex of schizophrenia cases is reduced in an isoform-specific manner unrelated to dysbindin-1 mRNA expression. *Human Molecular Genetics*, 18(20), 3851–63.
<http://doi.org/10.1093/hmg/ddp329>
- Tarasenko, M., Perez, V. B., Pianka, S. T., Vinogradov, S., Braff, D. L., Swerdlow, N. R., & Light, G. A. (2016). Measuring the capacity for auditory system plasticity: An examination of performance gains during initial exposure to auditory-targeted cognitive training in schizophrenia. *Schizophrenia Research*, 172(1–3), 123–130. <http://doi.org/10.1016/j.schres.2016.01.019>
- Tenhula, W. N., Strong Kinnaman, J. E., & Bellack, A. S. (2007). Is learning potential associated with social skills in schizophrenia? *Journal of Rehabilitation Research & Development*, 6, 827–836.
<http://doi.org/http://dx.doi.org/10.1682/JRRD.2006.09.0113>
- Tenison, C., Fincham, J. M., & Anderson, J. R. (2016). Phases of learning: How skill acquisition impacts cognitive processing. *Cognitive Psychology*, 87, 1–28.
<http://doi.org/10.1016/j.cogpsych.2016.03.001>
- Thimm, M., Krug, A., Kellermann, T., Markov, V., Krach, S., Jansen, A., ... Kircher, T. (2010). The effects of a DTNBP1 gene variant on attention networks: an fMRI study. *Behavioral and Brain Functions : BBF*, 6, 54.
<http://doi.org/10.1186/1744-9081-6-54>
- Thimm, M., Krug, A., Markov, V., Krach, S., Jansen, A., Zerres, K., ... Kircher, T. (2010). The impact of dystrobrevin-binding protein 1 (DTNBP1) on neural correlates of episodic memory encoding and retrieval. *Human Brain Mapping*, 31(2), 203–209. <http://doi.org/10.1002/hbm.20857>
- Thorsen, A. L., Johansson, K., & Løberg, E.-M. (2014). Neurobiology of Cognitive Remediation Therapy for Schizophrenia: A Systematic Review. *Frontiers in Psychiatry*, 5(August). <http://doi.org/10.3389/fpsyt.2014.00103>
- Thorup, A., Waltoft, B. L., Pedersen, C. B., Mortensen, P. B., & Nordentoft, M. (2007). Young males have a higher risk of developing schizophrenia: A Danish

- register study. *Psychological Medicine*, 37(4), 479–484.
<http://doi.org/10.1017/S0033291707009944>
- Toddenroth, D., Ganslandt, T., Castellanos, I., Prokosch, H. U., & Bürkle, T. (2014). Employing heat maps to mine associations in structured routine care data. *Artificial Intelligence in Medicine*, 60(2), 79–88.
<http://doi.org/10.1016/j.artmed.2013.12.003>
- Tsai, J., & Rosenheck, R. a. (2013). Psychiatric comorbidity among adults with schizophrenia: a latent class analysis. *Psychiatry Research*, 210(1), 16–20.
<http://doi.org/10.1016/j.psychres.2013.05.013>
- Twamley, E. W., Burton, C. Z., & Vella, L. (2011). Compensatory cognitive training for psychosis: who benefits? Who stays in treatment? *Schizophrenia Bulletin*, 37 Suppl 2(SUPPL. 2), S55–62. <http://doi.org/10.1093/schbul/sbr059>
- Twamley, E. W., Jeste, D. V., & Bellack, A. S. (2003). A Review of Cognitive Training in Schizophrenia. *Schizophrenia Bulletin*, 29(2), 359–382.
<http://doi.org/10.1093/oxfordjournals.schbul.a007011>
- van den Oord, E. J. C. G., Sullivan, P. F., Jiang, Y., Walsh, D., O'Neill, F. a, Kendler, K. S., & Riley, B. P. (2003). Identification of a high-risk haplotype for the dystrobrevin binding protein 1 (DTNBP1) gene in the Irish study of high-density schizophrenia families. *Molecular Psychiatry*, 8(5), 499–510.
<http://doi.org/10.1038/sj.mp.4001263>
- Vaskinn, A., Sundet, K., Friis, S., Ueland, T., Simonsen, C., Birkenaes, A. B., ... Andreassen, O. A. (2008). Can learning potential in schizophrenia be assessed with the standard CVLT-II? An exploratory study: Health and Disability. *Scandinavian Journal of Psychology*, 49(2), 179–186.
<http://doi.org/10.1111/j.1467-9450.2008.00627.x>
- Vaskinn, A., Sundet, K., Friis, S., Ueland, T., Simonsen, C., Birkenaes, A. B., ... Andreassen, O. A. (2009). Using the Wisconsin card sorting test to assess learning potential in normal IQ schizophrenia: Does it have potential? *Nordic Journal of Psychiatry*, 63(5), 405–411.
<http://doi.org/10.1080/08039480902879941>
- Ventura, J., Thames, A. D., Wood, R. C., Guzik, L. H., & Helleman, G. S. (2010). Disorganization and reality distortion in schizophrenia: A meta-analysis of the relationship between positive symptoms and neurocognitive deficits. *Schizophrenia Research*, 121(1–3), 1–14.

- <http://doi.org/10.1016/j.schres.2010.05.033>
- Vinogradov, S., Fisher, M., & de Villers-Sidani, E. (2012). Cognitive Training for Impaired Neural Systems in Neuropsychiatric Illness. *Neuropsychopharmacology*, 37(1), 43–76. <http://doi.org/10.1038/npp.2011.251>
- Vinogradov, S., Fisher, M., Holland, C., Shelly, W., Wolkowitz, O., & Mellon, S. H. (2009). Is serum brain-derived neurotrophic factor a biomarker for cognitive enhancement in schizophrenia? *Biological Psychiatry*, 66(6), 549–553. <http://doi.org/10.1016/j.biopsych.2009.02.017>
- Vinogradov, S., Fisher, M., Warm, H., Holland, C., Kirshner, M. a, & Pollock, B. G. (2009). The cognitive cost of anticholinergic burden: decreased response to cognitive training in schizophrenia. *The American Journal of Psychiatry*, 166(9), 1055–1062. <http://doi.org/10.1176/appi.ajp.2009.09010017>
- Vita, A., Barlati, S., Bellani, M., & Brambilla, P. (2014). Cognitive remediation in schizophrenia: background, techniques, evidence of efficacy and perspectives. *Epidemiology and Psychiatric Sciences*, 23(1), 21–5. <http://doi.org/10.1017/S2045796013000541>
- Vita, A., De Peri, L., Barlati, S., Cacciani, P., Cisima, M., Deste, G., ... Sacchetti, E. (2011). Psychopathologic, neuropsychological and functional outcome measures during cognitive rehabilitation in schizophrenia: a prospective controlled study in a real-world setting. *European Psychiatry*, 26(5), 276–283. <http://doi.org/10.1016/j.eurpsy.2010.03.008>
- Vita, A., Deste, G., De Peri, L., Barlati, S., Poli, R., Cesana, B. M., & Sacchetti, E. (2013). Predictors of cognitive and functional improvement and normalization after cognitive remediation in patients with schizophrenia. *Schizophrenia Research*, 150(1), 51–57. <http://doi.org/10.1016/j.schres.2013.08.011>
- Waghorn, G., Chant, D., Lloyd, C., & Harris, M. (2011). Earning and learning among Australian community residents with psychiatric disorders. *Psychiatry Research*, 186(1), 109–16. <http://doi.org/10.1016/j.psychres.2010.07.037>
- Wang, R., Lagakos, S. W., Ware, J. H., Hunter, D. J., & Drazen, J. M. (2007). Statistics in Medicine — Reporting of Subgroup Analyses in Clinical Trials. *New England Journal of Medicine*, 357(21), 2189–2194. <http://doi.org/10.1056/NEJMSr077003>
- Watzke, S., Brieger, P., Kuss, O., Schoettke, H., & Wiedl, K. H. (2008). A Longitudinal Study of Learning Potential and Rehabilitation Outcome in

- Schizophrenia. *Psychiatr Serv*, 59(3), 248–255. Retrieved from <http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=ovftj&NEWS=N&AN=00042727-200803000-00007%5Cnhttp://psychservices.psychiatryonline.org/cgi/reprint/59/3/248%5Cnhttp://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed8&NEWS=N&AN=2008394468>
- Watzke, S., Brieger, P., & Wiedl, K. (2009). Prediction of vocational rehabilitation outcome in schizophrenia: Incremental prognostic validity of learning potential beyond basic cognitive performance. *Journal of Cognitive Education and Psychology*, 8, 52–62. <http://doi.org/10.1891/1945-8959.8.1.52>.
- Wechsler, D. (1999). *Wechsler Abbreviated Scale of Intelligence: WASI*. (T. P. Corporation, Ed.).
- Wechsler, D. (2001). *Wechsler Test of Adult Reading: WTAR*. (The Psychological Corporation, Ed.). San Antonio, TX: Harcourt Assessment.
- Wei, Y. Y., Wang, J. J., Yan, C., Li, Z. Q., Pan, X., Cui, Y., ... Tang, Y. X. (2016). Correlation between brain activation changes and cognitive improvement following cognitive remediation therapy in schizophrenia: An activation likelihood estimation meta-analysis. *Chinese Medical Journal*, 129(5), 578–585. <http://doi.org/10.4103/0366-6999.176983>
- Weickert, C. S., Rothmond, D. A., Hyde, T. M., Kleinman, J. E., & Straub, R. E. (2008). Reduced DTNBP1 (dysbindin-1) mRNA in the hippocampal formation of schizophrenia patients. *Schizophrenia Research*, 98(1–3), 105–110. <http://doi.org/10.1016/j.schres.2007.05.041>
- Weickert, C. S., Straub, R. E., McClintock, B. W., Matsumoto, M., Weinberger, D. R., & Kleinman, J. E. (2004). Human Dysbindin (DTNBP1) Gene Expression in Normal Brain and in Schizophrenia Prefrontal Cortex and Midbrain. *Archives of General Psychiatry*, 61, 544–555. Retrieved from <http://archpsyc.jamanetwork.com/journal.aspx>
- Weickert, T. W., Goldberg, T. E., Gold, J. M., Bigelow, L. B., Egan, M. F., & Weinberger, D. R. (2000). Cognitive impairments in patients with schizophrenia displaying preserved and compromised intellect. *Archives of General Psychiatry*, 57(9), 907–13. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/10986554>
- Weingartz, S., Wiedl, K. H., & Watzke, S. (2008). Dynamic assessment of executive

- functioning: (How) can we measure change? *Journal of Cognitive Education and Psychology*, 7(3), 368–387.
<http://doi.org/http://dx.doi.org/10.1891/194589508787724088>
- White, C., Stirling, J., Hopkins, R., Morris, J., Montague, L., Tantam, D., & Lewis, S. (2009). Predictors of 10-year outcome of first-episode psychosis. *Psychological Medicine*, 39(9), 1447–56.
<http://doi.org/10.1017/S003329170800514X>
- Wiedl, K. H., & Wienöbst, J. (1999). Interindividual differences in cognitive remediation research with schizophrenic patients - indicators of rehabilitation potential? *International Journal of Rehabilitation Research*, 22(55–59), 55–59.
<http://doi.org/http://dx.doi.org/10.1097/00004356-199903000-00007>
- Wiedl, K. H., Wienöbst, J., Schöttke, H. H., Green, M. F., & Nuechterlein, K. H. (2001). Attentional characteristics of schizophrenia patients differing in learning proficiency on the Wisconsin Card Sorting Test. *Schizophrenia Bulletin*, 27(4), 687–696. <http://doi.org/10.1093/oxfordjournals.schbul.a006907>
- Wilkinson, L., & Friendly, M. (2009). History corner the history of the cluster heat map. *American Statistician*, 63(2), 179–184.
<http://doi.org/10.1198/tas.2009.0033>
- Wolf, C., Jackson, M. C., Kissling, C., Thome, J., & Linden, D. E. J. (2011). Dysbindin-1 genotype effects on emotional working memory. *Molecular Psychiatry*, 16, 145–155. <http://doi.org/http://dx.doi.org/10.1038/mp.2009.129>
- Woodberry, K. A., Giuliano, A. J., Ph, D., & Seidman, L. J. (2008). Reviews and Overviews Premorbid IQ in Schizophrenia : A Meta-Analytic Review. *American Journal of Psychiatry*, 165(May), 579–587.
- Woonings, F. M. J., Appelo, M. T., Kluiter, H., Slooff, C. J., & van den Bosch, R. J. (2002). Learning (potential) and social functioning in schizophrenia. *Schizophrenia Research*, 59, 287–296.
[http://doi.org/http://dx.doi.org/10.1016/S0920-9964\(02\)00163-9](http://doi.org/http://dx.doi.org/10.1016/S0920-9964(02)00163-9)
- World Health Organization. (1992). *International Classification of Diseases, Tenth Revision [ICD-10]*. Geneva: World Health Organization.
- World Health Organization. (2018). Schizophrenia. Retrieved May 7, 2018, from <http://www.who.int/en/news-room/fact-sheets/detail/schizophrenia>
- Wykes, T., Huddy, V., Cellard, C., McGurk, S. R., & Czobor, P. (2011). A meta-analysis of cognitive remediation for schizophrenia: methodology and effect

- sizes. *The American Journal of Psychiatry*, 168(5), 472–85.
<http://doi.org/10.1176/appi.ajp.2010.10060855>
- Wykes, T., Newton, E., Landau, S., Rice, C., Thompson, N., & Frangou, S. (2007). Cognitive remediation therapy (CRT) for young early onset patients with schizophrenia: an exploratory randomized controlled trial. *Schizophrenia Research*, 94(1–3), 221–230. <http://doi.org/10.1016/j.schres.2007.03.030>
- Wykes, T., Reeder, C., Corner, J., Williams, C., & Everitt, B. (1999). The effects of neurocognitive remediation on executive processing in patients with schizophrenia. *Schizophrenia Bulletin*, 25(2), 291–307.
<http://doi.org/http://dx.doi.org/10.1093/oxfordjournals.schbul.a033379>
- Wykes, T., Reeder, C., Huddy, V., Taylor, R., Wood, H., Ghirasim, N., ... Landau, S. (2012). Developing models of how cognitive improvements change functioning: mediation, moderation and moderated mediation. *Schizophrenia Research*, 138(1), 88–93. <http://doi.org/10.1016/j.schres.2012.03.020>
- Wykes, T., Reeder, C., Landau, S., Everitt, B., Knapp, M., Patel, A., & Romeo, R. (2007). Cognitive remediation therapy in schizophrenia: randomised controlled trial. *The British Journal of Psychiatry*, 190, 421–427.
<http://doi.org/10.1192/bjp.bp.106.026575>
- Wykes, T., Reeder, C., Landau, S., Matthiasson, P., Haworth, E., & Hutchinson, C. (2009). Does age matter? Effects of cognitive rehabilitation across the age span. *Schizophrenia Research*, 113(2–3), 252–258.
<http://doi.org/10.1016/j.schres.2009.05.025>
- Wykes, T., & Spaulding, W. D. (2011). Thinking about the future cognitive remediation therapy--what works and could we do better? *Schizophrenia Bulletin*, 37 Suppl 2, S80-90. <http://doi.org/10.1093/schbul/sbr064>
- Zai, G., Robbins, T. W., Sahakian, B. J., & Kennedy, J. L. (2016). A review of molecular genetic studies of neurocognitive deficits in schizophrenia. *Neuroscience & Biobehavioral Reviews*, 72, 50–67.
<http://doi.org/10.1016/j.neubiorev.2016.10.024>
- Zhang, J.-P., Burdick, K. E., Lencz, T., & Malhotra, A. K. (2010). Meta-analysis of genetic variation in DTNBP1 and general cognitive ability. *Biological Psychiatry*, 68(12), 1126–1133. <http://doi.org/10.1016/j.biopsych.2010.09.016>

Appendix

Appendix A

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Appendix B

Sample Characteristics, Predictor Variables and Cognitive Outcome Domains for Articles Included in Review

			CRT arm characteristics: Inpatients/Outpatients Mean Age (SD), [range] Mean Years Education (SD) Mean Est. Current IQ (SD) % Male	Active treatment intervention	Control treatment intervention	Pred. N	Predictor variables	Outcome Domains
Author (year), Country	Study Design	Sample N (CRT)						
Ahmed et al. (2015), USA	RCT	78 (42)	Inpatients 40.38 (10.97) 10.11 (2.49) 95.48 (13.85) 85.71%	Posit Science auditory & visual training	Group facilitated computer games	5	Covariates: est. Current IQ, years of education, program (forensic vs mental health), treatment hours Primary analysis: Antipsychotic dose	MCCB composite and domain scores: SoP, Attn/Vig, WM, Verbl, VisL, R-PS
Bark et al. (2003), USA	Secondary analysis of RCT, Medalia et al. (2000)	54 (36)	Inpatients 35.00 (7.07) 10.44 (2.14) NR 66.67%	Neuropsychologi cal Educational Approach to Remediation (NEAR)	Treatment as usual	8	PANSS general, positive and negative symptom subscales PANSS depression, cognitive, excitement, negative, and positive factor	Verbl&M, R-PS
Benoit et al. (2016), Canada	Single arm, pre-post trial	20 (20)	NR 35.55 (9.52) 11.63 (2.08) 90.30 (11.89) 65.00%	Math Arena™ (Sunburst Technology) and Thinkin' Things™ Collections 1, 2, 3 (Endmark Corp.)	Na	3	BCIS Self-Reflectiveness, BCIS Self-Certainty, Est. current IQ	CogState Research Battery (CSRB) composite and domain scores: SoP, Attn/Vig, WM, VisL, Verbl, R-PS

Biagianti et al. (2016), USA	Secondary analysis of 3 RCTs; Fisher et al. (2015), 2 ongoing	131 (131)	Outpatients 34.11 (14.55) 12.60 (2.36) 101.18 (12.54) 71.76%	Posit Science auditory training; incentivised with per session payments	Na	3	APS Plateau (<i>training task improvement on summary</i>) Covariates: Age, Baseline cognition	MCCB composite and domain scores: SoP, WM, Verbl&M, VisL&M, R-PS
Bosia et al. (2007), Italy	RCT	50 (27)	Outpatients NR NR NR NR	Cogpack (Marker Software)	1 hour computer-aided treatment and 2 hours supplementary occupational treatment each week	1	COMT allele	BACS, VerbM, WM, PsyM SoP, Attn, VerbF, R-PS
Bosia, Bechi et al. (2014), Italy	Single arm, pre-post trial	86 (86)	Outpatients 34.01 (2.46) 11.72 (2.78) 86.04 (12.25) 61.63%	Cogpack (Marker Software)	Na	11	COMT genotype, 5-HT1A-R genotype Covariates: Age, years of education, duration of illness, PANSS negative score, est. current IQ, baseline WCST Age, years of education, est. current IQ, duration of illness, PANSS negative, positive, general, total	R-PS

Bosia, Zanoletti et al. (2014), Italy	Single arm, pre-post trial	98 (98)	Outpatients 34.68 (9.84) 11.72 (2.48) 85.63 (12.17) 61.22%	Cogpack (Marker Software)	Na	4	COMT Genotype, Medication type (clozapine vs other) Covariates: Age, Years education	BACS, VerbM, WM, PsyM SoP, SoP, VerbF, R-PS
Bowie et al. (2014), Canada, USA	Secondary analysis of RCT; Bowie et al. (2012) early course and chronic CRT subgroups	39 (39)	Outpatients 40.08 (10.27) 13.40 (1.56) NR NR	Cogpack V5.1 (Marker Software), PSSCogRehab (Psychological Software Services), and Scientific Brain Training PRO (HAPPYneuron, Inc.) computer-based exercises	Na	2	Stage of illness (recent onset vs chronic), Duration of illness	BACS composite & domains, VerbM, WM, PsyM SoP, SoP, VerbF, ExeFun
Buonocore et al. (2017), Poland	Single arm, pre-post trial	98 (98)	Outpatients 33.98 (9.71) 11.67 (2.55) 86.27 (11.39) 59%	Cogpack (Marker Software)	Na	1	Treatment duration (3 mths vs 6 mths)	VerbM, WM, PsyM, SoP, VerbF, R-PS
Burton et al. (2015), USA	Secondary analysis of RCT, Twamley et al. (2012)	41 (20)	Outpatients* 48.0 (8.6)* 13.10 (1.7)* 65.83%*	Compensatory Cognitive Training (CCT)		3	COMT allele Covariates:* Ethnic minority, Premorbid IQ (*not included in summary; see Twamley et al. 2011)	Prospective memory Attn, VerbL&M, ExeFun

Burton et al. (2011), USA	Secondary analysis of RCT, Twamley et al. (2012)	69 (23)	Outpatients 44.4 (10.4) 13.3 (1.8) NR 65.2%	Compensatory Cognitive Training (CCT)	Standard pharmacotherapy	2	Baseline clinical insight (PANSS insight) Baseline cognitive insight (BCIS SR-SC - self-reflectiveness minus self-certainty)	Prospective memory, Attn, VerbL&M, VerbF, ExeFun, SoP, WM
Cella & Wykes (2017), UK	Secondary analysis of RCT, Reeder et al. (2017)	38 (38)	Outpatient 38.7 (10.1) 13.5 (2.6) NR 70%	CIRCuiTS	Na	6	Total tasks completed, Ave. tasks/session, Errorless learning, Total strategies selected, Total useful strategies used, Therapeutic alliance	VisM, R-PS
Choi and Medalia (2010)	Randomised to one of two treatment arms	72 (57)	Outpatients 38.18 (6.39) 11.41 (3.86) NR 65.5%	Arithmetic learning programs (How the West was 1 + 3 x 4, basic and motivationally enhanced versions)	Sample of convenience - treatment as usual	5	Baseline arithmetic skill, Treatment Self-Regulation Questionnaire, Baseline CPT-IP false positives, Intrinsic Motivation Inventory, Perceived Competency Scale Learning condition	Attn, Arithmetic skill
Choi et al. (2010), USA	3 mth follow-up							
Dickinson et al. (2010), USA	RCT; data combined from two parallel trials	62 (34)	Outpatients 46.9 (6.6) 12.2 (1.8) NR 65.7%	Computer-Assisted Cognitive Remediation for Schizophrenia; incentivised with payment for sessions	Game-like computer activities with low cognitive load	1	Age	Cognitive composites: Attn, WM, VerbL&M, VisL&M, ExeFun, SoP

Farreny et al. (2016), Spain	Secondary analysis of RCT; Farreny et al. (2012) REPYFLEC completors	62 (29)	Outpatients 39.5 (8.5) NR NR 65.5%	REPYFLEC		16	Sex, education, age, duration of illness, no. sessions attended, antipsychotic dose; PANSS symptoms (5); baseline verbal memory, baseline SoP, baseline ExeFun (5) Confirmatory analysis: Baseline BADS, WMS-III LM-II, TMT-B; baseline PANSS positive, excited & disorganised	BADS ExeFun composite
Farreny et al. (2013), Spain	Secondary analysis of RCT; Farreny et al. (2012)	62 (29)	Outpatients 39.5 (8.5) NR NR 65.5%	REPYFLEC	Stimulating and socializing activities Leisure control group (e.g., card games, board games, "coffee & talk")	2	PANSS negative symptoms (Kay et al., 1987) PANSS negative symptoms (Wallwork et al., 2012)	BADS ExeFun composite
Fisher et al. (2009), USA	RCT	55 (29)	Outpatients 42.86 (10.07) 13.48 (2.01) 103.55 (13.21) 68.97%	Posit Science auditory training; incentivised with per session payments	Computer games	1	Training task progression score (<i>training task improvement on summary</i>)	MCCB composite & domain scores: SoP, VerbWM, VerBL, VerbM, NonVerbWM, VisL, VisM, R-PS

Fisher et al. (2010), USA	Extension and follow up of RCT; Fisher et al. (2009)	32 (22)	Outpatients 45.95 (7.82) 13.32 (5.41) NR 77.27%	Posit Science auditory training (50 hrs) Posit Science auditory, visual & cognitive training (100 hrs); incentivised with per session payments	Computer games	1	Training dose	MCCB composite & domain scores: SoP, VerbWM, Verbl, VerbM, R-PS
Fisher et al. (2015), USA	RCT	86 (43)	Outpatients 21.70 (3.26) 12.88 (1.60) 102.63 (12.12) 72.09%	Posit Science auditory training; incentivised with per session payments	Computer games	2	Baseline reward anticipation (Temporal Experience of Pleasure Scale) Training task improvement (<i>not included in summary; see Bigaianti 2016</i>)	MCCB composite & domain scores: SoP, WM, Verbl, VerbM, VisL, VisM, R-PS
Fisher et al. (2016), USA	Extension and follow up of RCT; Fisher et al. (2009)	87 (46)	Outpatients 40.70 (11.81) 13.24 (2.25) 101.11 (16.69) 73.91%	Posit Science auditory training; incentivised with per session payments	Computer games	1	Change in serum BDNF level	MCCB composite & domain scores: SoP, WM, Verbl, VerbM, VisL, VisM, R-PS

Fiszdon et al. (2016), USA	RCT	75 (50)	Outpatients 47.22 (9.17) 12.5 (1.84) 94.40 (15.16) 78%	Drill & practice: PSS CogReHab (Bracy); payment for participation Strategy: Cognitive Remediation Therapy (Delahunty & Morice): WM A & B modules	Treatment as usual	3	Training task improvement: Sequenced recall digits auditory, Shape/place, Verbal memory	Distal: Attn/Vig, SoP, WM, Verbl&M, VerbF, VisL&M, ExeFun Proximal (training task): PSS CogReHab Attn/WM, Visuospatial memory, Verbal Memory
Franck et al. (2013), France	Parallel group randomized clinical with two active treatment arms	138 (92)	Outpatients 33.51 (6.88) NR NR 72.83%	1. RECOS 2. Cognitive Remediation Therapy (Delahunty & Morice) FesKits	Na	3	Premorbid IQ, Age, Intervention (specific vs general)	BADS ExeFun composite
Gomar et al. (2015), Spain	Parallel group randomized controlled trial	130 (43)	Inpatients & Outpatients 46.68 (9.97) 9.30 (2.86) 84.23 (16.05) 67.44%		1. Computerised typing program 2. Treatment as usual	2	Age, Antipsychotic dose	BADS ExeFun composite (Spanish ver.) RBMT VerbM & VisM (Spanish ver.)

Greenwood et al. (2011), UK	Secondary analysis of 3 RCTs (Wykes, Newton et al. 2007, Wykes, Reeder et al. 2007, Wykes et al. 2003) and 1 single arm trial, Wykes et al.	87 (61)	Outpatients* 36.09 (10.93)* 12.29 (2.04)* 96.84 (13.56)* 78.0%*	Cognitive Remediation Therapy (Delahunty & Morice)	Treatment as usual	2	COMT genotype Medication status <i>(not included in summary; see Wykes et al. 2007)</i>	R-PS WM
Haut et al. (2010), USA	Quasi-randomised controlled trial	30 (10)	Outpatients 36.4 (9.2) 13.2 (1.4) NR 80%	Cogpack (Marker Software)	1. Cognitive behavioural social skills training 2. Healthy control	11	Age, sex, ethnicity, years of education, Global Assessment Scale, SAPS & SANS global, BPRS total, no. hospitalisations, time since 1st & last hospitalization	WM: Picture 2-back Semantic memory: Lexical decision-hard
Kontis et al. (2013), UK	Secondary analysis of two studies; 1 RCT (Wykes, Reeder et al. 2007) and 1 single-arm trial.	134 (85)	Outpatients 38.07 (10.65) NR NR 68.24%	Cognitive Remediation Therapy (Delahunty & Morice)	Treatment as usual	6	Age, Age Group (younger < 40 years > older), Cognitive reserve proxy (premorbid IQ, WAIS-III vocabulary) Covariates: baseline cognition, baseline PANSS total	WM R-PS - cognitive flexibility R-PS - planning

Kurtz et al. (2007), USA	RCT	42 (23)	Outpatients 36.7 (12.2) 13.1 (1.9) NR 60.0%	PSS CogReHab (Bracy)	Computer skills training	5	Hours of training, Age, Age of illness onset, Duration of illness, no. hospitalisations	WM <i>Predictors not examined, VerbM, VisM, SoP, R-PS</i>
Lopez-Luengo and Vazquez (2003), Spain	RCT	24 (13)	Outpatients 34.7 (8.4) NR 92.0%	Attention Process Training (Sohlberg & Mateer)	Treatment as usual	6	Age, sex, duration of illness, no. of hospitalisations, diagnosis Training sessions	Attn, Verbl&M, ExeFun
Mak et al. (2013), Poland	RCT	81 (41)	Outpatients 34.0 (11.07) NR 46.34%	RehaCom - attention/concentration & topological memory	Treatment as usual	2	BDNF rs6265 polymorphism COMT rs4680 polymorphism	SoP, R-PS
Medalia et al. (2000, 2001), USA	RCT with parallel CRT treatment arms	54 (36)	Inpatients 35.00 (7.07) 10.44 (2.14) NR 66.67%	Neuropsychological Educational Approach to Remediation (NEAR)	Treatment as usual	2	Education level Type of medication (a/typical)	Verbl, VerbM, R-PS

Medalia et al. (2005), USA	Secondary analysis of 3 studies - 1 RCT (Medalia et al., 2001) and 2 single arm trials (1. Choi & Medalia, 2005, 2. Unknown	36 (36)	Inpatients 35.00 (7.07) 10.44 (2.14) NR 66.67%	Neuropsychological Educational Approach to Remediation (NEAR)	Na	17	Sex, age, socioeconomic status, baseline VerbM & R-PS, diagnosis (SZ vs SZA), comorbid substance abuse, treatment refractoriness <i>(contradictory reporting re PANSS scores so excluded)</i>	VerbM, R-PS
Panizzutti et al. (2013), USA	Secondary analysis of 2 RCTs, Fisher et al. (2009, 2015)	48 (48)	Outpatients 33.6 (13.1) NR 102.3 (14.3) 70.8%	Posit Science auditory training; incentivised with per session payments	Na	6	Age, gender, ethnicity, est. current IQ, anticholinergic burden, COMT gene	MCCB composite (global cognition)
Penadés et al. (2016), Spain	Secondary analysis of RCT, Penades et al., (2013)	35 (17)	Outpatient 36.35 (13.16) 11.59 (3.06) NR 70.59%	Cognitive Remediation Therapy (Delahunty & Morice)	Social skills training	12	Symptoms (PANSS)*, baseline cognition (WM, SoP, VerbM, VisM, ExeFun), age, years of education, duration of illness, antipsychotic dose, no. of hospitalisations Cortical thickness <i>*excluded from summary as subscales not reported</i>	Domain scores, WM, SoP, VerbM, NonVerbM, ExeFun Total cognitive improvement

Reeder et al. (2017), UK	RCT	93 (46)	Outpatient 38.7 (10.1) 13.5 (2.6) NR 70%	CIRCuiTS	Treatment as Usual	4	Total no. sessions, Mean no. task completed/session, Mean no. useful strategies used/session, Use of independent sessions	WM, VisM, R-PS Vis, R-PS Verb
Twamley et al. (2011), USA	Secondary analysis of RCT, Twamley et al. (2012)	33 (23)	Outpatients 44.4 (10.4) 13.3 (1.8) NR 65.2%	Compensatory Cognitive Training (CCT)	Standard pharmacotherapy	18	Age; sex; ethnicity; duration of illness; diagnosis; education; est. premorbid IQ; antipsychotic dose; attendance rate; participant rating of intervention; severity of positive, negative (PANSS) & depressive (HDRS) symptoms, self-reported cognitive problems & strategy use (CPSA), baseline Attn/Vig, baseline VerbM; baseline prospective memory	Attn/Vig, VerbM, Prospective Memory
Vinogradov et al. (2009), USA	Secondary analysis of RCT, Fisher et al. (2009)	49 (25)	Outpatients 41.44 (11.06) 12.88 (2.22) NR 68.0%	Posit Science auditory training; incentivised with per session payments	Computer games	4	Age, Est. current IQ, symptom severity, anticholinergic activity	MCCB composite & domain scores: SoP, VerbWM, Verbl, VerbM, NonVerbWM, VisL, VisM, R-PS

Wykes et al. (1999), UK	RCT	33 (17)	Majority outpatients 36.5 [19-55] 12 [9-16] NR 76.47%	Cognitive Remediation Therapy (Delahunty & Morice)	Intensive occupational therapy	8	Baseline cognitive performance (1 per regression), Age, Sex, Baseline symptoms (BPRS, Rosenberg Self-Esteem) Baseline functioning (Social Behaviour Schedule, Present State Exam), Medication type (a/typical)	WM, R-PS - cognitive flexibility, R-PS - planning
Wykes, Reeder et al. (2007), UK	RCT	85 (43)	Outpatients* 36.0 (NR)* NR NR 73.0%*	Cognitive Remediation Therapy (Delahunty & Morice)	Treatment as usual	1	Medication type (a/typical)	WM, R-PS - cognitive flexibility, R-PS - planning
Wykes, Newton et al. (2007), UK	RCT	40 (21)	Inpatients & Outpatients 18.8 (2.6) NR 85.3 (10.9) 62.0%	Cognitive Remediation Therapy (Delahunty & Morice)	Treatment as usual	1	Medication type (a/typical)	WM, R-PS - cognitive flexibility, R-PS - planning
Wykes et al. (2009), UK	Secondary analysis of RCT, Wykes, Reeder et al. (2007)	85 (43)	Outpatients* 36.0 (NR)* NR NR 73.0%*	Cognitive Remediation Therapy (Delahunty & Morice)	Treatment as usual	1	Age group (< 40 years >) Baseline self-esteem	WM, R-PS - cognitive flexibility, R-PS - planning

Note: APS = auditory processing speed; Attn = attention; Attn/Vig = attention/vigilance; BACS = Brief Assessment of Cognition; BADS = The Behavioural Assessment of the Dysexecutive Syndrome; BICS = Beck Cognitive Insight Scale; BPRS = Brief Psychiatric Rating Scale; CPSA = Cognitive Problems and Strategies Assessment; CPT-IP = continuous performance test – identical pairs; CRT = cognitive remediation therapy; est. = estimated; ExeFun = executive

functioning; HDRS = Hamilton Depression Rating Scale; LM-II = Logical Memory II; MCCB = *MATRICES Consensus Cognitive Battery*; na = not applicable; no. = number; NonVerbWM = nonverbal working memory; NR = not reported; PANSS = Positive and Negative Syndrome Scale; Pred. N = number of predictors in study; PsyMSoP = psychomotor speed of processing; R-PS = reasoning and problem solving; RBMT = Rivermead Behavioural Memory Test; RCT = randomised controlled trial; SAPS = Scale for the Assessment of Positive Symptoms; SANS = Scale for the Assessment of Negative Symptoms; SoP = speed of processing, SZ = schizophrenia; SZA = schizoaffective disorder; TMT-B = trial making test B; VerbFlu = verbal fluency; VerbL = verbal learning; VerbM = verbal memory; VisL = visual learning, VisM = visual memory; WAIS-III = Wechsler Adult Intelligence Scale 3rd edition; WCST = Wisconsin Card Sorting Test; WM = working memory; WMS-II = Wechsler Memory Scale 3rd edition

Appendix C

Statistical Technique and Outcome by Cognitive Domain/Measure

Author (year), Country	Analysis strategy; Statistical Technique	Cognitive Outcome variables	Results of statistical significance	No statistically significant results
Ahmed et al. (2015), USA	Modified ITT where post-treatment data was available. 1. Mixed model MANCOVA 2. Correlations	MCCB composite and domain scores: SoP: TMT-A, BACS Symbol Coding, Category fluency - animals Attn/Vig: CPT-IP WM: WMS-III Spatial Span, L-N Span Verbl: HVLT immediate recall VisL: BVMt immediate recall R-PS: NAB Mazes SocCog: Mayer-Salovey-Caruso Emotional Intelligence Test - managing emotions	Curr. IQ x MCCB Comp.: $F(1,74) = 7.99, p = 0.006, \eta^2_p = 0.098$ Curr. IQ x MCCB Attn: $F(1,74) = 3.99, p = 0.047, \eta^2_p = 0.051$ (Note: main effect across treatment group; direction unclear)	1st gen. antipsychotic dose x MCCB Comp. 2nd gen. antipsychotic dose x MCCB Comp. Curr. IQ x MCCB SoP, WM, Verbl, VisL, R-PS, SocCog Training hours and education x MCCB Comp. & Dom. Program (forensic vs mental health) x MCCB Comp. & Dom.
Bark et al. (2003), USA	Pearson correlations examining change scores	Verbl&M: WMS-R Logical Memory I, CVLT R-PS: WAIS-R Comprehension, ILS Problem-Solving	Greater baseline cognitive impairment, as measured on the PANSS, was associated with less change on the ILS-PS. Baseline PANSS Cognitive Factor x ILS-PS: $r = -0.453, p < 0.006$ (Note: not significant when analysed by separate treatment arm)	No significant associations found between: PANSS Positive, Negative & General Subscales or PANSS Positive, Negative, Excitement, Cognitive and Depression factors and WMS-R LM, CVLT, WAIS-R-CT PANSS Positive, Negative, General Subscales; PANSS Positive, Negative, Excitement, Depression factors; ILS- PS

Benoit et al. (2016), Canada	Partial correlations examining change scores	CogState Research Battery (CSRB) composite and domain scores: SoP: Detection Test Attn/Vig: Identification Test WM: One- & Two-Back Memory Test VisL: One Card Learning Test VerbL: International Shopping List Test R-PS: Groton Maze Learning Test SocCog: Social Emotional Cognition Test	Controlling for baseline cognitive performance, higher cognitive insight (being lower baseline BCIS self-certainty scores) was associated with improved cognition Baseline cognitive insight (self-certainty) x CSRB SoP: $r = -0.476$, $p = 0.039$, 23% var. explained Baseline cognitive insight (self-certainty) x CSRB VisM: $r = -0.464$, $p = 0.045$, 22% var. explained	Curr. IQ x CSRB composite, SoP, Attn, WM, VisL, VisM, VerbL, VerbM, R-PS, SocCog BCIS self-reflectiveness x CSRB composite, SoP, Attn, WM, VisL, VisM, VerbL, VerbM, R-PS, SocCog BCIS self-certainty x CSRB composite, Attn, WM, VisL, VerbL, VerbM, R-PS, SocCog
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Bigaianti et al. (2016), USA	ITT analysis. Latent growth curve model	MCCB composite and domain scores: SoP: TMT-A, Category fluency - animals WM: WMS-III Spatial San, L-N Span Verbl&M: HVLIT immediate & delayed recall VisL&M: BVMT immediate & delayed recall R-PS: NAB Mazes (recent onset used D-KEFS Tower of London)	Controlling for baseline cognitive performance, better baseline cognitive performance predicted better post-intervention performance. Baseline MCCB Comp. x MCCB Comp: $\beta = .80, p < .001$ Baseline MCCB SoP x MCCB SoP: $\beta = .66, p < .001$ Baseline MCCB VisWM x MCCB VisWM: $\beta = .54, p < .001$ Baseline MCCB VerbWM x MCCB VerbWM: $\beta = .64, p < .001$ Baseline MCCB Verbl x MCCB Verbl: $\beta = .76, p < .001$ Baseline MCCB VerbM x MCCB VerbM: $\beta = .65, p < .001$ Baseline MCCB VisL x MCCB VisL: $\beta = .69, p < .001$ Baseline MCCB VisM x MCCB VisM: $\beta = .56, p < .001$ Baseline MCCB R-PS x MCCB R-PS: $\beta = .39, p < .001$ Controlling for baseline cognitive performance, a slower APS plateau reached after 20 hours of training predicted lower post-intervention cognitive gains . APS Plateau x MCCB Comp.: $\beta = -.15, p < .05$ APS Plateau x MCCB SoP: $\beta = -.20, p < .001$ APS Plateau x MCCB VerbWM: $\beta = -.29, p < .001$ APS Plateau x MCCB VisWM: $\beta = -.22, p < .01$ APS Plateau x MCCB VisL: $\beta = -.23, p < .001$ APS Plateau x MCCB VisM: $\beta = -.30, p < .001$ APS Plateau x MCCB R-PS: $\beta = -.27, p < .05$	Controlling for baseline cognitive performance, APS Plateau x MCCB Verbl APS Plateau x MCCB VerbM Age did not predict post-intervention cognitive performance
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Bosia et al. (2007), Italy	Repeated Measures ANOVA Mixed Model	BACS, VerbM: words recall WM: digit sequencing PsyMot SoP: token motor task Sel. Attn: symbol coding VerbF: semantic fluency, letter fluency (COWAT) R-PS: Tower of London CogFlex: WCST Sus. Attn: CPT	Significant time by group interaction for WCST performance (no. preservative errors): $F(3,45) = 2.86, p = .04$. Met carriers on active treatment showed greater improvement compared to Val/Val on placebo	COMT allele x all other cognitive outcome measures
Bosia, Bechi et al. (2014), Italy	1. GLM Analysis using proxy effect size to evaluate cognitive change; pre-post change score divided by standard error of sample 2. Pearson's correlations	R-PS: WCST perseverative errors	Years of education x R-PS: $F = 5.04, p < .033$ Baseline WCST x R-PS: $F = 55.26, p < .0001$ COMT genotype x R-PS: $F = 4.42, p < .045$ COMT genotype by 5-HT1A-R genotype interaction x R-PS: $F = 5.49, p < .026$ (<i>COMT Met Carriers by 5-HT1A G/G group made greater improvements compared to COMT Val/Val by 5-HT1A-R G/G group</i>)	5-HT1A-R genotype Age, duration of illness, est. current IQ, PANSS positive, negative, general & total scores
Bosia, Zanoletti et al. (2014), Italy	GLM Analysis using proxy effect size to evaluate cognitive change; pre-post change score divided by standard error of sample.	BACS, VerbM: words recall WM: digit sequencing PsyMot SoP: token motor task SoP: symbol coding VerbF: semantic fluency, letter fluency (COWAT) R-PS: Tower of London	Val/Val participants treated with other antipsychotics, being characterised by higher dopamine D2 blocking activity, showed worse performances on SoP (BACS symbol coding; $p = .04$) compared to COMT Met carriers treated with other antipsychotics, COMT genotype by medication type interaction x SoP: $F = 5.86, p = 0.018$	Age, years of education, COMT genotype, medication type x BACS VerbM, WM, SoP, PsyMot SoP, VerbF, R-PS COMT allele by medication type interaction x BACS VerbM, WM, PsyMot SoP, VerbF, R-PS

Bowie et al. (2014), Canada, USA	Pearson correlations examining residual change scores	BACS composite & domains, VerbM: words recall WM: digit sequencing PsyMot SoP: token motor task SoP: symbol coding VerbF: semantic fluency, letter fluency (COWAT) ExeFun: Tower of London	Early course of illness predicted greater cognitive improvement across PsyMot SoP, ExeFun, SoP domains. Stage of illness x BACS PsyMot SoP: $F(1,35) = 6.2, p = 0.017, n^2_p = 0.15$ Stage of illness x BACS ExeFun.: $F(1,35) = 7.5, p = 0.009, n^2_p = 0.18$ Stage of illness x BACS SoP: $F(1,35) = 4.1, p = 0.049, n^2_p = 0.11$ A shorter duration of illness was associated with greater change on BACS composite score, Duration of illness x BACS Comp.: $r = -0.43, p = 0.001$	Stage of illness x BACS VerbF, WM, VerbM Duration of illness x BACS domain level scores
Buonocore et al. (2017), Poland	Repeated measures ANOVA	BACS - VerbM: words recall; WM: digit sequencing; PsychMot: token motor task; SoP: symbol coding; VerbF: semantic & letter production; R-PS: Tower of London	Duration x R-PS, group who completed 72 sessions of CRT had sig. higher scores compared to those who completed 36 sessions ($F = 2.65, p = .03$)	Duration x VerbM, WM, PsychMot, SoP, VerbF
Burton et al. (2015), USA	Mixed factorial ANOVA	Prospective memory: Memory for Intentions Screening Test Attn: WAIS-III Digit Span Forward Verbl&M: HVLT-R immediate & delayed recall ExeFun: WCST		COMT allele x change in cognition Ethnic minority status, premorbid IQ x change in cognition

Burton et al. (2011), USA	Pearson correlations examining change scores on neuropsychological measures	Prospective memory: Memory for Intentions Screening Test Attn: WAIS-III Digit Span Forward VerbL&M: HVLT-R VerbF: COWAT ExeFun: WCST SoP: WAIS-III Digit Symbol WM: WAIS-III Letter-Number Sequencing		Baseline clinical insight x prospective memory, Attn, VerbL&M, VerbF, ExeFun, SoP, WM Baseline cognitive insight x prospective memory, Attn, VerbL&M, VerbF, ExeFun, SoP, WM
Cella & Wykes (2017), UK	Correlations between therapy characteristics and change scores	VisM: ROCF immediate recall R-PS Vis: WCST % errors	Massed practice-ave. tasks/session x VisM: $r = -0.4, p < 0.05$; x R-PS Vis: $r = -0.38, p < 0.05$ Strategy use-useful x VisM: $r = -0.29, p < 0.05$ Therapeutic alliance x VisM: $r = 0.38, p < 0.05$; x R-PS Vis: $r = -0.35, p < 0.05$	Massed practice-ttl tasks comp.: VisM & R-PS Vis Errorless learning: VisM & R-PS Vis Strategy use-ttl no. strategies selected: VisM & R-PS Vis
Choi and Medalia (2010)	ANOVA Step-wise multiple regression	Attn: CPT-IP no. false positives Arithmetic skill: arithmetic test used by Columbia Universit Teacher's College (measure of task learning)	The motivational math game condition made greater gains in arithmetic and Attn relative to the basic math group & control, Learning condition x arithmetic improvement: $p = .03$ Learning condition x Attn improvement: $p = < .05$	Baseline arithmetic ability, treatment self-regulation, intrinsic motivation, Attn x post-arithmetic ability
Choi et al. (2010), USA	ANCOVA (treatment intensity)		Higher perceived self-competency scores predicted greater change in arithmetic scores at post-assessment & 3 mth follow up. Baseline Perceived Competency Scale (PCS) x post-arithmetic ability: $\beta = .33, p = .02$ Baseline Perceived Competency Scale (PCS) x 3 mth follow-up arithmetic ability: $\beta = .38, p = .03$	Treatment intensity x arithmetic improvement

Dickinson et al. (2010), USA	Modified ITT; min. 3 sessions and completed post-assessments Correlations	Cognitive composites: Attn: Stroop colour/word interference; CPT-II WM: N-back, WAIS-III LNS Verbl&M + VisL&M (episodic memory): HVLt learning & delay; RBANS Story memory test learning & delay; BVMT learning & delay ExeFun: BACS Tower of London, D-KEFS Twenty Questions Task, TMT-B SoP: WAIS-III Digit Symbol, D-KEFS TMT-A, Stroop colour/word colour naming		Age x Attn, WM, Verbl&M/VisL&M, ExeFun, SoP
Farreny et al. (2016), Spain	1. Partial correlations (partial Spearman correlation for TMT-A, TMT-B) examining BADS outcome 2. Confirmatory stepwise regression	BADS ExeFun composite - Rule Shift Cards, Action Program, Key Search, Temporal Judgment, Zoo Map, Six Elements	Better baseline ExeFun predicted post-intervention improvement in executive functioning: Baseline BADS ExeFun x BADS ExeFun: $B = 0.77$ (95% CI = 0.53-1.05), $p < .0001$, partial $R^2 = 0.60$ <i>Better baseline ExeFun and baseline PANSS disorganised subscale predicted improvement at 6 mth follow-up in ExeFun:</i> <i>Baseline BADS ExeFun x BADS f/up ExeFun: $B = 0.85$ (0.46-1.59), $p < .0002$, partial $R^2 = 0.33$</i> <i>Baseline PANSS disorganised x BADS f/up ExeFun: $B = 0.52$ (0.05-1.03), $p < .03$, partial $R^2 = 0.19$</i>	Sex, education, age, antipsychotic dose, duration of illness, no. sessions attended, PANSS (negative, positive, disorganised, excited, depressed), WMS-III LM-I, WMS-III LM-II, TMT-A, TMT-B x BADS executive functioning

Farreny et al. (2013), Spain	Correlation	BADS ExeFun composite		Baseline PANSS negative symptoms x BADS ExeFun composite
Fisher et al. (2009), USA	Pearson's bivariate correlations	MCCB composite & domain scores: SoP: symbol coding, category fluency, TMT-A VerbWM: Letter-number span VerbL, VerbM: HVLt learning & recall NonVerbWM: Spatial Span VisL, VisM: BVMT learning & recall R-PS: BACS Tower of London SocCog: Mayer-Salovey-Caruso Emotional Intelligence Test - managing emotions	Training task progress predicts improvement in VerbWM and global cognition. Auditory training progression score x MCCB VerbWM: $r = 0.46, p < .03$ Auditory training progression score x MCCB Composite: $r = 0.39, p < .04$	Auditory training progression score x all other MCCB domain scores
Fisher et al. (2010), USA	Repeated measures ANCOVA (baseline to 6 mth follow up)	MCCB composite & domain scores: SoP: symbol coding, category fluency, TMT-A VerbWM: Letter-number span VerbL, VerbM: HVLt learning & recall R-PS: BACS Tower of London, TMT-B	Higher training dose (100 vs 50hrs) and/or broad-spectrum training predicted durable gains on measures of global cognition (composite) and SoP, Training dose x MCCB composite: $p = .02$ Training dose x MCCB SoP: $p = .04$	Training dose x MCCB VerbWM, VerbL, VerbM, R-PS

Fisher et al. (2015), USA	Pearson's correlations	MCCB composite & domain scores: SoP: category fluency, TMT-A WM: Letter-number span, WMS-III Spatial Span VerbL, VerbM: HVLT learning & recall VisL, VisM: BVMT learning & recall R-PS: D-KEFS Tower Test	Baseline reward anticipation (Temporal Experience of Pleasure Scale) was significantly associated with improvements in global cognition and VerbM. Baseline reward anticipation x MCCB Composite: $r = 0.52$, $p < .01$ Baseline reward anticipation x MCCB VerbM: $r = 0.51$, $p = .01$ <i>Improvement in auditory processing speed was significantly associated with improvements in global cognition. Auditory processing speed improvement x MCCB Global cognition: $r = -0.47$, $p < .01$</i>	Baseline reward anticipation x SoP, WM, VisL/M, R-PS
Fisher et al. (2016), USA	ITT with last observation carried forward. Pearson's correlations	MCCB composite & domain scores: SoP: symbol coding, category fluency, TMT-A WM: Letter-number span, WMS-III Spatial Span VerbL, VerbM: HVLT learning & recall VisL, VisM: BVMT learning & recall R-PS: BACS Tower of London		Change in serum BDNF level x MCCB composite and domain scores

Fiszdon et al. (2016), USA	Pearson correlations examining standardised residual change scores	Distal: Attn/Vig: WAIS-III Digit sequencing task, CPT SoP: TMT-A WM: WAIS-III Digits backward VerbL&M: CVLT-II 1-5, WMS-R LM immediate & delayed VerbF: FAS VisL&M: ROCFT immediate & delayed ExeFun: WCST, TMT-B Proximal (training task): PSS CogReHab Attn/WM: Sequenced Recall Digits - auditory Visuospatial memory: Shape/Place Verbal Memory - visual word list recall	Improvement on training tasks associated with auditory working memory, visuospatial memory, and verbal memory predicted greater change across measures of WM, VisuosL, VerbL&M. Post assessment, Seq. recall digits auditory x CVLT-II: $r = 0.370, p < 0.01$ Seq. recall digits auditory x Rey-O immediate: $r = 0.493, p < 0.001$ Seq. recall digits auditory x WAIS-III Digits backward: $r = 0.425, p < 0.001$ Shape/place x CVLT-II: $r = 0.333, p < 0.01$ Shape/place x Rey-O immediate: $r = 0.340, p < 0.01$ Shape/place x WAIS-III Digits backward: $r = 0.304, p < 0.05$ Verbal memory x CVLT-II: $r = 0.290, p < 0.05$ Verbal memory x Rey-O immediate: $r = 0.308, p < 0.05$ Verbal memory x WAIS-III Digits backward: $r = 0.338, p < 0.01$ <i>2 month follow up</i> <i>Seq. recall digits auditory x CVLT-II: $r = 0.280, p < 0.05$</i> Higher premorbid IQ, as measured on the French NART, was associated with less improvement on BADS at post-assessment. Premorbid IQ x BADS executive functioning composite: $p = 0.017$	All other interactions between proximal (computer training task) measures Training task improvement x Attn/Vig, SoP, VerbM, VerbF, VisM, ExeFun
Franck et al. (2013), France	Linear mixed model, including interactions	BADS ExeFun composite: Rule Shift Cards, Action Program, Key Search, Temporal Judgment, Zoo Map, Six Elements	Higher premorbid IQ, as measured on the French NART, was associated with less improvement on BADS at post-assessment. Premorbid IQ x BADS executive functioning composite: $p = 0.017$	Age x BADS executive functioning composite at either post-assessment or 6-month follow-up No evidence that a specific (RECOS) compared to a general (CRT) response to baseline cognitive profile predicts response

Gomar et al. (2015), Spain	ITT; missing observations multiply imputed Correlations examining change scores	BADS ExeFun composite (Spanish ver.) RBMT VerbM & VisM (Spanish ver.)		Age x BADS ExeFun composite & RBMT VerbM & VisM Antipsychotic dose x BADS executive functioning composite & RBMT
Greenwood et al. (2011), UK	Mixed model ANOVA	R-PS: WCST categories achieved & perseverative errors WM: WAIS-III Digit span		COMT polymorphism x R-PS, WM <i>Medication status x R-PS, WM</i>
Haut et al. (2010), USA	Correlations examining change scores	WM: Picture 2-back Semantic memory: Lexical decision-hard	Years of education x Picture 2-back: $r = 0.32, p = 0.22$	Age, sex, ethnicity, education years, Global Assessment Scale, SAPS & SANS global, BPRS total, no. hospitalisations, time since 1st & last hospitalisation x Semantic memory Age, sex, ethnicity, Global Assessment Scale, SAPS & SANS global, BPRS total, no. hospitalisations, time since 1st & last hospitalisation x WM

Kontis et al. (2013), UK	Hierarchical regression	WM: WAIS-III Digit span R-PS - cognitive flexibility: WCST (no. categories achieved) R-PS - planning: Modified Six Elements Test, Total Score	Overall, increased Age was associated with poorer post-treatment WM, after controlling for premorbid IQ ($B = -0.1$, 95% CI = $-0.14 - -0.06$, $t = -4.56$, $df = 109$, $p < 0.001$, $r^2 = 0.578$) or vocabulary ($B = -0.1$, 95% CI = $-0.14 - -0.05$, $t = -4.37$, $df = 111$, $p < 0.001$, $r^2 = 0.516$) Premorbid IQ was associated with WM improvements in younger ($B = 1.93$, 95% CI = $0.34 - 3.53$, $t = 2.42$, $df = 63$, $p = 0.018$) but not older participants For both younger and older participants, baseline WM ($B = 0.53$, 95% CI = $0.34 - 0.73$, $t = 5.54$, $df = 63$, $p < .001$; $B = 0.50$, 95% CI = $0.28 - 0.73$, $t = 4.60$, $df = 41$, $p < .001$, respectively), R-PS cognitive flexibility ($B = 0.68$, 95% CI = $0.46 - 0.91$, $t = 5.97$, $df = 62$, $p < .001$; $B = 0.58$, 95% CI = $0.30 - 0.86$, $t = 4.15$, $df = 38$, $p < .001$, respectively), and R-PS planning ($B = 0.33$, 95% CI = $0.10 - 0.60$, $t = 2.82$, $df = 61$, $p = .006$; $B = 0.51$, 95% CI = $0.24 - 0.77$, $t = 3.90$, $df = 38$, $p < .001$, respectively) predicted post-intervention performance within the respective domains Symptoms were significant predictors of R-PS planning performance in older participants, controlling for premorbid IQ ($B = -0.03$, 95% CI = $-0.06, -0.002$, $t = -2.18$, $df = 37$, $p = 0.035$) or vocabulary ($B = -0.03$, 95% CI = $-0.06, -0.001$, $t = -2.08$, $df = 39$, $p = 0.044$), but not younger participants	Within the respective Age Groups, Premorbid IQ x R-PS cognitive flexibility and planning Vocabulary x WM, R-PS cognitive flexibility and planning PANSS Total (controlling for measures of cognitive reserve) x WM, R-PS cognitive flexibility
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Kurtz et al. (2007), USA	ITT including those who had completed a min. 15 hrs training	WM: WAIS-III Digit Span, Arithmetic, Letter-Number Sequencing <i>Predictors not examined, VerbM: WMS-III Logical Memory I and II, CVLT-II VisM: ROCFT SoP: WAIS-III Digit Symbol and Symbol Search, TMT, Grooved Pegboard, Letter Fluency R-PS: WAIS-III Block Design, The Penn Conditional Exclusion Test, The Booklet Category Test</i>	Exploratory analysis of predictors of WM change scores only (no other stat. sig. domain changes), Training hours x WM improvement Age, age of illness onset, duration of illness, no. of hospitalisations x WM improvement
Lopez-Luengo and Vazquez (2003), Spain	1. Repeated measure ANCOVA 2. Correlation examining change scores	Attn: CPT, Cancellation task, Dichotic listening task, Dual task, PASAT, TMT A & B, Everyday Attention Questionnaire VerbL&M: Spain-Complutense Verbal Learning Test ExeFun: WCST	1. Age, gender, duration of illness, no. of hospitalisations, diagnosis x Attn, VerbL&M, ExeFun change scores 2. No. training sessions x Attn, VerbL&M, ExeFun change scores
Mak et al. (2013), Poland Medalia et al. (2000, 2001), USA	Mann-Whitney test Repeated measure ANCOVA	SoP: TMT-A, Stroop R-PS: WCST, TMT-B VerbL: CVLT VerbM: WMS-R Logical Memory R-PS: WAIS-R Comprehension, ILS Problem-Solving	Neither COMT rs4680 or BDNF rs6265 polymorphisms were associated with SoP or R-PS improvements Education level x VerbL, VerbM, R-PS Type of medication x VerbL, VerbM, R-PS

Medalia et al. (2005), USA	ANOVA examining RCI Status (improvement vs non-improvement on min. 1 DV)	VerbM: WMS-R Logical Memory R-PS: WAIS-R Comprehension, ILS Problem-Solving	Participants with a shorter inpatient stay were more likely to be Improvers, Treatment refractoriness x RCI status: $F(1,30) = 11.34, p = .002$	No significant associations found between: Sex, age, socioeconomic status x RCI status Baseline VerbM x RCI status Baseline R-PS x RCI status Diagnosis, presence of comorbid substance abuse x RCI status
Panizzutti et al. (2013), USA	Set-based analysis examining the aggregate effect of common variation in the COMT gene (42 SNPs) Examined change score	MCCB composite (global cognition)	Prelim. evidence that the aggregate effect of variation in the COMT gene (SNPs mostly located in the 3' end of the COMT gene) is associated with cognitive improvement, $p = 0.02$. Rs165599 x global cognition: $BETA = -0.29, p = 0.004$ Rs9265 x global cognition: $BETA = -0.27, p = 0.006$ Rs5993891 x global cognition: $BETA = -0.33, p = 0.021$ Rs758373 x global cognition: $BETA = -0.33, p = 0.021$ Rs2239395 x global cognition: $BETA = -0.33, p = 0.021$ Rs2240713 x global cognition: $BETA = -0.36, p = 0.027$ Rs739368 x global cognition: $BETA = 0.66, p = 0.040$ Rs1544325 x global cognition: $BETA = 0.19, p = 0.043$ Evidence that those with the A/A homozygotes on rs165599 showed greater improvement in global cognition compared to those with G/G homozygotes: $p < 0.05$	Age, gender, ethnicity, est. current IQ, anticholinergic burden x global cognition

Penadés et al. (2016), Spain	ITT analysis examining change scores; 1. Linear regression models (stepwise) 2. Correlations using DODS design matrix provided by QDEC in FreeSurfer	Total cognitive improvement (increment of change scores) Domain scores, WM: WAIS-III Digit Span, Letter-Number Sequencing, Arithmetic. SoP: WAIS-III Digit Symbol, TMT-A. VerbM: RAVLT, WMS-III Logical Memory I & II. NonVerbM: WMS-III Visual Reproduction I & II, Faces I & II. ExeFun: WCST, TMT-B, ToL	1. Baseline ExeFun x total cognitive improvement: $t = -2823$, $p = 0.008$ Baseline NonVerbM x total cognitive improvement: $t = -3755$, $p < 0.001$ 2. Greater cortical thickness in frontal and temporal lobes x NonVerbM improvement	Baseline symptoms, age, years of education, length of illness, daily antipsychotic doses, number of hospitalisations x cognitive domain Baseline WM, SoP, VerbM x total cognitive improvement
Reeder et al. (2017), UK	Correlations between therapy characteristics and change scores	WM: digit span VisM: ROCF immediate recall R-PS Verb: Hayling Sentence Completion R-PS Vis: WCST % errors	No. sessions completed x R-PS Vis: $r = -0.31$ Tasks completed x VisM: $r = 0.39$ No. useful strategies x VisM: $r = 0.24$	No. sessions x WM, VisM, R-PS Verb Tasks completed/session: WM, R-PS No. useful strategies: WM, R-PS Independent session use: all

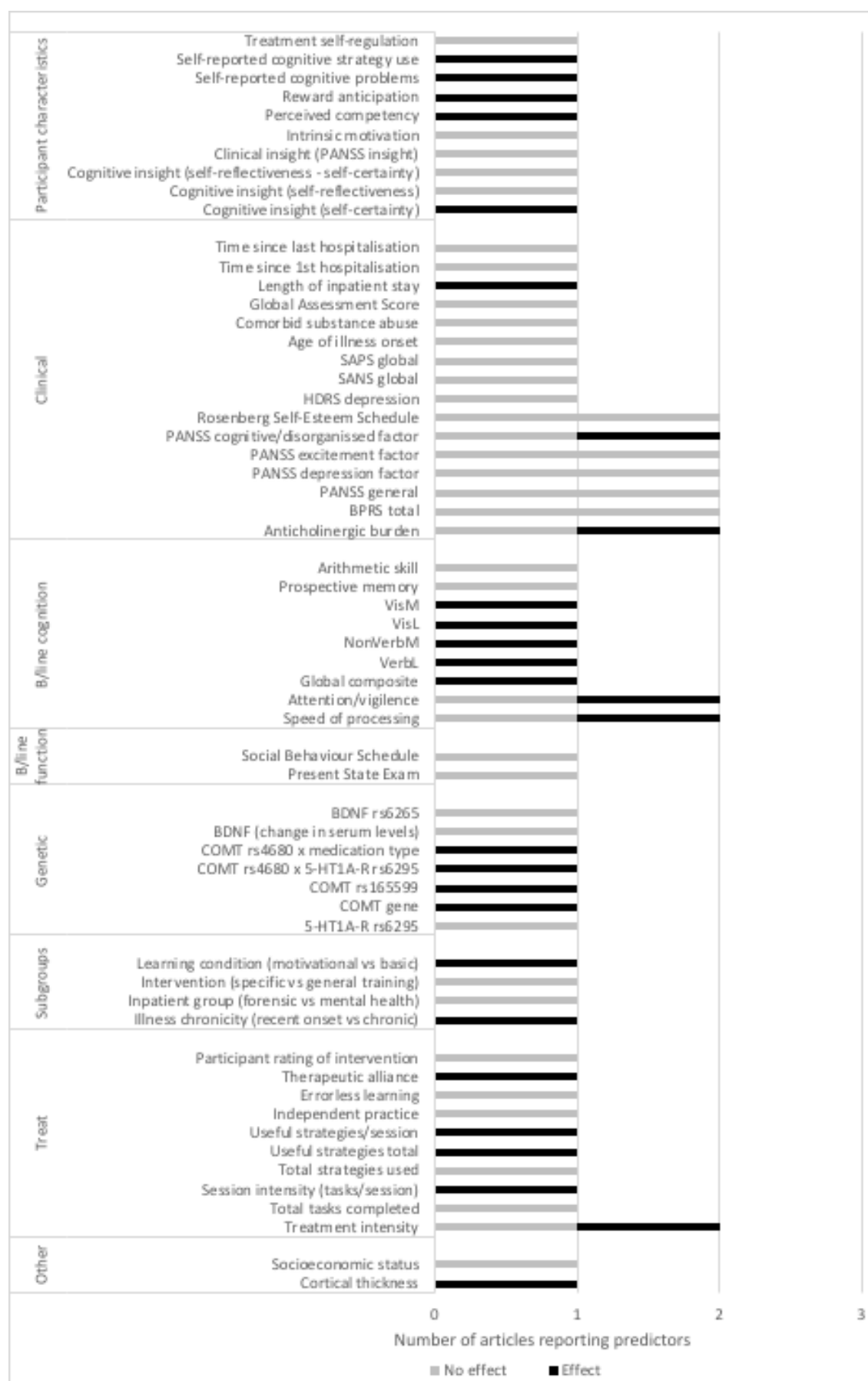
Twamley et al. (2011), USA	Pearson correlations examining change scores (post - pre) for variables showing sig. time x group effects T-tests for categorical variables	Attn/Vig: digit span forward VerbM: HVLt-R % retained <i>Prospective memory: MIST (6mth f/up only)</i>	Higher level of negative symptom severity ($r = .45, p = .045$), higher levels of self-reported cognitive problems ($r = .48, p = .033$), and lower baseline digit span forward ($r = -.73, p < .001$) were associated with improvement in Attn/Vig Higher level of negative symptom severity ($r = .50, p = .025$) and lower self-reported cognitive strategy use ($r = -.48, p = .033$) were associated with improvement in VerbM (% retained); no longer sig. at 6mths f/up <i>Age ($r = .48, p = .027$) was associated with improvements in prospective memory at 6mths f/up only; not included in summary</i>	Age, estimated premorbid IQ, education level, duration of illness, PANSS positive, HDRS depression, antipsychotic dosage, attendance rate, participant rating of intervention, sex, ethnic minority status, diagnosis x Attn/Vig & VerbM <i>Estimated premorbid IQ, education level, duration of illness, PANSS positive & negative, HDRS depression, antipsychotic dosage, attendance rate, participant rating of intervention, self-reported cognitive problems sex, ethnic minority status, diagnosis x prospective memory at 6mths f/up</i>
Vinogradov et al. (2009), USA	Pearson correlations examining z score change (post - pre) Multiple regression with global cognition z score change as DV Multivariate ANOVA examining difference between lowest and highest quartiles of serum anticholinergic activity	MCCB composite and domain scores: SoP: symbol coding, category fluency, TMT-A VerbWM: Letter-number span VerbL, VerbM: HVLt learning & recall NonVerbWM: Spatial Span VisL, VisM: BVMT learning & recall R-PS: BACS Tower of London SocCog: Mayer-Salovey-Caruso Emotional Intelligence Test - managing emotions	Anticholinergic activity was negatively correlated with improvement in global cognition ($r = -.46, p = .02$) and uniquely accounted for 20% of the variance in global cognition change (partial $r = .20$); participants with lower serum anticholinergic activity showed greater cognitive gains compared to those with higher anticholinergic activity	Age, IQ, symptom severity x improvement in global cognition Anticholinergic activity x SoP, VerbWM, NonVerbWM, VerbL&M, VisL&M, R-PS

Wykes et al. (1999), UK	Logistic regression using forward stepwise method, examining domain level improvement threshold index (pre - post change / baseline std error for ttl sample. If => 50% of within domain tests increased min. 1 std error of ttl sample's baseline score, categorised as improved within domain)	WM: Visual span, sentence span, WAIS-R Digit span, Dual span R-PS - cognitive flexibility: Hayling Sentence Completion Task, TMT B - A, Response inhibition, COWAT, Stroop Neuropsychological Screening Test, WCST R-PS - planning: Tower of London, Six Elements		Baseline performance on measures of cognition, age, sex, Social Behaviour Schedule, Present State Exam, Brief Psychiatric Rating Scale, Rosenberg Self Esteem Schedule x Domain level improvement threshold indices Trend level indication that CRT participants taking atypical antipsychotics benefited more than those taking typical antipsychotics (78% vs 13%) however not a significant predictor in logistic regression
Wykes, Reeder et al. (2007), UK	Linear mixed modelling	WM: WAIS-III Digit Span total R-PS - cognitive flexibility: WCST categories achieved R-PS - planning: BADS profile score	CRT/medication type interaction such that participants receiving CRT who were taking either clozapine or typical medication benefited more on BADS compared to those receiving other atypical medications	Medication type x WM, R-PS cognitive flexibility
Wykes, Newton et al. (2007), UK	Linear mixed modelling	WM: WAIS-III Digit Span total R-PS - cognitive flexibility: WCST categories achieved R-PS - planning: Modified Six Elements Test total score		Medication type x WM, R-PS cognitive flexibility and planning

Wykes et al. (2009), UK	Linear mixed modelling	WM: WAIS-III Digit Span total R-PS - cognitive flexibility: WCST categories achieved R-PS - planning: BADS profile score	<i>Age group x R-PS cognitive flexibility at 6 mths follow-up, For the younger age group there was a significant effect of CRT on cognitive flexibility ($z = 3.09$, $p = 0.002$, est. increase 1.5 points, 95% CI from 0.5 to 2.4)</i>	For the older age group there was no effect of CRT on R-PS cognitive flexibility or planning at post- treatment or 6 mth follow-up
			<i>Age group x R-PS planning at post-treatment, For the younger age group, there was a significant effect of CRT on planning ($z = 2.6$, $p = 0.011$, estimated increase 2.1 points, 95% CI from 0.5 to 3.7) but not at follow-up</i>	Younger age group x cognitive flexibility at post-treatment Younger age group x planning at follow-up
				Age group x WM Self-esteem x WM, R-PS cognitive flexibility & planning

Note: APS = auditory processing speed; Attn = attention; Attn/Vig = attention/vigilance; BACS = Brief Assessment of Cognition; BADS = The Behavioural Assessment of the Dysexecutive Syndrome; BICS = Beck Cognitive Insight Scale; BPRS = Brief Psychiatric Rating Scale; BVMT = Brief Visuospatial Memory Test; CogFlex = cognitive flexibility; Comp. = composite; CPSA = Cognitive Problems and Strategies Assessment; CPT-IP = continuous performance test – identical pairs; CRT = cognitive remediation therapy; est. = estimated; CVLT = California Verbal Learning Test; Curr. = current; D-KEFS = Delis-Kaplan Executive Function System; Dom. = domain; DV = dependent variable; ExeFun = executive functioning; gen. = generation; HDRS = Hamilton Depression Rating Scale; HVLTL = Hopkins Verbal Learning Test; ILS = Independent Living Scale; ITT = intention to treat; LM-I/LM-II = Logical Memory I/II; LN Span = letter-number span; MCCB = *MATRICES Consensus Cognitive Battery*; MIST = Memory for Intentions Screening Test; na = not applicable; NART = National Adult Reading Test; no. = number; NonVerbWM = nonverbal working memory; NR = not reported; PANSS = Positive and Negative Syndrome Scale; PASAT = Paced Auditory Serial Addition Task; Pred. = Predictor; PsyMSoP = psychomotor speed of processing; R-PS = reasoning and problem solving; RBMT = Rivermead Behavioural Memory Test; RCI = reliable change index; RCT = randomised controlled trial; ROCFT = Rey-Osterrieth Complex Figure; SAPS = Scale for the Assessment of Positive Symptoms; SANS = Scale for the Assessment of Negative Symptoms; SoP = speed of processing, SocCog = social cognition; Sus. = sustained; SZ = schizophrenia; SZA = schizoaffective disorder; TMT-B = trial making test B; ToL = Tower of London; VerbFlu = verbal fluency; VerbL = verbal learning; VerbM = verbal memory; VerbWM = verbal working memory; VisL = visual learning, VisM = visual memory; WAIS-III = Wechsler Adult Intelligence Scale 3rd edition; WCST = Wisconsin Card Sorting Test; WM = working memory; WMS = Wechsler Memory Scale.

Appendix D



Supplementary Figure D4. Horizontal bar graph showing count of articles that examined predictors of cognitive response to cognitive remediation therapy, grouped by category. Grey = no association found. Black = association found.

Note. Reflects predictors with less than 3 articles. Est. = estimated; BPRS = Brief Psychiatric Rating Scale; PANSS = Positive and Negative Syndrome Scale; SZ = schizophrenia; SZA = schizoaffective disorder; No. = number; hrs = hours.

Appendix E
Strength of Evidence Summary by Predictor Variable

Predictor of cognitive outcome		Strength of evidence for combined analyses of specific predictors; % of articles ^a				
Category / Predictor	Count of Articles	A priori hypothesis	Theory/ evidence based	Measured pre-randomisation	Valid measure	Test of interaction
Demographics						
Age	17	6%	6%	Na	Na	12%
Age Group (< 40 years >)	2	100%	100%	Na	Na	50%
Years of Education	8		13%	Na	Na	13%
Sex	7		29%	Na	Na	
Est. Current IQ	5			60%	100%	
Est. Premorbid IQ	3	33%	33%	33%	100%	33%
Ethnicity	3		33%	Na	Na	
Baseline clinical						
Duration of Illness	7	14%	29%	Na	Na	
PANSS negative	5	33%	50%	83%	100%	
No. hospitalisations	5			Na	Na	
Antipsychotic type	5	20%	20%	Na	Na	40%
Antipsychotic dose	5		20%	Na	Na	
PANSS positive	4	25%	25%	75%	100%	
PANSS total	3			25%	100%	25%
SZ vs SZA diagnosis	3		67%	Na	Na	
Baseline cognition						
R-PS	7		14%	57%	100%	43%
VerbM	4		50%	100%	100%	25%
WM	3			67%	100%	67%
Treatment						
Training dose	8	25%	38%	Na	Na	13%
Task improvement	3	33%	67%	Na	Na	33%
Genetic						
COMT Val158Met	6	67%	100%	Na	Na	67%

Note. Blanks mean that no included articles met criteria. ^aPercentage of articles that met criteria, for example, PANSS positive, 1 of 4 studies (25%) reported a priori hypothesis about the relationship between positive symptoms and cognitive outcome.

Appendix F

Summary of Studies to Examine Dynamic and Static Measures of Learning Potential (LP) and Task Performance in Schizophrenia Research

Author (year)	LP Type ^a	LP Measure	Intervention	Outcome Domain	Outcome
Learning Potential					
Wiedl et al. (1999)	Dynamic, categoric	WCST using Schöttke algorithm ^b based on the number of correct responses; learners = improved at least 15 points; non-learners = improved less than 15 points	Yes; 1 hour of IPT training	Skills acquisition	Was able to predict non-learners and high scorers but required inclusion of education level to predict learners. Learners with high educational level improved; learners with low educational level did not.
Wiedl et al. (2001)	Dynamic, categoric	WCST using Schottke algorithm based on the number of correct responses; learners = improved at least 15 points; non-learners = improved less than 15 points	No	Attention	Learner types differed in their level of target discrimination ability (d'); sig. diff. between high scorers and non-learners. Using discriminant analysis, learner status was predicted by d' (Attn), response criterion & distractibility.
Woonings et al. (2002)	Dynamic, categoric & dimensional	WCST using Schöttke algorithm based on the number of categories, being the number of times 10 correct sorts were achieved	Yes; 8 mths rehabilitation including CRT	Rehabilitation Evaluation Hall & Baker (REHAB) General Behaviour subscale	Static measures (trial 1) of WCST was sig. correlated with post rehabilitation change. No association with dynamic measure of WCST (trial 3). Of categoric learner groups, post rehabilitation change did not differ by group status (i.e., non-learner vs learner).
Sergi et al. (2005)	Static, dimensional Dynamic, dimensional	Static = WCST trial 1 Dynamic = WCST trial 3 over trial 1 gain	Yes; 1 hour of work skills training	Work skill acquisition	13% of variance in work skill tasks was explained by trial 1 WCST; LP explained a further 15%. After 3 mths, figures were 6% and 13%.

Kurtz & Wexler (2006)	Dynamic, categoric (also measured CVLT-II without training so a static measure of LP)	Group first split based on standard WCST into intact and impaired; impaired engaged in train-test. Median split of change in pre-post t-scores for total errors used to differentiate strong-learner from poor-learners	No	Cognition & functioning measures	Cognition: groups strong- vs poor-learner significant difference on brief test of attention, CVLT-II. Functioning: no difference between learning groups.
Fiszdon et al. (2006)	Static, categoric Dynamic, categoric	Static = Matrix Reasoning scaled score Dynamic = CVLT-II using Schöttke algorithm based on recall	No (test-train-test semantic clustering training)	Readiness for psychosocial rehabilitation	MicroModule Learning Test; MMLT performance: High scorers differed from non-learners. Using regression, both static and dynamic were predictive of outcome, with dynamic accounting for 8.6% over and above static; when LP in first, static did not account for unique variance above and beyond dynamic measure.
Rempfer et al. (2006) (mixed diagnoses; 1/3 SZ)	Dynamic, categoric	WCST using Schöttke algorithm based on the number of correct responses; learners = improved at least 15 points; non-learners = improved less than 15 points	No	Cognition	Sig. diff. between high scorers and non-learners across measures of Attn, WM, SoP. Learners were not sig. diff. from either group. Learners were sig. diff. from non-learners on measures of VerbM & WM.
Tenhula et al. (2007)	Dynamic, dimensional	WCST residualised change scores from baseline to post-instruction for raw number of errors & residualised change scores for correct categories. CT residualised change score from baseline to post-WCST training for number of errors	Yes; 8 x social skills training	Social skills Performance on Category Test	Were able to generalise training on WCST to CT. WCST improvements and ability to generalise was unrelated to performance on measure of social skill. WCST was related to concurrent social functioning such that poorer WCST was related to lower social competence.
Vaskinn et al. (2008)	Static, categoric	CVLT-II; List 1 recall & learning slope to derive non-learners, learners, high-achievers	No	Validation	Differences in semantic clustering techniques across groups.

Watzke et al. (2008)	Dynamic, categoric	WCST using Schöttke algorithm based on the number of correct responses; learners = improved at least 15 points; non-learners = improved less than 15 points	Yes	Vocational rehabilitation	Work capability: at program termination, learners were sig. diff. than non-learners on measure of work capability. At 3 mth follow-up, learners had a higher level of functioning compared with non-learners.
Watzke et al. (2009)	Static, categoric Dynamic, categoric	Static = WCST trial 1 Dynamic = WCST trial 3	Yes	Vocational rehabilitation	LP was a better predictor of work capability and the level of vocational reintegration than basic cognitive performance.
Vaskinn et al. (2009)	Dynamic, categoric & dimensional	Categoric: WCST using Schöttke algorithm based on the number of correct responses Dimensional: WCST using gain scores based on number of correct	No	Cognition Social functioning	Dimensional: Cognition: category switching was sig. associated with LP, explaining circa 20% of variance. Social functioning: LP did not predict. Categoric: Not conducted due to small group sizes. Concluded that categorical approach has limited sensitivity in a normal IQ sample.
Kurtz et al. (2010)	Static, dimensional Dynamic, dimensional	Static = CVLT-II gain score Dynamic = WCST gain score	No	Functioning (UPSA)	CVLT-II was sig. correlated with UPSA. WCST was not correlated with UPSA. Neither measure of LP explained variance in UPSA beyond baseline neurocognition, negative symptoms and estimated verbal IQ.
Fiszdon et al. (2010)	Dynamic, categoric & dimensional	CVLT-II a/ list 1 score; b/ list 5 score; c/ categorical LP index based on confidence interval around list 5 score; d/ regression residuals regressing list 1 on list 5 scores; e/ post-pre- learning score; f/ gain score	Yes (CRT D&M & NET) but was not analysed in terms of LP	Global functioning	Quality of Life Scale (QLS) @ intake & 2 mths: pre-training was not predictive of QLS. Post, pre-post, & regression were all sig. correlated with intake and 2 mth QLS. Gain scores deemed as not good by study authors.

Rempfer et al. (2011)	Static, dimensional Dynamic, dimensional	Static = WCST trial 1 Dynamic = WCST trial 3 over trial 1 gain	Yes; 9 x grocery shopping skills training	Skills acquisition	Dynamic not static version of WCST explained sig. portion of variance in TOGSS (Test of Grocery Shopping Skills); however no pre-post change in TOGSS.
Rempfer et al. (2012)	Dynamic, categoric	Rey Osterrieth Complex Figure Test (ROCFT) using Schöttke algorithm to determine high performers, learners & non-learners based on change in recall performance	No	Cognition	Groups differed sig. in performance improvements on recall; learners demonstrated sig. greater improvements compared to other two groups.
Davidson et al. (2016)	Dynamic, categoric	CVLT-II; list 1 vs list 3 (post list 2 train) regression	Yes; 4 wks PSS CogReHab & 4 wks CRT D&M	Skills acquisition	Pre-post performance on computerised cognitive tasks (PSS CogReHab); improvement on Verbal Memory & Visual-Spatial skill was predicted by LP not List 1; thus support for incremental.

Training Task Performance

Fisdon et al. (2005) (mixed diagnoses)	Training task performance	Digit span (equivalent to digit span forward, a measure of both Attn & WM)	Yes; NET for six months + work skills training	Normalisation on trained memory task	Attn, VerbM, test latency & hostility accounted for over 70% variance and had 83% accuracy in predicting normalisation.
Adcock et al. (2009)	Training task performance	Auditory training progression	Yes; auditory training	Global cognition	Cognition: improvement on training tasks correlated with improvement on verbal WM and Global cognition.
Fisher et al. (2009)	Training task performance	Auditory training progression	Yes; auditory training	Verbal memory	Greater progression showed most improvement on measures of VerbM and Cognitive composite.
Surti et al. (2011)	Training task performance	Auditory training progression	Yes; auditory training	Visual memory	Achievement on 4 training tasks were sig. associated with improvement in VisM.

Murthy et al. (2012)	Training task performance	Auditory training processing speed: learners = change ≥ 40 ms; non-learners = change < 40 ms	Yes; auditory training	Cognition	CogState® composite scores at 3rd assessment were sig. diff. between learners and non-learners. Learners also showed improvement over baseline scores whereas non-learners returned to 1st assessment performance.
Fisher et al. (2015)	Training task performance	Auditory training processing speed	Yes; auditory training	Cognition	Decrease in auditory processing speed (i.e., better performance) was sig. associated with gains in cognitive composite
Biagianti et al. (2016)	Training task performance	Auditory training processing speed	Yes; auditory training	Cognition	APS plateau (target engagement) mediates response to CRT, being associated with improvements in global cognition, SoP, Verbal WM, R-PS outcomes after controlling for baseline cognition. Baseline cognitive performance underpinned APS plateau.
Fiszdon et al. (2016)	Training task performance	PSS CogReHab training tasks (drill & practice) and strategy focused training	Yes; max. 40 sessions over 8 weeks	Cognition	Cognition: improvement on training tasks correlated with improvement on verbal learning & memory, VisM, & WM.
Tarasenko et al. (2016)	Training task performance	Range of measures from 1st hour of auditory processing training; baseline & best auditory processing speed score, number of levels completed, % improvement post training.	Yes; auditory training	Cognition, demographics, clinical	Demographic/clinical: None Cognition: baseline & best APS correlated with all cognitive domains; APS improvements correlated with verbal memory; training levels completed marginally associated with auditory attention. Level 1 baseline & best APS sig. negatively correlated with auditory Attn & WM i.e., better auditory Attn & WM = better able to discriminate shorter sounds. Also, VerbM correlated with improvement at level 1 and after 1 hour.

Note. APS = auditory processing speed; Attn = attention; CRT = cognitive remediation therapy; CRT D&M = Delahunty & Morice's CRT; CT = Category Test; CVLT-II = California Verbal Learning Test-II; diff. = difference; IPT = Integrated Psychological Therapy Programme; Mths = months; NET = Neurocognitive Enhancement Therapy; PSS CogReHab = Psychological Software Services CogReHab software; R-PS = reasoning and problem solving; sig. = significant; SoP = speed of processing; UPSA = UCSD Performance-Based Skills Assessment; VerbM = verbal memory; VisM = visual memory; WCST = Wisconsin Card Sorting Test; wks = weeks; WM = working memory.

^aOf the LP Types, 'dynamic' involved a test-train-test paradigm, 'static' involved repeated trials but no period of instruction, 'categoric' referred to analysing LP scores as a categoric variable, typically classifying participants into learner/non-learner groups, 'dimensional' referred to analysing LP score as a continuous variable. ^bSchottke algorithm, see "Attentional characteristics of schizophrenia patients differing in learning proficiency on the Wisconsin Card Sorting Test", by K. H. Wiedl, J. Wienöbst, H. H. Schöttke, M. F. Green, K. H. Nuechterlein, 2001, Schizophrenia Bulletin, 27, pp. 690-691.

Appendix G

Certificates of Ethical Approval: Study 2, CRT Intervention

G1: St Vincent's Hospital, Certificate of Ethical Approval



**ST VINCENT'S
HOSPITAL**
MELBOURNE

A FACILITY OF ST VINCENT'S HEALTH AUSTRALIA

St Vincent's Hospital
(Melbourne) Limited
ABN 22 052 110 755

41 Victoria Parade Fitzroy VIC 3065
PO Box 2900 Fitzroy VIC 3065

Telephone 03 9288 2211
Facsimile 03 9285 3399
www.svhm.org.au

17 September 2014

Prof Susan Rossell
Monash Alfred Psychiatry Research Centre (MAPrc)
Level 4, 607 St Kilda Road
Melbourne VIC 3004

Dear Prof Rossell,

HREC-A Protocol number: HREC-A 101/14

'Investigating factors that influence the efficacy of cognitive remediation therapy in individuals with schizophrenia.'

The St Vincent's Hospital (Melbourne) Human Research Ethics Committee-A has reviewed and approved the aforementioned study.

Approval Status: FINAL

Period of Approval: 17 September 2014 – 17 September 2018

Ethical approval is given in accordance with the research conforming to the *National Health and Medical Research Council Act 1992* and the *National Statement on Ethical Conduct in Human Research (2007)*.

Ethical and governance approval is given for this research project to be conducted at the following sites:

- St Vincent's Hospital (Melbourne)

Approved documents

The following documents have been reviewed and approved:

Document	Version	Date
National Ethics Application Form (NEAF)	2	10/09/2014
Victorian Specific Module (VSM)	2	09/09/2014
Research Protocol	1.3	09/09/2014
Participant Information and Consent Form (PICF)	1.1	09/09/2014

UNDER THE STEWARDSHIP OF MARY AIKENHEAD MINISTRIES

Facilities
St Vincent's Hospital Melbourne
Caritas Christi Hospice
St George's Health Service
Prague House

Participant Withdrawal of Consent Form	1.0	20/08/2014
Recruitment Poster	1.2	09/09/2014
Information Sheet	1.1	14/08/2014
Recruitment Brochure	1.3	09/09/2014
CRT – Pre-assessment Pack	11	01/08/2014
CRT – Patient Group Baseline Assessment Pack	11	01/08/2014

St Vincent's HREC-A Protocol number: HREC-A 101/14
Please quote these numbers on all Correspondence

Approval is subject to:

- The Principal Researcher is to ensure that all associate researchers are aware of the terms of approval and to ensure the project is conducted as specified in the application and in accordance with the National Statement on Ethical Conduct in Human Research (2007).
- Immediate notification to the Research Governance Unit of any serious adverse events on participants.
- Immediate notification of any unforeseen events that may affect the continuing ethical acceptability of the project;
- Notification and reasons for ceasing the project prior to its expected date of completion;
- Notification of proposed amendments to the study;
- Submission of an annual report, due on the anniversary date of approval, for the duration of the study.
- Submission of reviewing HREC approval for any proposed modifications to the project;
- Submission of a final report and papers published on completion of project;
- Projects may be subject to an audit or any other form of monitoring by the Research Governance Unit at any time.

The HREC wishes you and your colleagues every success in your research.

Yours sincerely,



Anita Arndt
Senior Administrative Officer and HREC-A Secretary
Research Governance Unit
St Vincent's Hospital (Melbourne)

G2: Swinburne University of Technology, Certificate of Ethical Approval

5/5/2015 RE: SHR Project 2014/251 - Ethics clearance (Expedited Review: SVH HREC-A 101/14) [CORRECTED Chief Investigator]

RE: SHR Project 2014/251 - Ethics clearance (Expedited Review: SVH HREC-A 101/14) [CORRECTED Chief Investigator]

Astrid Nordmann

Sent: Monday, 29 September 2014 10:04 AM

To: Susan Rossell

Cc: RES Ethics; Maree Reser

To: Prof. Rossell, FHAD

Dear Prof. Rossell

SHR Project 2014/251 Investigating factors that influence the efficacy of cognitive remediation therapy in individuals with schizophrenia

Prof. Susan Rossell, FHAD; Ms Maree Reser (Student researcher)

Approved Duration: 29/09/2014 to 17/09/2018

I refer to the application for Swinburne ethics clearance for the above Swinburne-administered collaborative project based on the prior ethical review of the protocol and related documents by St Vincent's Hospital Human Research Ethics Committee (SVH HREC Project No HREC-A 101/14).

Relevant documentation pertaining to the application was received in hard copy on 23 September 2014, and additional documents submitted via email on 26 September 2014. Expedited ethical review of the proposed research was undertaken by a delegate of Swinburne's Human Research Ethics Committee (SUHREC) significantly on the basis of the St Vincent's Hospital HREC review.

I am pleased to advise that, as submitted to date and concerns Swinburne, ethics clearance has been given for the project to proceed in line with standard on-going ethics clearance conditions here outlined. (Nb St Vincent's Hospital HREC may need to be apprised of the Swinburne ethics clearance. Should the proposed research, as regards research conducted under Swinburne auspices, require additional/other HREC review, please forward a copy of the clearances issued and approved consent instruments being used to our office for the record as soon as practicable. Should further detail or documentation be required for endorsement, we will let you know.)

- All human research activity undertaken under Swinburne auspices must conform to Swinburne and external regulatory standards, including the current *National Statement on Ethical Conduct in Human Research* and with respect to secure data use, retention and disposal.
- The named Swinburne Chief Investigator/Supervisor remains responsible for any personnel appointed to or associated with the project being made aware of ethics clearance conditions, including research and consent procedures or instruments approved. Any change in chief investigator/supervisor requires timely notification and SUHREC endorsement.
- The above project has been approved as submitted for ethical review by or on behalf of SUHREC. Amendments to approved procedures or instruments ordinarily require prior ethical appraisal/ clearance. SUHREC must be notified immediately or as soon as possible thereafter of (a) any serious or unexpected adverse effects on participants 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. (Reports and requests made to St Vincent's Hospital HREC also being submitted to Swinburne Research for processing/endorsement may suffice.)
- A duly authorised external or internal audit of the project may be undertaken at any time.

5/5/2015

RE: SHR Project 2014/251 - Ethics clearance (Expedited Review: SVH HREC-A 101/14) [CORRECTED Chief Investigator]

Please contact the Research Ethics Office if you have any queries about Swinburne on-going ethics clearance, citing the SUHREC project number. A copy of this clearance email should be retained as part of project record-keeping.

Best wishes for the project.

Yours sincerely,
Astrid Nordmann
Acting Secretary, SUHREC

Dr Astrid Nordmann
Research Ethics Officer
Swinburne Research (H68)
Swinburne University of Technology
PO Box 218, Hawthorn, VIC 3122
Tel: +613 9214 3845
Fax: +613 9214 5267
Email: anordmann@swin.edu.au

G3: MonashHealth, Certificate of Ethical Approval

Monash Medical Centre

 3 June 2016 Prof Susan Rossell Monash Alfred Psychiatry Research Centre (MAPrc) Level 4, 607 St Kilda Road Melbourne Vic 3004	Research Support Services Monash Health Monash Medical Centre 246 Clayton Road Clayton Victoria 3168 Australia	Level 2 I Block Australia	Tel (03) 9594 4611 Fax (03) 9594 6306
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Dear Prof Rossell,

Study title: Investigating Factors that Influence the Efficacy of Cognitive Remediation Therapy in People with Schizophrenia

Monash Health HREC Ref: 16245X

Protocol number: HREC-A 101/14

Thank you for submitting a Site Specific Assessment Form for authorisation of the above project at Monash Health.

I am pleased to inform you that authorisation has been granted for this project to be conducted at the Monash Medical Centre Clayton campus of Monash Health.

The following conditions apply to this research project at your site. These conditions are additional to those imposed by the Human Research Ethics Committee that granted ethical approval:

The Principal Investigator is required to notify Research Support Services, Monash Health of the following:

1. Any change in protocol and the reason for that change together with an indication of ethical implications (if any)
2. Serious or unexpected adverse effects of project on subjects and steps taken to deal with them
3. Any unforeseen events that might affect continued ethical acceptability of the project
4. Any expiry of the insurance coverage provided in respect of sponsored trials
5. Discontinuation of the project before the expected date of completion, giving reasons
6. Any change in personnel involved in the research project including any study member resigning from Monash Health &/or the study team.

At the conclusion of the project or every twelve months if the project continues, the Principal Investigator is required to complete and forward an annual report to Research Support Services.

List of Approved Documents:

Document	Version	Date
Monash Health Participant Information and Consent Form based on Master Participant Information and Consent Form Version 2.0 dated 23/07/2015	1.0	01/03/2016
Monash Health Withdrawal of Consent Form based on Master Withdrawal of Consent Form Version 1.0 dated 20/08/2014	1.0	01/03/2016
Monash Health Booking Cover-letter based on Master Booking Cover-letter Version 1.2 dated 14/08/2014	1.0	01/03/2016
Monash Health Booking Email based on Master Booking Email Version 1 dated 01/08/2014	1.0	01/03/2016
Monash Health CRT Pre-Assessment Pack based on Master CRT Pre-Assessment Pack Version 11 dated August 2014	1.0	01/03/2016

Monash Health CRT Brochure based on Master CRT Brochure Version 2.0 dated 23/07/2015	1.0	01/03/2016
Monash Health CRT Information Flyer	1.0	18/03/2016
Monash Health CRT Baseline Assessment based on Master CRT Baseline Assessment Version 11 dated August 2014	1.0	01/03/2016
Monash Health Interest Flyer based on Master Interest Flyer Version 2.0 dated 23/07/2015	1.0	01/03/2016
Monash Health Interest Letter Personalised based on Master Interest Letter Personalised Version 2.0 dated 23/07/2016	1.0	01/03/2016
Monash Health Participant Ad based on Master Participant Ad Version 2.0 dated 23/07/2015	1.0	01/03/2016
Monash Health Participant Ad with tabs based on Master Participant Ad with tabs Version 2.0 dated 23/07/2015	1.0	01/03/2016
Monash Health Screening Phone Patients	1.0	01/03/2016

If you should have any queries about your project please contact Mr Michael Kios on 9594 4606 or via email michael.kios@monashhealth.org or Ms Deborah Dell on 9594 4605 or via email deborah.dell@monashhealth.org

Research Support Services wishes you and your colleagues every success in your research.

Yours sincerely



Dr James Doery
Deputy Committee Chair, HREC

Attachments:
Agreement X1

Cc: Ms Maree Reser
Cc: A/Prof Suresh Sundram

Checklist: Post-ethics approval requirements that must be met before a research project can commence at a study site.

Requirements	Yes/No/NA
CTN Acknowledgement for Commercially Sponsored Studies The PI must forward a copy of the CTN Acknowledgement to Research Support Services	NA
CTN Lodgement for Collaborative Group/Investigator Driven Studies The PI or nominated delegate is requested to make an appointment with the Monash Health Research Support Services contact for the study deborah.dell@monashhealth.org or michael.kios@monashhealth.org so that the lodgment may be completed by both the investigator and Research Support Services. The banking details for payment to the TGA will need to be brought along to this appointment, in order to finalise notification to the TGA. The fee for lodging a CTN is \$335.	NA
Clinical Trial Research Agreement The PI must forward an original fully executed copy of the CTRA to Research Support Services	No
Indemnity The PI must forward an original fully executed copy of the Indemnity to Research Support Services	NA
Radiation If applicable, the RGO must contact the Medical Physicist so that the study may be notified to the Radiation Risk Section of the Department of Health and Human Services.	NA
Other Commonwealth statutory requirements Ensure compliance with the following e.g. Office of the Gene Technology Regulator, NHMRC Licensing Committee, NHMRC Cellular Therapies Advisory Committee.	NA
Declaration of Interest /Gifts and Benefits It is recommended that the Monash Health Principal Investigator and research team are familiar with the "HR - Conflict of Interest (Operational)" policy and the "HR - Declaration of Gifts, Benefits & Hospitality" procedure available on PROMT. In the event that a member of the Monash Health research team for this project has an item to declare, a Declaration Form available on PROMPT should be completed and submitted to Human Resources.	Yes

MonashHealth Site Additions

Clayton Community Mental Health Service and Southern Community Mental Health Service

HREC Amendment Form

In the event that an ethically approved research project requires amendment, this form must be submitted to the reviewing HREC by the Coordinating Principal Investigator (CPI).
 The CPI is responsible for notifying all site Principal Investigators (PIs) of the amendment, in order for them to discuss it with their Research Governance Officer (RGO).
 An amendment **must not** be implemented at a site until the HREC amendment has been approved by the reviewing HREC and (if applicable) Site Specific Assessment (SSA) amendment has been authorised at the site.

Research Project Details

HREC Reference Number	HRECA-101/14	CPI for Research Project	Prof. Susan Rossell
Local Reference Number	16245X	HREC Approval Date	17.09.2014
Date of this Form	27.07.2016		
Project Title	Investigating factors that influence the efficacy of cognitive remediation therapy in people with schizophrenia.		
Mode of HREC Approval	☒ Single state only ☐ National Mutual Acceptance		
Sponsor Billing Address			
CPI Address	Monash Allied Psychiatry Research Centre, Level 4, 607 St Kilda Road, Melbourne VIC 3004		

Amendment Details

Explain the changes that have occurred or are intended (may include changes in procedure, direction of project, source/manner of recruitment, number of participants or changes to research personnel)

Two additional recruitment sites are being added:

Clayton Community Mental Health Service: intention to recruit up to 35 participants
 Southern Community Mental Health Service: intention to recruit up to 25 participants

Reason for the changes (include a comment on the impact on the research project and the participants at sites for which the reviewing HREC is responsible)

Additional participants are required to support the research project. This has no foreseeable impact on the research project or for existing participants.

Do these changes raise any ethical issues?

If Yes, identify the ethical issues

MonashHealth	
Correspondence and attachments noted by Dr James Doery, Deputy Chair HREC.	
Signed:	☐ Yes ☒ No
Date:	18.8.2016

G4: The Alfred, Certificate of Ethical Approval



ETHICS COMMITTEE CERTIFICATE OF APPROVAL

This is to certify that

Project No: 373/14

Project Title: Investigating factors that influence the efficacy of cognitive remediation therapy in people with schizophrenia.

Principal Researcher: Professor Susan Rossell

Protocol Version 1.3 dated: 25-Aug-2014

Participant Information and Consent Form Version 1.3 dated: 25-Aug-2014

was considered by the Ethics Committee on 25-Sep-2014, meets the requirements of the National Statement on Ethical Conduct in Human Research (2007) and was APPROVED on 30-Sep-2014

It is the Principal Researcher's responsibility to ensure that all researchers associated with this project are aware of the conditions of approval and which documents have been approved.

The Principal Researcher is required to notify the Secretary of the Ethics Committee, via amendment or progress report, of

- Any significant change to the project and the reason for that change, including an indication of ethical implications (if any);
- Serious adverse effects on participants and the action taken to address those effects;
- Any other unforeseen events or unexpected developments that merit notification;
- The inability of the Principal Researcher to continue in that role, or any other change in research personnel involved in the project;
- Any expiry of the insurance coverage provided with respect to sponsored clinical trials and proof of re-insurance;
- A delay of more than 12 months in the commencement of the project; and,
- Termination or closure of the project.

Additionally, the Principal Researcher is required to submit

- A Progress Report on the anniversary of approval and on completion of the project (forms to be provided);

The Ethics Committee may conduct an audit at any time.

All research subject to the Alfred Hospital Ethics Committee review must be conducted in accordance with the National Statement on Ethical Conduct in Human Research (2007).

The Alfred Hospital Ethics Committee is a properly constituted Human Research Ethics Committee in accordance with the National Statement on Ethical Conduct in Human Research (2007).

SPECIAL CONDITIONS

None

SIGNED:

Professor John J. McNeill
Chair, Ethics Committee

Please quote project number and title in all correspondence

G5: Mind Australia, Certificate of Ethical Approval



Professor Susan Rossell
 Monash Alfred Psychiatry Research Centre
 The Alfred Hospital
 Level 4, 607 St Kilda Road
 Melbourne 3004
Susan.rossell@monash.edu

Dear Susan

Re. Investigating factors that influence the efficacy of cognitive remediation in people with schizophrenia

Mind Australia's Research and Evaluation Committee (Committee) considered the above named project at its August meeting, and fully supports the project. The Committee saw the project as providing those who volunteer with an opportunity to participate in *cognitive remediation therapy* and benefit from the possibilities it offers for managing one's health and wellbeing.

Albeit, cognisant that ethics approval has been obtained, the Committee is keen to pass on a few considerations that members believe could facilitate project recruitment and foster ongoing participation.

The Committee considered it would be helpful if the Participant Information Sheet/Consent Form (PIS/CF) contained a concise, non-technical explanation of Cognitive Remediation Therapy. The members agreed this would enhance the confidence of those reading the documentation providing them with an understanding of what the therapy is, and the basis on which claims to improving cognitive skills is asserted. To refine the targeting of this information and as a means to facilitating overall sustained engagement, the Committee considered, if not already in place, the project would benefit from having input from a lived experience advisory committee.

Given the length of the study and the requirement for those participating to provide a blood sample, the Committee would appreciate the study giving consideration to the consistent use of the term "volunteer" throughout the project's documentation

As a further support to building engagement, the Committee suggested the hosting of information sessions. These could be open to potential volunteers and their families, carers and friends with the aim of familiarising the audience with the study, plus demonstrating the types of activities that volunteers would be involved in. As a companion to the suggested information session, the potential value of publication of an information booklet was identified. Due to the length of the study such an information source could prove instrumental in facilitating ongoing engagement. As well as for the volunteers, the booklet could contain information targeting health professionals, families, carers and others important in the life of the volunteers who are likely to be significant in promoting the benefits of participating in the study and supporting the volunteer to stay engaged so as to complete a minimum of 24 sessions.

Central Office 86-92 Mount Street | PO Box 592 | Heidelberg Vic 3084
 p 1300 286 463 f 03 9455 7999 e info@mindaustalia.org.au w mindaustalia.org.au
 Mind Australia ABN 22 005 063 589



The Committee had mixed views regarding the project flyer – some members found it too busy, while others thought it to be highly appropriate with a concise coverage of all salient points. In contrast, the study's poster was described as being attractive and appropriately informative with the only tensions expressed relating to the use of capitals and the highlighting (bold) of the supplementary eligibility criteria rather than the primary. And members identified the inappropriate use of the double negative (reference to brain injury) which may be an error.

The Committee thanks you for providing the opportunity to consider this important study, and provide the project team with its feedback.

Please note the responsibilities linked to this approval include:

1. Keeping the Committee advised of any project changes. This extends to lodging copies of amended documentation for which ethics approval was required
2. Providing 6 monthly updates on your project (using the Committee's template)
3. Providing a final report on the completion of the research (using the Committee's template)
4. Presenting the research findings at the Mind Colloquia (at a mutually suitable date and time)

Link to Committee report templates:

<http://www.mindaustralia.org.au/about-mind/research/research-application.html>

Should you require any further information concerning the Committee's research approval process, or reporting requirements, please contact either Lisa Brophy or Mary Swift.

We wish you every success with the study and look forward to receiving our six (6) monthly progress updates and a final project report.

Yours sincerely

Dr Lisa Brophy
Director of Research
P. 9455 7905/0438544097

Lisa.brophy@mindaustralia.org.au

Link to Mind Research <http://www.mindaustralia.org.au/about-mind/research.html>

Ms Mary Swift
Research and Evaluation Committee Secretariat
P. 9455 7942

mary.swift@mindaustralia.org.au

G6: Peninsula Health, Certificate of Ethical Approval
Approval to distribute recruitment material.



Premier's Award
Metropolitan
Health Service
of the Year
2007, 2009

**RESEARCH
PROGRAM**

**PO Box 192
MOUNT ELIZA 3930**

Tel: 9788 1473
9788 1474
Fax: 9788 1487

iclarino@phcn.vic.gov.au

Frankston
Hospital

Rosebud
Hospital

Mental Health
Services

Aged Care,
Rehabilitation &
Palliative Care Services

Primary and
Community Health

www.peninsulahealth.org.au

Peninsula Health

PO Box 52
Frankston Victoria 3199 Australia
Telephone 03 9784 7777

HUMAN RESEARCH ETHICS COMMITTEE

Research Recruitment Request Approval

22 June 2015

Ms Maree Reser
Brain and Psychological Sciences Research Centre
Faculty of Health, Arts and Design
Swinburne Institute of Technology
HAWTHORN VIC 3122

Dear Ms Reser

PROJECT TITLE: Investigating factors that influence the efficacy of cognitive remediation therapy
in people with schizophrenia

Thank you for your request for assistance in recruitment of participants for the above-mentioned project. The Alfred Ethics Committee Certificate of Approval of 30 September 2014 is noted. Peninsula Health is pleased to grant approval for the display of advertisements and Information Leaflets.

The documents reviewed and approved for use at Peninsula Health include:

Project Advertisement:	Version 2.2 submitted 4 June 2015
Participant Brochure:	Version 1.3

On completion of your project please submit a summary of the results to the Research Program.

Best wishes for a successful research project.

Yours sincerely

Dr Fergus Kerr
Executive Director, Medical Services
Quality and Clinical Governance

Executive Sponsor Research

*At Peninsula Health we value:
Service Integrity Compassion Respect Excellence*

Approval to engage staff in recruitment activities.



Premier's Award
Metropolitan
Health Service
of the Year
2007, 2009

**OFFICE
FOR
RESEARCH**

**PO Box 52
FRANKSTON VIC
3199**

Tel: 9784 2679
9784 2680

ictavarino@phcn.vic.gov.au

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•

Primary and
Community Health

www.peninsulahealth.org.au

Peninsula Health

PO Box 52
Frankston Victoria 3199 Australia
Telephone 03 9784 7777

HUMAN RESEARCH ETHICS COMMITTEE

Research Recruitment Request Approval

16 November 2015

Ms Maree Reser
Brain and Psychological Sciences Research Centre
Faculty of Health, Arts and Design
Swinburne Institute of Technology
HAWTHORN VIC 3122

Dear Ms Reser

PROJECT TITLE: Investigating factors that influence the efficacy of cognitive remediation therapy in people with schizophrenia

Thank you for your request for assistance in recruitment of participants for the above-mentioned project. The Alfred Ethics Committee Certificate of Approval of 6 August 2015 is noted. Peninsula Health is pleased to grant approval for the display of advertisements and information leaflets and to inform staff of the project.

The documents reviewed and approved for use at Peninsula Health include:

Document	Version
Project Advertisement:	Version 3.0: 23 July 2015
Participant Brochure:	Version 2.0: 23 July 2015

On completion of your project please submit a summary of the results to the Research Program.

Best wishes for a successful research project.

Yours sincerely

Dr Fergus Kerr
Executive Director, Medical Services
Quality and Clinical Governance

Executive Sponsor Research

At Peninsula Health we value:
Service Integrity Compassion Respect Excellence

G7: Swinburne University of Technology, Final Report Acknowledgment

Mail - mreser@swin.edu.au

<https://outlook.office.com/owa/?realm=liveswinburneed...>

FW: Acknowledgement of Report for SUHREC Project - 2014/251

Sally Fried on behalf of RES Ethics

Wed 27/06/2018 10:35 AM

To: Maree Reser <mreser@swin.edu.au>;

Cc: RES Ethics <resethics@swin.edu.au>;

FYI Maree...Sally

-----Original Message-----

From: resethics@swin.edu.au <resethics@swin.edu.au>

Sent: Wednesday, 27 June 2018 10:35 AM

To: Susan Rossell <srossell@swin.edu.au>

Cc: RES Ethics <resethics@swin.edu.au>

Subject: Acknowledgement of Report for SUHREC Project - 2014/251

Dear Susan,

Re: Final Report for the project 2014/251

'Investigating factors that influence the efficacy of cognitive remediation therapy in individuals with schizophrenia (StVH Ref: - HREC-A 101/14)' (Report Date: 27-06-2018)

The Final report for the above project has been processed and satisfies the reporting requirements set under the terms of ethics clearance.

Thank you for your attention to this matter.

Regards

Research Ethics Team

Swinburne Research (H68)

Swinburne University of Technology

PO Box 218

HAWTHORN VIC 3122

Tel: 03 9214 3845

Fax: 03 9214 5267

Email: resethics@swin.edu.au

G8: St Vincent's Hospital, Final Report Acknowledgment



**ST VINCENT'S
HOSPITAL**
MELBOURNE

A FACILITY OF ST VINCENT'S HEALTH AUSTRALIA

St Vincent's Hospital
(Melbourne) Limited
ABN 22 052 110 755

41 Victoria Parade Fitzroy VIC 3065
PO Box 2900 Fitzroy VIC 3065

Telephone 03 9231 2211
Facsimile 03 9231 3399
www.svhm.org.au

15 May 2018

Prof Susan Rossell
Monash Alfred Psychiatry Research Centre (MAPrc)
Level 4, 607 St Kilda Road
Melbourne VIC 3004

Dear Prof Rossell,

HREC Protocol number: 101/14

'Investigating factors that influence the efficacy of cognitive remediation therapy in individuals with schizophrenia.'

Thank you for submitting an Annual Progress Report for the aforementioned study.

The following documents have been reviewed and approved:

- Final Report – St Vincent's Hospital (Melbourne), dated 23 April 2018

Approval Status: (STUDY COMPLETED)

Approval is given in accordance with the research conforming to the *National Health and Medical Research Council Act 1992* and the *National Statement on Ethical Conduct in Human Research 2007 (updated May 2015)*.

Approval is subject to:

- The Principal Researcher is to ensure that all associate researchers are aware of the terms of approval and to ensure the project is conducted as specified in the application and in accordance with the National Statement on Ethical Conduct in Human Research 2007 (updated May 2015).
- The Principal Researcher is to notify the Research Governance Unit of all significant safety issues in accordance with the *NHMRC Guidance: Safety monitoring and reporting in clinical trials involving therapeutic goods (including all updates)*.
- Submit an Annual Safety Report for the duration of the project.
- Immediate notification of any unforeseen events that may affect the continuing ethical acceptability of the project;
- Notification and reasons for ceasing the project prior to its expected date of completion;
- Notification of approved amendments to the study.
- Submission of reviewing HREC approval for any proposed modifications to the project;

UNDER THE STEWARDSHIP OF MARY AIKENHEAD MINISTRIES

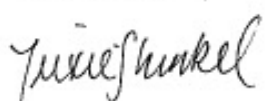
Facilities
St Vincent's Hospital Melbourne
Caritas Christi Hospice
St George's Health Service
Prague House

- Submission of a final report and papers published on completion of project;
- Projects may be subject to an audit or any other form of monitoring by the Research Governance Unit at any time.

St Vincent's Hospital Reference: 101/14

Please quote these numbers on all Correspondence

Yours sincerely,



Dr Trixie Shinkel
Admin Assistant
Research Governance Unit
St Vincent's Hospital (Melbourne)

G9: The Alfred, Final Report Acknowledgment



Alfred Health
Alfred Hospital Ethics Committee

PROGRESS or FINAL REPORT ACKNOWLEDGEMENT

I hereby acknowledge receipt of the report relating to Project 373/14

This acknowledgement is applicable to:

- ☐ Progress report – site form:
- ☐ Progress report – project form covering sites:
- ☒ Project final report
- ☐ Site closure report:

A handwritten signature in black ink, appearing to read "Angela Henjak".

Signature:

Date 05/06/2018

Angela Henjak (Manager, Ethics & Research Governance)

NOTE: For clinical trials involving an investigational drug or device an Annual Safety Report is required. The sponsor is responsible for completing the annual safety report and submitting this to the reviewing HREC. For investigator initiated studies, the report should be completed by the Principal Investigator from the institution responsible for the trial.

Appendix H

Participant Information and Consent Form



Participant Information Sheet and Consent Form

Full Project Title: Investigating factors that influence the efficacy of cognitive remediation therapy in people with mental illness.

Short Title: Predictors of CRT Efficacy in Schizophrenia

Protocol No. 373/14

Principal Researcher: Professor Susan Rossell

Associate Researchers: Dr Neil Thomas, Dr Wei Lin Toh, Dr Caroline Gurvich

Student Researcher: Ms Maree Reser

1. Introduction

Cognitive Remediation Therapy is a treatment that has shown to be effective improving cognitive skills such as memory, attention and thinking speed. In this context, you are invited to take part in this research project, which aims to further our existing understanding of Cognitive Remediation as a crucial therapy to enhance everyday functioning in people with severe mental illnesses who live in Australia.

This Participant Information and Consent Form tells you about the research project. It explains the procedures involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully. Ask questions about anything that you do not understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or healthcare worker.

Participation in this research is voluntary. If you do not wish to take part, you do not have to. You will receive the best possible care whether you take part or not.

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:

- understand what you have read;
- consent to take part in the research project;
- consent to participate in the research processes that are described;
- consent to the use of your personal and health information as described

You will be given a copy of this Participant Information and Consent Form to keep.

2. What is the purpose of this research project?

As is true with many medicines and forms of therapy, some people seem to benefit from their use more than others. The reasons for this vary. Some people might not have a problem in the area the therapy targets. Because of that, nothing changes. Others may not improve much because the therapy does not meet their particular needs. For others, it is not clear why they do not benefit. The purpose of this study is to investigate what factors might influence how effective Cognitive Remediation Therapy is for clients with severe mental illness. We hope that this study will help us understand more about who is likely to benefit



from Cognitive Remediation Therapy so that we can better match a person and their specific needs with the most appropriate form of help.

A total of 100 individuals will take part in this study. All participants involved in the study will receive Cognitive Remediation Therapy. The research is being conducted by Swinburne University of Technology in collaboration with the Monash Alfred Psychiatry Research Centre (MAPrc). The results of this research will be used by the Student Researcher Maree Reser to obtain a Swinburne Doctorate of Psychology (Clinical).

3. What does participation in this research project involve?

If you fit the eligibility criteria and decide to participate, you will be required to provide consent before attending the first of four testing sessions. The first one, at the beginning of the study (Baseline), will take around 6 hours and will be broken into two 3-hour sessions. The next session, halfway through the study, will take around 1 hour to complete. At the end of the study will be a 3-hour testing session, followed in two months by a final 1-hour session.

As this study will also investigate genetic factors that might influence Cognitive Remediation Therapy outcomes, unless previously provided, you will be asked in the first testing session to provide a blood sample. You will also be required to participate in the Cognitive Remediation Therapy (computer-based cognitive training), attending at least 24 sessions.

Program:

Session Description	Duration	Frequency
Test Session 1 (Baseline): Introduction and interview session. Following your signing of this informed consent form, a number of assessments will be carried out. This will start with an interview. First we will ask you for your basic demographic information such as your date of birth, age and educational background. We will then ask you about your past and current medical and psychiatric history and your experiences (if any) of schizophrenia and depression. You will then be required to respond to a general assessment that will measure cognitive or thinking processes that include, amongst others, memory, attention and problem solving. You will then be asked to give a blood sample.	6 hours, broken into two 3 hour sessions	Once, at beginning of study
Cognitive Remediation Therapy (CRT): After the initial assessment you will participate in the computer-based training, which targets basic auditory (hearing) and visual (seeing) processes. This will require the use of headphones. In each training session you will work on a range of training tasks. Tasks will vary across training sessions.	1 hour training sessions	1 to 3 times per week, attending a minimum of 24 sessions
Test Session 2: Halfway through the CRT (so after two months) will be a brief assessment of select cognitive processes, such as processing speed and verbal learning and memory.	1 hour	Once, after 8 weeks of CRT
Test Session 3: Soon after you have finished the CRT we will repeat some parts of the initial assessment. This will not include the demographic questionnaire and you will not need to give blood again.	3 hours	Once, at the end of CRT
Test Session 4: Eight weeks after you complete the CRT, we will complete the final assessment. As with Session 2, this will be a brief assessment of select cognitive processes, such as processing speed and verbal learning and memory.	1 hour	Once, 8 weeks after completing CRT



You will have the opportunity to take rest breaks during the assessment sessions. A follow-up telephone call will be made between visits to monitor your interest.

You will not be paid for your participation in the Cognitive Remediation Therapy, but you will be reimbursed for your testing time to the amount of \$40 per 3-hour session (testing sessions 1 and 3) and \$15 per 1-hour session (testing sessions 2 and 4).

It is important to mention that different members of the research team will conduct the assessment sessions, whereas the Doctoral student (Ms Maree Reser) will conduct the CRT sessions. For the cognitive training you will be using a computer (that we will provide), however previous computer experience and/or skills are not required.

4. Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

Your decision about whether to take part or not, or to take part and then withdraw, will not affect your routine treatment or your relationship with those treating you.

5. What are the possible benefits?

We cannot guarantee or promise that you will receive any benefits from this research; however, Cognitive Remediation Therapy might provide benefits improving your cognitive abilities such as memory, attention, thinking speed and planning skills. In addition, the findings gained from this research may contribute toward better diagnostic and therapeutic methods in the future.

6. What are the possible risks?

Clinical assessment

The clinical assessment will involve the discussion of personal experiences. As such, there is the possibility that you may find the topic of these discussions distressing. The likelihood of distress is low however, as these questionnaires have been designed for research purposes. Furthermore, the investigators are trained and experienced with asking clinical questions in a careful and considerate manner so as to avoid causing psychological distress.

Cognitive assessment

These are standard assessments that have been designed for research purposes. There are low risks associated with them. People can become tired, so adequate breaks and rest periods will be provided.

Blood sampling

Having blood taken may cause some discomfort or bruising. Sometimes, the blood vessel may swell, or blood may clot in the blood vessel, or the spot from which tissue is taken could become inflamed. Rarely, there could be a minor infection or bleeding. If this happens, it can be easily treated.



7. Can I have other treatments during this research project?

While you are participating in this research project, you should continue with the same medications or treatments that you have been taking. It would be helpful if you advised the CRT specialist, Maree Reser, about any changes in your medications during your participation in the research project.

It is also desirable that your local doctor be advised of your decision to participate in this research project. If you do have a local doctor, we strongly recommend that you inform them of your involvement in this research project.

8. What if new information arises during this research project?

During the research project, new information about the risks and benefits of the project may become known to the researchers. If this occurs, you will be told about this new information and the researcher will discuss whether this new information affects you.

9. What if I withdraw from this research project?

If you decide to withdraw, please notify a member of the research team before you withdraw. To facilitate the accuracy of later analyses, please note that a copy of your data collected to that point will be kept on file. If you choose to withdraw that data, please let a member of staff know at the time of withdrawal from the study.

10. How will I be informed of the results of this research project?

A summary of the general findings of this research will be made available to you via either post or email, if you have consented to receive such further communication. These results will potentially be published in appropriate scientific journals and presented at academic conferences. All data in this report will be presented as group data, thereby maintaining your confidentiality.

11. What will happen to information about me?

Any information obtained for the purpose of this research project that can identify you will be treated as confidential and securely stored. It will be disclosed only with your permission, or in compliance with the law.

The data that is collected from you will be coded, that is, reference to your identity will be replaced with a code. Data will be stored securely in a locked facility (e.g., locked filing cabinet) or under password protection (if electronic) and will only be accessible by the research team. All data will be stored for 7 years at the Monash Alfred Psychiatry research centre. Data derived from the present study may also be compared with that from previous research conducted by the same investigators.

In any publication and/or presentation, information will be provided in such a way that you cannot be identified, except with your permission. All participants will remain anonymous, with results presented as pooled group data only.



12. What will happen to my blood sample?

- The donated blood sample will be coded (labelled with your unique study ID number), frozen and stored securely at the Baker IDI Genomics and Systems Laboratory. This process will be overseen by Dr Kıymet Bozaoglu.
- You will be given the option of donating the blood sample for this research only OR donating the blood sample to a research bio-databank "Cognitive and genetic explanations of mental illnesses (CAGEMIS)" for this research as well as future research projects. There is more information about this in section 13: *Optional storage of data in a databank*
- If you donate the blood sample for this research project ONLY, the blood sample will be stored for up to seven years after the completion of this research project and then destroyed.
- The blood sample will be used to analyse particular genes that have been shown to be related to cognitive functioning.
- In any publication or presentation arising from results gained from your genetic analysis, information will be provided in such a way that you cannot be identified, except with your permission. As a participant, you will remain anonymous, with results presented as group data only. A summary of the general findings of this research will be made available to you via either post or email, if you have consented to receive such further communication.

13. Optional storage of data in a databank

If you agree, data from this current study will also be included in the CAGEMIS bio-databank that will facilitate research into symptoms, cognitive explanations and genetic factors involved in schizophrenia. Information will be coded in this databank, and stored as outlined above, in line with standard Alfred policy. You will be given an additional information sheet and consent form describing this databank. Agreeing to your data being entered into the CAGEMIS bio-databank is entirely optional. If you later decide to withdraw your data from the CAGEMIS bio-databank, your data will be removed from it.

14. How can I access my information?

In accordance with relevant Australian and/or Victorian privacy and other relevant laws, you have the right to access the information collected and stored by the researchers about you. You also have the right to request that any information, with which you disagree, be corrected. Please contact the principal researcher if you would like to access your information.

15. What happens if I am injured as a result of participating in this research project?

If you suffer an injury as a result of your participation in this research project, please contact the research staff. Hospital care and treatment will be provided by the public health care system (Medicare) at no cost to you if you are eligible for Medicare benefits and elect to be treated as a public patient.



16. Who is organising and funding the research?

This research project is being conducted by Professor Susan Rossell, Drs Neil Thomas, Caroline Gurvich and Wei Lin Toh, and Ms Maree Reser (student researcher). It is funded using funds allocated to Prof. Rossell.

No member of the research team will receive a personal financial benefit from your involvement in this research project (other than their standard wages).

17. Is this research project approved?

The ethical aspects of this research project have been approved by the Human Research Ethics Committees of the Alfred Hospital and Swinburne University of Technology.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research* (2007) produced by the National Health and Medical Research Council of Australia. This statement has been developed to protect the interests of people who agree to participate in human research studies.

18. Who can I contact?

Who you may need to contact will depend on the nature of your query, therefore, please note the following:

For further information or appointments:

If you want any further information concerning this project or if you have any medical problems which may be related to your involvement in the project (for example, any side effects), you can contact the principal researcher Professor Susan Rossell on 03 9076 6850 or the student researcher Maree Reser at 9214 3604 or on 0451 169 656.

For complaints:

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Name: Ms Emily Bingle

Position: Research Governance Officer, Research & Ethics Unit, Alfred Health.

Telephone: 03 9076 3619

You will need to tell Ms Bingle the following Alfred Health project number: 373/14.



Consent

Site: The Monash-Alfred Psychiatry Research Centre, The Alfred Hospital

Full Project Title: *"Investigating factors that influence the efficacy of cognitive remediation therapy in people with mental illness."*

I have read, or have had read to me in a language that I understand, this document and I understand the purposes, procedures and risks of this research project as described within it.

I give permission for my doctors, other health professionals or hospitals to release information to Monash Alfred Psychiatry Research Centre concerning my disease and treatment that is needed for this project. I understand that such information will remain confidential.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

☐ I freely agree to participate in this research project as described.

☐ I understand that participation will involve providing a blood sample that will be used for genetic testing.

I understand that I will be given a signed copy of this document to keep.

Participant's name (printed).....

Signature

Date

Name of witness to participant's signature (printed)

Signature

Date

Declaration by researcher: I have given a verbal explanation of the research project, its procedures and risks, and I believe that the participant has understood that explanation.

Researcher's name (printed)

Signature

Date

☐ I am interested in receiving information about the CAGEMIS bio-databank

☐ I would like to receive information regarding the outcomes of this study.



Withdrawal of Consent

Site: The Monash-Alfred Psychiatry Research Centre, The Alfred Hospital

Full Project Title: *"Investigating factors that influence the efficacy of cognitive remediation therapy in people with mental illness."*

Principal Researcher: Professor Susan Rossell
 Monash Alfred Psychiatry research centre
 Level 4, 607 St Kilda Rd
 Melbourne, Victoria, 3004

Telephone: 03 9076 6850
Fax: 03 9207 1545
Email: Susan.Rossell@monash.edu

*To withdraw from this project, please mail or fax this form to the principal researcher at the contact details above. You will receive confirmation on our receipt.

I hereby wish to WITHDRAW my consent to participate in the research project detailed above.

You **MAY / MAY NOT** (please circle) use information already collected about me during my involvement in this research project, as detailed below:

- ☐ Genetic data from blood sample
- ☐ Demographic and other background information collected during the initial assessment
- ☐ Results from the cognitive tests I completed
- ☐ Information about my progress on the Cognitive Remediation Training tasks

I understand that my withdrawal from participating in the Cognitive Remediation Training **WILL NOT** affect my participation in other current or future research projects at MAPrc or the Alfred Hospital.

I understand that my withdrawal **WILL NOT** affect my treatment or any relationship with MAPrc and the Alfred Hospital.

Participant's Name (printed):

.....

Signature

Date

Appendix I

Posit Science Approval to use Training Task Screenshots

Seth Oakley <support@positscience.com>

Fri 20/04/2018 12:49 AM

To: Maree Reser <mreser@swin.edu.au>;

Please do not write below this line

Dear Maree Reser,

We believe we have successfully addressed your recent request for support from Posit Science ([#140629](#)). The complete ticket history with all comments can be reviewed below. If we have not successfully addressed your help submission, our apologies. To re-open your ticket please reply to this message.

Seth Oakley (Posit Science)

Apr 19, 7:49 AM PDT

Hello Maree Reser,

Thank you for the reply. You may use the following images in the manner you described:

<https://www.brainhq.com/sites/default/files/images/ex-icon/bsp-visualsweeps-ss-01.jpg>

<https://www.brainhq.com/sites/default/files/images/ex-icon/bsp-eyefordetail-ss-01.jpg>

<https://www.brainhq.com/sites/default/files/images/ex-icon/bsp-hawkeye-ss-01.jpg>

<https://www.brainhq.com/sites/default/files/images/ex-icon/attn-doubleddecision-ss-01.jpg>

<https://www.brainhq.com/sites/default/files/images/ex-icon/attn-targettracker-ss-01.jpg>

Regards,

Seth Oakley

Posit Science

San Francisco, CA

Appendix J

Baseline Means and (Standard Deviations) for Demographic, Clinical, and Cognitive Characteristics by Response Group

Characteristic	Response Group			
	Improved (<i>n</i> = 12)	No Change (<i>n</i> = 4)	Declined (<i>n</i> = 3)	Mix (<i>n</i> = 3)
<i>Demographics</i>				
Age (years)	38.00 (11.76)	40.25 (7.27)	43.67 (0.58)	30.33 (5.77)
Years of education	13.58 (1.83)	14.25 (1.89)	14.00 (1.41)	14.33 (2.31)
<i>Clinical</i>				
Years of illness	12.78 (9.43)	13.25 (13.00)	18.00 (6.93)	3.33 (3.22)
Medication (CPZ mg/day)	902.08 (581.49)	955.44 (747.58)	433.33 (251.66)	511.11 (482.28)
CDSS	2.33 (2.46)	5.75 (6.95)	2.67 (3.06)	10.00 (5.29)
PANSS-positive	14.92 (4.10)	14.25 (7.41)	16.00 (5.20)	19.00 (3.61)
PANSS-negative	12.42 (3.97)	13.50 (7.42)	16.33 (5.03)	10.33 (5.77)
PANSS-general	27.75 (7.68)	28.75 (5.38)	29.67 (5.03)	37.00 (2.00)
<i>Intellectual status</i>				
Premorbid IQ ^a	102.25 (9.37)	111.00 (6.98)	108.68 (2.31)	115.67 (6.66)
Current IQ ^b	90.75 (10.31)	102.25 (7.93)	97.00 (16.46)	109.33 (6.66)
<i>Learning potential</i>				
HVLT-R learning score ^c	0.10 (1.26)	-1.30 (1.48)	-0.58 (2.04)	-0.60 (1.71)
BVMT-R learning score ^c	-0.14 (1.29)	-0.24 (1.02)	0.45 (0.68)	0.51 (1.80)
<i>Cognition (MCCB)</i>				

Speed of processing	40.67 (11.27)	38.75 (10.72)	47.67 (6.66)	52.33 (12.74)
Attention/vigilance	38.83 (9.00)	43.50 (9.33)	47.00 (15.87)	41.00 (12.12)
Working memory	41.83 (7.38)	45.50 (7.33)	46.00 (14.11)	42.33 (5.77)
Verbal learning	35.75 (8.72)	37.00 (6.68)	41.67 (12.74)	43.67 (5.69)
Visual learning	33.58 (7.72)	45.00 (12.83)	43.00 (15.62)	31.67 (13.50)
Reasoning & PS	42.83 (9.34)	41.75 (6.95)	56.67 (3.06)	37.67 (8.50)
Social cognition	39.58 (12.77)	40.25 (8.62)	41.33 (6.66)	35.33 (13.32)
Cognitive composite	32.25 (7.72)	36.50 (9.75)	44.33 (16.26)	34.33 (4.04)

Note. Response Group: Improved = reliable change index of ≥ 1.64 , being the 90% confidence interval, in at least one domain and performance maintained across other domains; No change = $\text{RCI} < 1.64$ and > -1.64 ; Declined = $\text{RCI} \leq -1.64$ and none ≥ 1.64 ; Mixed = at least one domain ≥ 1.64 and one domain ≤ -1.64 . n = number; M = mean; SD = standard deviation; CPZ = Chlorpromazine equivalent; CDSS = Calgary Depression Scale for Schizophrenia; PANSS = Positive and Negative Syndrome Scale; HVLT-R = Hopkins Verbal Learning Test-Revised; BVMT-R = Brief Visual Memory Test-Revised; MCCB = MATRICS Consensus Cognitive Battery; PS = problem solving.

^aPremorbid IQ was measured with the Wechsler Test of Adult Reading (WTAR). ^bCurrent IQ was measured with the Wechsler Abbreviated Scale of Intelligence (WASI)-2 subtest version; ^clearning score = greater of Trial 2 or Trial 3 score - Trial 1 score, standardised.

Appendix K
Clinical Presentation at Baseline and Post-Intervention by Response Group

Characteristic	Median (Interquartiles)			
	Improved (<i>n</i> = 12)	Declined (<i>n</i> = 3)	Mixed (<i>n</i> = 3)	No Change (<i>n</i> = 4)
<i>Baseline</i>				
CDSS	1.00 (1.00-3.75)	2.00 (0.00-6.00)	8.00 (6.00-16.00)	3.00 (1.25-13.00)
PANSS-positive	13.00 (12.00-19.75)	13.00 (13.00-22.00)	20.00 (15.00-22.00)	12.50 (8.25-22.00)
PANSS-negative	13.00 (8.50-14.50)	17.00 (11.00-21.00)	7.00 (7.00-17.00)	11.50 (7.75-21.25)
PANSS-general	25.50 (21.50-34.00)	29.00 (25.00-35.00)	37.00 (35.00-39.00)	29.00 (23.50-33.75)
<i>Post-intervention</i>				
CDSS	1.00 (0.00-3.75)	2.00 (0.00-4.00)	11.00 (5.00-15.00)	2.00 (0.00-10.00)
PANSS-positive	11.00 (7.75-16.00)	9.00 (8.00-11.00)	12.00 (11.00-18.00)	10.50 (8.25-12.00)
PANSS-negative	12.00 (9.25-15.00)	20.00 (13.00-20.00)	15.00 (13.00-20.00)	12.00 (8.50-15.50)
PANSS-general	25.00 (21.25-29.50)	27.00 (25.00-30.00)	30.00 (27.00-45.00)	27.50 (22.50-31.75)

Note. Response Group: Improved = reliable change index of ≥ 1.64 , being the 90% confidence interval, in at least one domain and performance maintained across other domains; No change = $\text{RCI} < 1.64$ and > -1.64 ; Declined = $\text{RCI} \leq -1.64$ and none ≥ 1.64 ; Mixed = at least one domain ≥ 1.64 and one domain ≤ -1.64 . CDSS = Calgary Depression Scale for Schizophrenia; PANSS = Positive and Negative Syndrome Scale.

Appendix L

Summary of Study Outcomes Examining Associations Between DTNBP1 and Cognitive Functioning

Author (year)	Cohort	SNP / Haplotype	SoP	Attn	WM	VerbM	VisM	GenM	R-PS	Est. Curr. IQ	Est. PM IQ	Other
<i>Human studies</i>												
Burdick et al. (2006)	Patient & HC	^c Haplotype rs1018381										<i>g</i> <i>g</i>
Fallgatter et al. (2006) ²	HC	rs2619528 rs760761 rs1474588 rs2619539 rs3213207 rs1011313 rs885773 rs1000117		pf bf pf bf pf bf pf bf pf bf pf bf pf bf pf bf								
Burdick et al. (2007)	Patient	^c Haplotype										IQ decline
Donohoe et al. (2007)	Patient	^d Haplotype		X	x VerbWM VisWM	X	X				x	x inhibition
Stefanis et al. (2007)	HC	rs760761 rs2619522 rs1018381 rs2619539 rs3213207 rs1011313 rs2005976		Attn Attn x x x x x	x VbVsWM x x x x x x					IQ IQ IQ IQ IQ IQ IQ		

Luciano et al. (2009) English cohort	HC	rs742105	x		VerbM				g , F-SA, VerbA
		rs1047631	x			x			g , F-SA , VerbA
		rs2619539	x			x			g , F-SA, VerbA
		rs3213207	SoP			x			x g , F-SA, VerbA
		rs2619528	SoP			x			x g , F-SA, VerbA
		rs760761	SoP			x			x g , F-SA, VerbA
		rs2619522	SoP			x			x g , F-SA, VerbA
		rs17470454	x			x			x g , F-SA, VerbA
		rs1018381	x			x			x g , F-SA, VerbA
		rs1011313	x			x			x g , FS-A, VerbA
		rs2619538	x			x			x g , F-SA, VerbA
		^d Haplotype	SoP			x			g , F-SA, VerbA
Luciano et al. (2009) Australian cohort	HC	rs1018381	x	x	x		x	PM IQ	x FluidA, VerbA
		rs1011313	x	x	VerbM		x	x	x FluidA, VerbA
		rs2619522	x	x		x	x	x	x FluidA, VerbA
		rs2619528	x	x		x	x	x	x FluidA, VerbA
		rs909706	x	x		x	x	x	x FluidA, VerbA
Markov et al. (2009) ²	HC	rs1018381							bf verbal fluency
Alfimova et al. (2010)	Patient & HC	rs2619522			VerbM				
		rs1018381				x			
Fallgatter et al. (2010) ²	Patient	rs2619528	pf bf						
		rs1474588	pf bf						
		rs2619539	pf bf						
		rs3213207	pf bf						
		rs1011313	pf bf						
		rs885773	pf bf						
		rs1000117	pf bf						

Fatjo-Vilas et al. (2010)	Patient & HC	rs2619537 rs1018381 rs2619522 rs760761 rs2743864 rs1011313 rs3213207 rs2619539 rs760666 rs1047631 aHaplotype bHaplotype						x x R-PS x x x x x x x x x x	x x x x x x x x IQ x x x x	
Hashimoto et al. (2010)	Patient & HC	cHaplotype	X		VerbM	X	x		x	VIQ, PIQ, WAIS measures
Markov et al. 2010	HC	rs1018381		bf						
Strohmaier et al. (2010)	Patient & HC	38 SNPs incl rs1047631 rs3213207 rs1011313 rs2619528 rs2619522 rs1018381 rs1474605 rs2619538	x x x x x x x x x							
Thimm et al. (2010a) ²	HC	rs1018381				Bf				
Thimm et al. (2010b)	HC	rs1018381		Attn-A Attn-O Attn-E						

Greenwood et al. (2011)	Patient & HC	rs2619528		x	x		x	x	x	x SpatP, FaceM
		rs2619522		x	x		x	x	x	x SpatP, FaceM
		rs1018381		x	x		x	x	x	x SpatP, FaceM
		rs909706		x	x		x	x	x	x SpatP, FaceM
Wolf et al. (2011)	HC	rs1047631			EmotW					
					M					
Baek et al. (2012) ¹	Patient & HC	rs2619539	x	Attn	x	x	VisL/M		R-PS	x composite
		rs3213207	x	x	x	x	x		x	x composite
		SNP _{new}	x	x	x	x	x		R-PS	x composite
		rs1011313	x	x	x	x	x		x	x composite
		rs760761 _{LD}	x	Attn	WM	x	x		x	composite
		rs1018381	x	Attn	WM	x	x		x	composite
Simon et al. (2013)	Patient & HC	rs1011313	x	x	x	x			x	x VerbA
		rs909706	x	x	x	x			x	x VerbA
		rs1018381	x	x	x	x			x	x VerbA
		rs2619539	x	x	x	x			x	x VerbA
		rs2619528	x	x	x	x			x	x VerbA
		rs3213207	x	x	x	x			x	x VerbA
		rs760761	x	x	x	x			x	x VerbA
		rs2619522	x	x	x	x			x	x VerbA
		rs2619538	x	x	x	x			x	x VerbA

Author (year)	Cohort	SNP / Haplotype	SoP	Attn	WM	VerbM	VisM	GenM	R-PS	Est. Curr. IQ	Est. PM IQ	Other
<i>Animal studies</i>												
Feng et al. (2008)	Sandy mice						LT-M					
Takao et al. (2008)	Sandy mice				SpatWM							Spatial M
Bhardwaj et al. (2009)	Sandy mice						ST-M					
Cox et al. (2009)	Sandy mice						VisL					Spatial L&M
Jentsch et al. (2009)	Sandy mice				SpatWM							
Karlsgodt et al. (2011)	Sandy mice				SpatWM							
Papaleo et al. (2012)	Sandy mice				SpatWM							
Bhardwaj et al. (2015)	Sandy mice				SpatWM							Spatial L&M

Note. **Bolded** domains = significant association reported; x/unbolded domains = no significant association found. Attn = attention; Attn-A = attention alerting; Attn-E = attention executive control; Attn-O = attention orienting; bf = brain function; composite = cognitive composite; DTNBP1 = dystrobrevin-binding protein 1 gene; Est. Curr. IQ = estimated current IQ; Est. PM IQ = estimated premorbid IQ; EmotWM = emotional working memory; F-SA = fluid-spatial ability; FSIQ = fullscale IQ; FaceM = face memory; FluidA = fluid ability; g = general cognitive ability; GenM = general memory; HC = healthy control; LT-M = long-term memory; pf bf = prefrontal brain function; PIQ = performance IQ; R-PS = reasoning and problem solving; response inhib. = response inhibition; sim = WAIS-R similiarities subtest; SNP = single nucleotide polymorphism; SoP = processing speed; SpatP = spatial processing; SpatWM = spatial working memory; ST-M = short-term memory; Verba = verbal ability; VerbM = verbal memory; VisM = visual memory; VIQ = verbal IQ; vocab = WAIS-R vocabulary subtest; WAIS = Wechsler Adult Intelligence Scale-Revised; WM = working memory; picture comp. = WAIS-R picture completion subtest.

¹Baek et al. (2012) reported nominal associations, most of which did not remain significant after adjusting for multiple comparisons; rs760761 and rs1018381 remained significant in the Attn domain.

²No differences found on behavioural measures of cognition; significant differences in neural activity comparing risk to non-risk carriers.

^Lrs760761 was in almost complete linkage disequilibrium with rs2619522 and rs2619528.

^aCTCGG at SNPs rs1018381, rs2619522, rs760761, rs2743864, rs1011313 early-onset families

^bACT at SNPs rs3213207, rs2619539, rs760666 adult-onset families

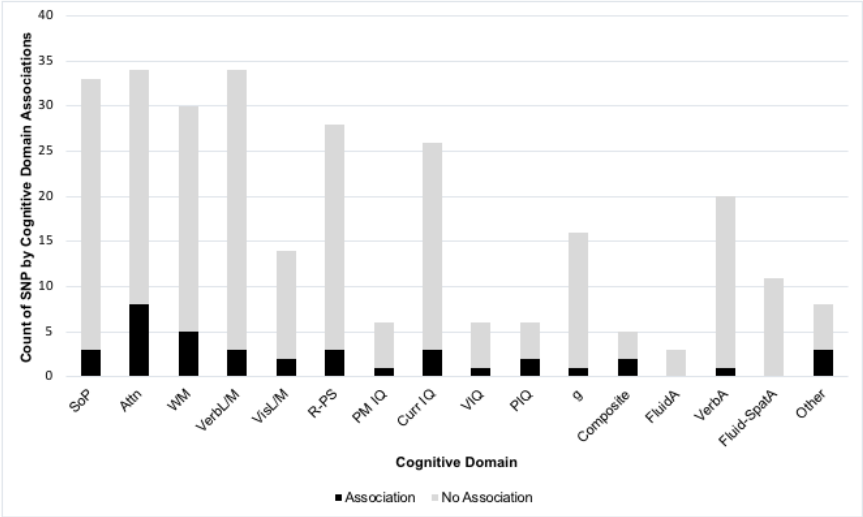
^c1-1-1 at SNPs rs3213207, rs1011313, rs760761 (Numakawa et al. 2004)

^dCAT at SNPs rs2619539, rs3213207, rs2619538 (Williams et al. 2004)

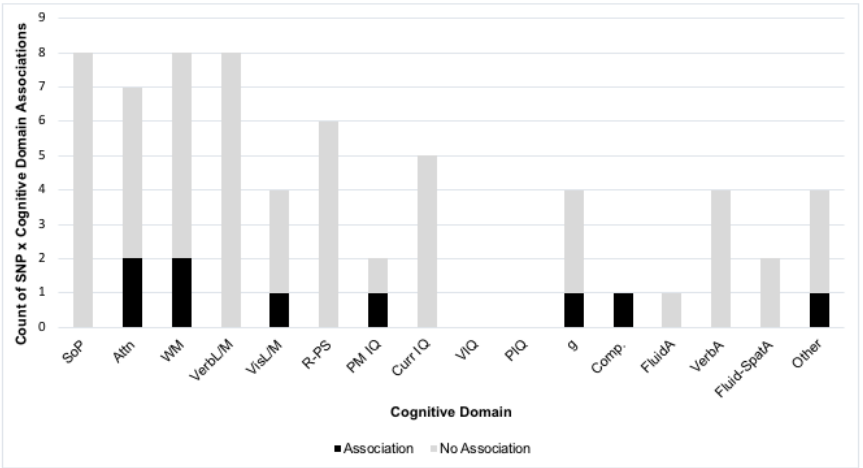
^eCTCTAC at SNPs rs909706, rs1018381, rs2619522, rs760761, rs2619528, rs1011313 (Funke et al. 2004)

Appendix M

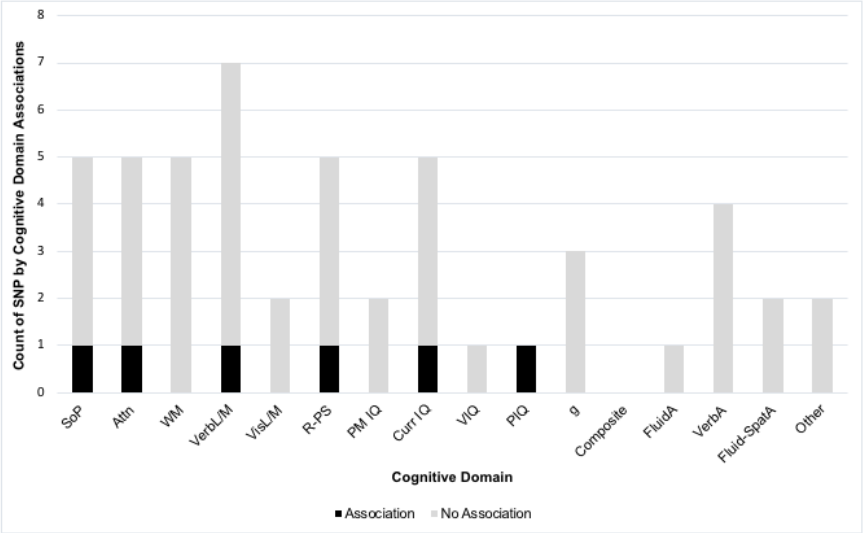
A. Combined DTNBP1 SNPs



B. rs1018381



C. rs2619522



Supplementary Figure M9 A-C. Stacked bar-graph showing a count of significant (black) and nonsignificant (grey) associations between frequently examined DTNBP1 single nucleotide polymorphism (SNP) and cognitive domains. A = 6 SNPs combined; B = rs1018381; C = rs2619522.

Note. Combined = rs1018381 (16 articles), rs2619522 (10 articles), rs1011313 (11 articles), rs760761 (8 articles), rs2619539 (9 articles), rs3213207 (10 articles). SoP = speed of processing; Attn = attention; WM = working memory; VerbL/M = verbal learning and/or memory; VisL/M = visual learning and/or memory; R-PS = reasoning and problem-solving; PM IQ = premorbid IQ; VIQ = verbal IQ; PIQ = performance IQ; g = general cognitive ability; Composite = cognitive composite; FluidA = fluid ability; VerbA = verbal ability; Fluid-SpatA = fluid spatial ability; Other = other areas of cognition.

Appendix N

The Alfred, Certificate of Ethical Approval: Study 3, DTNBP1



ETHICS COMMITTEE CERTIFICATE OF APPROVAL

This is to certify that

Project No: 415/17

Project Title: Exploring the association between the gene for encoding dysbindin and indicators of cognitive capacity for change

Principal Researcher: Professor Susan Rossell

was considered for Low Risk Review and APPROVED on 04/09/2017

It is the Principal Researcher's responsibility to ensure that all researchers associated with this project are aware of the conditions of approval and which documents have been approved.

The Principal Researcher is required to notify the Secretary of the Ethics Committee, via amendment or report, of

- Any significant change to the project and the reason for that change, including an indication of ethical implications (if any);
- Serious adverse effects on participants and the action taken to address those effects;
- Any other unforeseen events or unexpected developments that merit notification;
- The inability of the Principal Researcher to continue in that role, or any other change in research personnel involved in the project;
- A delay of more than 12 months in the commencement of the project; and,
- Termination or closure of the project.

Additionally, the Principal Researcher is required to submit

- A Final Report on completion of the project.

Approval covers the project as described in the application (including any modifications made prior to approval). Low Risk projects are subject to audit and ethical approval may be withdrawn if the project deviates from that proposed and approved.

SPECIAL CONDITIONS

None

SIGNED:

Professor John J. McNeil
Chair, Ethics Committee

Please quote project number and title in all correspondence

Appendix O

Authorship Indication Forms

O1: Factors that influence the efficacy of cognitive remediation therapy in schizophrenia: Systematic review of literature.



Swinburne Research

Authorship Indication Form For PhD (including associated papers) candidates

NOTE

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

DECLARATION

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

Factors that influence the efficacy of cognitive remediation therapy in schizophrenia: systematic review of literature.

First Author

Name: Maree Reser Signature: [Signature]

Percentage of contribution: 80 % Date: 19/06/2018

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

Responsible for database searches, article selection, and data extraction. Completed initial draft of article.
Processed revisions and managed submission to journal.

Second Author

Name: Reneta Slikboer Signature: [Signature]

Percentage of contribution: 12 % Date: 9/7/2018

Brief description of your contribution to the 'paper':

Independently reviewed articles against eligibility criteria. Provided feedback on draft manuscript.

Third Author

Name: Susan Rossell Signature: [Signature]

Percentage of contribution: 8 % Date: 19/06/2018

Brief description of your contribution to the 'paper':

Provided supervisory input into the draft manuscript.

Fourth Author

Name: _____ Signature: _____

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

Brief description of your contribution to the 'paper':

Principal Coordinating Supervisor: Name: Prof. Susan Rossell Signature: [Signature]

Date: 19/06/2018

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

O2: What predicts individual response to Cognitive Remediation Therapy?



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Authorship Indication Form

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DECLARATION

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

What predicts individual response to cognitive remediation therapy?

First Author

Name: Maree Reser Signature: *M. Reser*

Percentage of contribution: 90 % Date: 19/06/2018

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

Participant recruitment and facilitation of CRT sessions. Selection of statistical techniques, data analysis, and completion of initial draft of article. Processed revisions and managed submission to journal.

Second Author

Name: Susan Rossell Signature: *S. Rossell*

Percentage of contribution: 10 % Date: 19/06/2018

Brief description of your contribution to the 'paper':

Provided direction on study design and provided supervisory input into the draft manuscript.

Third Author

Name: _____ Signature: _____

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

Brief description of your contribution to the 'paper':

Fourth Author

Name: _____ Signature: _____

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

Brief description of your contribution to the 'paper':

Principal Coordinating Supervisor: Name: Prof. Susan Rossell Signature: *S. Rossell*

Date: 19/06/2018

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

O3: Exploring differential patterns and predictors of response to cognitive remediation in individuals diagnosed with schizophrenia-related disorders.



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NOTE

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

DECLARATION

We hereby declare our contribution to the publication of the 'paper' entitled: Exploring differential patterns and predictors of response to cognitive remediation therapy in individuals diagnosed with schizophrenia-related disorders.

First Author

Name: Maree Reser Signature: [Signature]

Percentage of contribution: 90 % Date: 19/06/2018

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

Participant recruitment and facilitation of CRT sessions. Selection of method of analysis, data analysis, and completion of initial draft of article. Processed revisions and managed submission to journal.

Second Author

Name: Susan Rossell Signature: [Signature]

Percentage of contribution: 10 % Date: 19/06/2018

Brief description of your contribution to the 'paper':

Provided direction on study design and provided supervisory input into the draft manuscript.

Third Author

Name: _____ Signature: _____

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

Brief description of your contribution to the 'paper':

Fourth Author

Name: _____ Signature: _____

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

Brief description of your contribution to the 'paper':

Principal Coordinating Supervisor: Name: Prof. Susan Rossell Signature: [Signature]

Date: 19/06/2018

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

O4: Does the DTNBP1 genotype predict MATRICS Consensus Cognitive Battery performance in schizophrenia and health controls?



Swinburne Research

Authorship Indication Form For PhD (including associated papers) candidates

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

DECLARATION

We hereby declare our contribution to the publication of the 'paper' entitled: Does the DTNBP1 genotype predict MATRICS Consensus Cognitive Battery performance in schizophrenia and healthy controls?

First Author

Name: Maree Reser Signature: [Signature]

Percentage of contribution: 80% Date: 19/06/2018

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

Data cleaning and analysis. Research and development of ideas presented in article.
Completed initial draft of article. Processed revisions and managed submission to journal.

Second Author

Name: Kiymet Bozaoglu Signature: [Signature]

Percentage of contribution: 5% Date: 21/06/2018

Brief description of your contribution to the 'paper':

Extracted DNA for genetic analysis and provided specialist advice. Reviewed draft manuscript.

Third Author

Name: Caroline Gurvich Signature: [Signature]

Percentage of contribution: 3.3% Date: 06/06/2018

Brief description of your contribution to the 'paper':

Founding co-contributor to CAGEMIS database. Reviewed draft manuscript.

Fourth Author

Name: Erica Neill Signature: [Signature]

Percentage of contribution: 3.3% Date: 19/06/2018

Brief description of your contribution to the 'paper':

Founding co-contributor to CAGEMIS database. Reviewed draft manuscript.

Principal Coordinating Supervisor: Name: Prof. Susan Rossell Signature: [Signature]

Date: 19/06/2018

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

Note. Dr Bozaoglu provided and authorised use of an e-signature.



Swinburne Research

Authorship Indication Form For PhD (including associated papers) candidates

NOTE

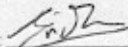
This Authorship Indication form is a statement detailing the percentage of the contribution of each author in each associated 'paper'. This form must be signed by each co-author and the Principal Coordinating Supervisor. This form must be added to the publication of your final thesis as an appendix.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

DECLARATION

We hereby declare our contribution to the publication of the 'paper' entitled: **Does the DTNBP1 genotype predict MATRICS Consensus Cognitive Battery performance in schizophrenia and healthy controls?**

~~XXXXXXXXXX~~ **For Fifth Author**

Name: Eric Tan

Signature: 

Percentage of contribution: 3.3 %

Date: 6/6/18

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

~~XXXXXXXXXX~~ **For Senior Author**

Name: Susan Rossell

Signature: 

Percentage of contribution: 5 %

Date: 19/06/2018

Brief description of your contribution to the 'paper':

Founding co-contributor to CAGEMIS database. Reviewed draft manuscript.

Third Author

Name: _____

Signature: _____

Percentage of contribution: _____ %

Date: ____/____/____

Brief description of your contribution to the 'paper': Co-founder of CAGEMIS database.

Provided direction on study design. Provided supervisory input into the draft manuscript.

Fourth Author

Name: _____

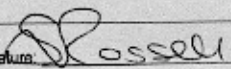
Signature: _____

Percentage of contribution: _____ %

Date: ____/____/____

Brief description of your contribution to the 'paper':

Principal Coordinating Supervisor: Name: Prof. Susan Rossell

Signature: 

Date: 19/06/2018

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