

Measuring Cognition Across Mood and Psychotic Disorders

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The research described in Chapters 4, 5 and 6 was conducted with the support of the web-based platform, TestMyBrain.org, a resource maintained and supported by The Many Brains Project, Inc.

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Chapter 2: I wrote the protocol for the systematic literature search and the meta-analysis with input from James Walters and our summer undergraduate research student, Sian Cleaver. I performed the literature searches, extracted the relevant data and wrote the scripts for the meta-analyses and ran these. Sian Cleaver conducted an independent literature search and contacted the authors of studies for data. Sian also ran a subset of meta-analyses for her summer project, the results of which were not presented in this thesis. We independently reviewed papers for inclusion. We also independently assigned each task to a domain based on previous research and the MATRICS initiative and then reviewed our level of agreement. Where this was disagreement over inclusion of a paper or the assignment of a task to a domain, we consulted with James Walters.

Chapter 3: The data analysed in this chapter was taken from the Cognition in Mood, Psychosis and Schizophrenia Study (CoMPaSS). James Walters is the principal investigator of CoMPaSS, which was originally designed and conducted as part of his clinical training research fellowship under the supervision of Michael Owen (chief investigator). Field teams in Cardiff, Leeds and Hull recruited participants under the supervision of James Walters. Trained members of the field team, including James and myself, conducted clinical ratings. I wrote the paper that arose as a result of this work with input from the other authors (see section “Associated publications”) and parts of this paper formed the basis for this chapter.

Chapters 4-6: The research described in Chapters 4-6 was conducted with the support of the web-based platform, TestMyBrain.org, a resource maintained and supported by The Many Brains Project, Inc. The Many Brains Project created the online versions of the tasks included in this study and provided a customised website based on my specifications. I created the online questionnaire using the online resource, Online Survey (formally Bristol Online Survey). I recruited and assessed 65 participants for the validation study with the assistance of the NCMH field team, who accompanied me on visits and on occasion, administered the MATRICS Consensus Cognitive Battery under my supervision. Undergraduate placement students conducted telephone screenings for the validation study under my supervision. For the main recruitment phase, I wrote the invitation letters and emails and these were then sent out by members of NCMH.

Associated publications

Lynham, A., Hubbard, L., Tansey, K. E., Hamshere, M. L., Legge, S. E., Owen, M. J., Jones, I. R., Walters, J. T. R. (in press) Examining cognition across the bipolar / schizophrenia diagnostic spectrum. *Journal of Psychiatry and Neuroscience*.

Summary

Cognitive impairments are present in both schizophrenia and bipolar disorder and are strong predictors of functional outcomes for patients. One barrier in cognitive research of these disorders is the lack of large, well-characterised cross-disorder samples with cognitive data. The aims of this thesis were to examine cognition across the bipolar / schizophrenia diagnostic spectrum and to develop a new online cognitive battery for use in psychiatric research.

Cognition was examined in participants with bipolar disorder, schizoaffective disorder and schizophrenia through a meta-analysis of existing studies and analysing data from a large well-characterised sample. The main finding was that there is a gradient of increasing cognitive impairment from bipolar disorder through schizoaffective disorder – bipolar type to schizoaffective disorder – depressive type and schizophrenia. Participants with the subtypes of schizoaffective disorder differed in their cognitive performance. Lifetime history of psychosis was associated with cognitive performance across disorders.

An online cognitive battery was developed to assess the domains outlined by the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative. The battery was validated against the MATRICS Consensus Cognitive Battery and showed that the tasks provided valid measurements of the majority of the MATRICS domains. A large sample of participants with a range of psychiatric disorders was recruited online. An examination of cognition in participants with major depressive disorder, bipolar disorder and schizophrenia showed that cognitive profiles were similar across disorders but participants with schizophrenia have more severe impairments than participants with bipolar disorder. An important concluding observation was that poorer cognitive performance was associated with poorer functional outcome across disorders.

The findings of this thesis add to a growing literature showing the importance of examining cognitive function across psychiatric disorders. To date, it is the first study to develop and utilise an online cognitive assessment for psychiatric research.

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Chapter 1: Introduction

1.1 Overview

Schizophrenia and bipolar disorder are among the most severe forms of mental illness and are leading causes of disability amongst young people worldwide.

Schizophrenia is a psychotic disorder characterised by the presence of delusions, hallucinations and disorganised thinking. The disorder is also characterised by the presence of negative symptoms such as affective flattening, asociality, anhedonia and avolition. Whilst the psychosis experienced can be episodic in course, negative symptoms and cognitive impairments persist outside these episodes, which significantly impact their social and occupational functioning. Bipolar disorder is a mood disorder marked by recurrent episodes of depression and mania. It is an episodic illness with a better functional outcome than schizophrenia, including fewer or no negative symptoms and milder cognitive impairments.

Despite the diagnostic distinction between schizophrenia and bipolar disorder, there are overlaps in clinical presentation and underlying biology. Depression is common in patients with schizophrenia and psychosis is common in bipolar disorder. There is evidence that there are common genetic risk variants for both disorders, as well as similarities in underlying neurobiology. Therefore, researchers have proposed that a better approach to diagnostic classification may be to focus on dimensional measures of psychopathology. One dimension that has been the focus of research studies is cognition.

Cognitive impairments are present in both schizophrenia and bipolar disorder. These impairments persist during remission and are not alleviated by current treatments. More severe impairments have been linked to poor functional outcomes and are therefore a key target in the development of new treatments. Furthermore, it is hoped that examination of cognitive impairments across disorders will lead to an understanding of the underlying neurobiology of these disorders. However, a barrier in cognitive research is the lack of large, well-characterised cross-disorder samples with cognitive data.

1.2 Classification of the functional psychoses

Descriptions of mental illness can be found throughout history, although the first attempts to create a comprehensive classification of psychiatric disorders began in the mid-nineteenth century [1]. In 1852, Benedict Morel described the case of a 14-year-old boy whose academic ability had declined, had become withdrawn, was suffering memory loss and talked of killing his father. Morel believed the boy had deteriorated because of “brain degeneration of hereditary origin” and used the term, “démence précoce” to describe a mental deterioration at an early age [2]. In the same decade, Jules Baillarger and Jean-Pierre Falret independently presented descriptions of patients who experienced alternating periods of extreme high (mania) and low mood (depression) [3, 4]. Baillarger called the illness, “folie à double forme”, meaning dual-form insanity [4]. Falret referred to it as, “folie circulaire”, meaning circular insanity and suggested that there may be a genetic basis observing that the illness clustered in families [3].

In 1863, Karl Kahlbaum distinguished between two groups of mental disorders based on their clinical courses, “*vercordia*” and “*versania*” [3]. *Vercordia* included disorders with a remitting course, such as depression and mania. *Versania* consisted of disorders with a progressive course resulting in dementia. It is thought these descriptions influenced the work of Emil Kraepelin, which provided a basis for the development of modern classifications of psychotic and affective disorders [3]. Between 1883 and 1899, Kraepelin published six editions of his influential textbook, “*Compendium der Psychiatrie*”, presenting a comprehensive classification of mental disorders [4]. Kraepelin differentiated organic psychosis from functional psychosis and observed that patterns of symptoms occur together. The functional psychoses were separated into two distinct categories, “*dementia praecox*” and “*manic-depressive psychosis*”. He believed that these disorders had distinct courses of illness and therefore the prognosis of patients could be predicted. *Dementia praecox* was described as a cognitive deterioration occurring early in life, accompanied by incapacitating symptoms of suspicious thoughts, hallucinations, apathy and withdrawal. The prognosis for this disorder was considered to be poor. *Manic-depressive psychosis* was described as an episodic disorder characterised by mood symptoms and a more benign outcome than *dementia praecox*. The term encompassed all possible mood dysfunction, including depression, mania and

mixed states, as Kraepelin believed these were manifestations of a single disease process [5]. These classifications became the foundation of modern classifications, which view bipolar disorder and schizophrenia as distinct disorders.

1.2.1 Bipolar disorder

Kraepelin viewed mania, depression and mixed states as a unitary disorder [5]. Kleist challenged this view in the mid-twentieth century, proposing a distinction between bipolar psychosis and unipolar psychosis (either depression or mania) [3]. This contrasts modern classifications, where unipolar mania is also classified as bipolar disorder and unipolar depression is considered under depressive disorders. The term, “bipolar disorder”, was first introduced to replace the older term, “manic depressive disorder” in the third edition of the American diagnostic system, the Diagnostic and Statistical Manual of Mental Disorders (DSM) [6]. This change reflected the polarity of mania and depression and the circularity of the disorder, distinguishing it from unipolar depression. The term, “hypomania”, was also introduced to describe a less impairing state of high mood and patients who only experience hypomanic episodes are given a diagnosis of bipolar II disorder [5]. The World Health Organisation’s International Classification of Diseases (ICD) also adopted these terms, although unlike the DSM’s bipolar I disorder and bipolar II disorder, ICD does not distinguish mania and hypomania as subtypes of bipolar disorder. Table 1-1 shows the current diagnostic criteria for bipolar disorder according to DSM-5 and ICD-10. Bipolar disorder is characterised by recurrent episodes of mania or hypomania, which can be accompanied by episodes of depression [7, 8]. Mania is defined as a period of at least one week where an elevated, expansive or unusually irritable mood is present and includes symptoms such as inflated self-esteem, decreased need for sleep, pressure of speech, racing thoughts and distractibility [7, 8]. This mood change must be prominent and result in impairment in functioning. Hypomania is defined as high mood that lasts at least four days but does not result in significant impairment [7, 8]. Depression describes a period of at least two weeks where a persistent low mood is present and includes symptoms such as diminished interest in activities, changes in appetite or sleep, psychomotor agitation or retardation, fatigue, loss of self-esteem and suicidal ideation or attempts [7, 8].

Table 1-1 Summary of diagnostic criteria for bipolar I disorder and bipolar II disorder

DSM-5		ICD-10	
Bipolar I Disorder	Bipolar II Disorder	Bipolar Disorder (Mania)	Bipolar Disorder (Hypomania)
<p>A. Meets criteria for manic episode.</p> <p>B. Not better explained by schizoaffective disorder, schizophrenia or other psychotic disorder.</p> <p>Manic Episode</p> <p>A. Abnormally and persistently elevated, expansive or irritable mood and persistently increased activity or energy lasting at least one week and present most of the day, nearly every day (unless hospitalisation is necessary).</p> <p>B. Three or more of the following symptoms (four if mood is only irritable):</p> <ol style="list-style-type: none"> 1. Inflated self-esteem / grandiosity 2. Decreased need for sleep 3. More talkative / pressure of speech 4. Flight of ideas / racing thoughts 5. Distractibility 6. Increase in goal-directed activity / psychomotor agitation 7. Excessive involvement in activities that have a high potential for painful consequences <p>C. Marked impairment in functioning or hospitalisation or psychotic features.</p> <p>D. Not attributable to substance use or another medical condition.</p>	<p>A. Criteria met for at least one hypomanic episode and at least one major depressive episode.</p> <p>B. There has never been a manic episode.</p> <p>C. Not better explained by schizoaffective disorder, schizophrenia or other psychotic disorder.</p> <p>Hypomanic Episode</p> <p>A. Abnormally and persistently elevated, expansive or irritable mood and persistently increased activity or energy lasting at least four days and present most of the day, nearly every day.</p> <p>B. Three or more of the symptoms (four if mood is only irritable) listed under criterion (B) for manic episode.</p> <p>C. An unequivocal change in functioning.</p> <p>D. The disturbance in mood and the change in functioning are observable.</p> <p>E. Not severe enough to cause marked impairment in social or occupational functioning or hospitalisation or psychotic features.</p> <p>F. Not attributable to the physiological of a substance or another medical condition.</p>	<p>A. Meets criteria for manic episode.</p> <p>B. At least one previous affective episode</p> <p>Manic Episode</p> <p>A. Predominantly elevated, expansive or irritable mood for at least one week (unless severe enough to require hospital admission).</p> <p>B. Three or more of the following signs (four if mood is only irritable) leading to severe interference with functioning:</p> <ol style="list-style-type: none"> 1. Increased activity / restlessness 2. More talkative / pressure of speech 3. Flight of ideas / racing thoughts 4. Loss of normal social inhibitions and inappropriate behaviour 5. Decreased need for sleep 6. Inflated self-esteem / grandiosity 7. Distractibility or constant changes in activity or plans 8. Behaviour that is foolhardy or reckless and whose risks the individual does not recognise 9. Marked sexual energy <p>C. Delusions or hallucinations may be present (not criterion G1(1)).</p> <p>D. Not attributable to substance use or organic mental disorder.</p>	<p>A. Meets criteria for hypomanic episode.</p> <p>B. At least one previous affective episode</p> <p>Hypomanic Episode</p> <p>A. Elevated or irritable mood to a degree that is definitely abnormal for the individual and sustained for at least four consecutive days.</p> <p>B. Three or more of the signs present leading to some interference with personal functioning in daily living:</p> <ol style="list-style-type: none"> 1. Increased activity / restlessness 2. Increased talkativeness 3. Distractibility / difficulty in concentration 4. Decreased need for sleep 5. Increased sexual energy 6. Mild over-spending / reckless or irresponsible behaviour 7. Increased sociability / over-familiarity <p>C. Does not meet criteria for mania, bipolar affective disorder, depression, cyclothymia or anorexia nervosa.</p> <p>D. Not attributable to substance use or organic mental disorder.</p>

DSM-5, Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition, ICD-10, International Classification of Diseases – Tenth Edition

1.2.2 Schizophrenia

Eugen Bleuler introduced the term, “schizophrenia”, in 1911 [9]. The term was derived from the Greek roots, “schizien” meaning “to split” and “phren” meaning “mind”. Bleuler adopted a psychological approach to studying his patients, observing their speech and behaviour and performance on psychological tests. Bleuler placed less emphasis on delusions and hallucinations and believed the symptoms of schizophrenia were the result of an underlying psychological deficit, a “splitting” of psychic functions [1, 9]. This view was later opposed by Kurt Schneider who argued that specific psychotic symptoms differentiated schizophrenia from other psychotic disorders and these symptoms have become known as “first-rank” or “Schneiderian” symptoms [1]. These symptoms include voices discussing or commenting in third person, passivity, subjective experience of thought withdrawal, insertion or broadcast and delusional perception. These symptoms were incorporated into modern diagnostic classification systems, including the DSM and ICD. However, studies have called into question the idea that first rank symptoms are specific to patients with schizophrenia [10, 11]. Therefore, the special case of first rank symptoms was removed in the latest edition of the DSM (DSM-5) [12].

The works of Kraepelin, Bleuler and Schneider influenced the criteria for schizophrenia described in current classification systems. Both the DSM-5 and ICD-10 conceptualise schizophrenia as a psychotic disorder characterised by the presence of hallucinations, delusions, disorganised speech and behaviour, catatonia and negative symptoms (see Table 1-2 for current diagnostic criteria) [7, 8].

Hallucinations are perceptions in the absence of outside stimuli. These are most commonly auditory hallucinations, but patients can also present with visual, olfactory, tactile or gustatory hallucinations [1]. Delusions are false beliefs, which are held with conviction even in the face of contradictory evidence and do not fit with a patient’s cultural background. Disorganised speech is also known as formal thought disorder and refers to the disintegration of thought processes [1]. This results in speech that is disjointed, lacks logical structure, derails from the topic of conversation or contains neologisms. Negative symptoms are the loss of affective functions and volition [1]. These include blunted emotional responses, poverty of

speech (alogia) and loss of enjoyment (anhedonia), motivation (avolition) and social drive [1].

Table 1-2 Summary of diagnostic criteria for schizophrenia

DSM-5	ICD-10
<p>A. At least two symptoms present for at least one month. One of the two symptoms must be delusions, hallucinations or disorganised speech:</p> <ol style="list-style-type: none"> 1. Delusions 2. Hallucinations 3. Disorganised speech 4. Grossly disorganised or catatonic behaviour 5. Negative symptoms <p>B. Marked reduction in occupational or social functioning, or personal care or hygiene.</p> <p>C. Continuous signs of disturbance must persist for at least six months and may include periods of prodromal or residual symptoms.</p> <p>D. Schizoaffective disorder and mood disorder with psychotic features have been ruled out because either 1) no mood episodes have occurred concurrently with 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.</p> <p>E. Not attributable to the physiological effects of a substance or another medical condition.</p> <p>F. If autism spectrum disorder or a communication disorder of childhood onset has been previously diagnosed, the diagnosis of schizophrenia is made only if prominent delusions or hallucinations are present for at least one month.</p>	<p>G1. At least one symptom listed under (1) or two symptoms listed under (2) present most of the time for at least one month:</p> <p>(1)</p> <ol style="list-style-type: none"> A. Thought echo, insertion, withdrawal or broadcasting B. Delusions of control, influence, passivity, clearly referred to body or limb movements or specific thoughts, actions or sensations; delusional perception C. Hallucinatory voices giving a running commentary on the patient's behaviour or discussing patient in third person, or coming from some part of the body D. Persistent delusions of other kinds that are culturally inappropriate and completely impossible <p>(2)</p> <ol style="list-style-type: none"> A. Hallucinations in any modality occurring every day for at least one month, accompanied by delusions or persistent over-valued ideas B. Neologisms, breaks or interpolations in the train of thought resulting in incoherent or irrelevant speech C. Catatonic behaviour D. Negative symptoms <p>G2. Most commonly used exclusion clauses</p> <p>(1) If patient meets criteria for affective episode, criteria listed under G1 must be met before disturbance of mood developed.</p> <p>(2) Not attributable to organic brain disease or to alcohol or drug-related intoxication, dependence or withdrawal.</p>

DSM-5, Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition, ICD-10, International Classification of Diseases – Tenth Edition

1.2.3 Diagnostic issues

Modern classification systems maintain the distinction between schizophrenia and bipolar disorder defined by Kraepelin despite overlap in symptom presentations between the disorders. Psychosis is common in bipolar I disorder and studies have estimated that between a half and two-thirds of patients experience at least one psychotic symptom over the lifetime course of their illness [13-15]. It is estimated that approximately 40% of patients with schizophrenia meet criteria for depressive disorder at some point in their illness, although estimates range between 20-60% depending on clinical factors, such as whether patients are in the early stages of illness or chronic and acutely unwell or post-psychotic [16]. Kraepelin himself went on to question his dichotomy remarking that “No experienced diagnostician would deny that cases where it seems impossible to arrive to a clear decision, despite extremely careful observation, are unpleasantly frequent” [17]. In 1933, Jacob Kasanin described a group of patients exhibiting symptoms of both psychosis and mood and coined the term, acute schizoaffective psychoses [18]. Patients with schizoaffective disorder exhibit symptoms of both schizophrenia and mood disorder but do not strictly meet the criteria for either alone (see Table 1-3) [7, 8]. Schizoaffective disorder can be further separated into subtypes depending on the polarity of the mood episode (mania or depression). The diagnosis has drawn criticism due to studies demonstrating poor reliability [19, 20] and stability [21]. The relationship between schizoaffective disorder and both schizophrenia and bipolar disorder is uncertain with theories supporting schizoaffective disorder being a schizophrenia or bipolar disorder sub-type, a comorbidity of schizophrenia and mood disorder, an independent disorder, or the midpoint of a spectrum ranging from a predominantly affective disorder to predominantly psychotic disorder [22]. The latter hypothesis suggests that prototypical bipolar disorder and schizophrenia lie on the extreme ends of a diagnostic spectrum with schizoaffective disorder occupying an intermediate position, representing patients who have features of both disorders [23].

Table 1-3 Diagnostic criteria for schizoaffective disorder

DSM-5	ICD-10
<p>A. An uninterrupted period of illness during which there is a major mood episode (major depressive or manic) concurrent with Criterion A of schizophrenia.</p> <p>B. Delusions or hallucinations for at least two weeks in the absence of mood episode.</p> <p>C. Symptoms that meet criteria for a major mood episode are present for the majority of the total duration of the active and residual portions of the illness.</p> <p>D. Not attributable to the effects of a substance or another medical condition.</p> <p>Bipolar type: Manic episode is part of the presentation.</p> <p>Depressive type: Major depressive episode is part of the presentation.</p>	<p>G1. The disorder meets criteria for one of the affective disorders of moderate or severe degree.</p> <p>G2. At least one of the following present most of the time for at least two weeks:</p> <ol style="list-style-type: none"> 1. Thought echo, insertion, broadcast or withdrawal 2. Delusions of control, influence, passivity, clearly referred to body or limb movements or specific thoughts, actions or sensations 3. Hallucinatory voices giving a running commentary on the patient's behaviour or discussing patient in third person, or coming from some part of the body 4. Persistent delusions of other kinds that are culturally inappropriate and completely impossible but not merely grandiose or persecutory 5. Grossly irrelevant or incoherent speech or frequent use of neologisms 6. Intermittent but frequent catatonic behaviour <p>G3. Criteria G1 and G2 must be met within the same episode and concurrently for at least part of the episode. Symptoms from both must be prominent in the clinical picture.</p> <p>G4. Not attributable to organic brain disease or to alcohol or drug-related intoxication, dependence or withdrawal.</p> <p>Manic type: Criteria for schizoaffective disorder and manic episode must be met.</p> <p>Depressive type: Criteria for schizoaffective disorder and depressive episode of at least moderate severity must be met.</p> <p>Mixed type: Criteria for schizoaffective disorder and mixed bipolar affective disorder must be met.</p>

One issue is that current diagnostic criteria continue to rely on observations of patterns of symptoms, as the disease mechanisms of these disorders are largely unknown [24]. As noted above, this means there are no clear boundaries between

certain diagnoses, as they have overlapping symptoms. There is also heterogeneity within single diagnoses such that patients with the same diagnosis can exhibit widely different symptoms and outcomes. This categorical approach to classification that relies on symptom presentation rather than biology is considered a barrier to the development of treatments [25]. It has been proposed that a better approach to diagnostic classification may be to focus on dimensional measures of psychopathology [24, 26, 27]. One such attempt to use a dimensional approach is the National Institute for Mental Health's Research Domain Criteria (RDoC) [25, 28]. RDoC is not a clinical diagnostic tool but a framework for conducting research, which it is hoped will lead to an improved understanding of the underlying mechanisms of psychiatric disorders. An understanding of the biological basis of psychiatric disorders is considered the first step in the future development of a valid approach to diagnostic classification [25, 28].

The RDoC framework is based on three assumptions: i) that mental illnesses are disorders of brain circuitry, ii) that the research approaches adopted in clinical neuroscience can identify neural circuit dysfunction, and iii) that genetic and neuroscience research will identify "bio-signatures" [25]. The RDoC approach is represented in a two-dimensional matrix where each row is a dimension of behaviour or neurobiology and each column is a unit or measurement that is used to assess that dimension [29]. The dimensions are arranged into five systems: negative valence, positive valence, cognition, social processing and arousal or regulatory systems. The columns are genes, molecules, cells, circuits, physiology, behaviour, self-reports and paradigms. It is hoped that the RDoC will encourage researchers to focus less on specific disorders and more on behaviours that are likely to have biological underpinnings. One criticism of RDoC is the lack of emphasis on what is already known about the clinical symptoms and aetiology of psychiatric disorders [24]. Certain diagnoses are more clinically similar than others. Owen and colleagues have proposed a model of diagnostic classification that incorporates dimensional approaches, as well as representing existing relationships between diagnoses [24, 27, 30]. This model includes intellectual disability, autism, schizophrenia, schizoaffective disorder and bipolar disorder given evidence of overlapping genetic and environmental risk factors (see Figure 1-1). It is proposed that these disorders occupy a gradient of neurodevelopmental impairment indexed

by the contributions of genetic and environmental risk. The following sections outline what is currently known about the epidemiology, aetiology and course of schizophrenia, schizoaffective disorder and bipolar disorder.

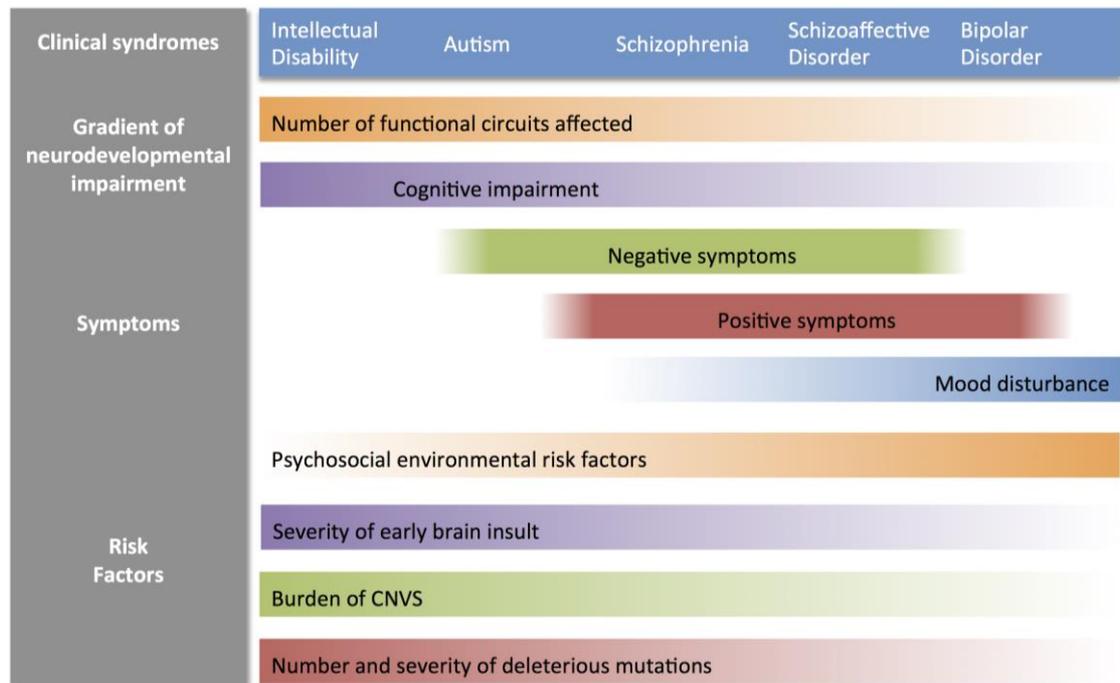


Figure 1-1 Hypothesised relationship between diagnoses (adapted from Owen (2014))

1.3 Epidemiology

Lifetime prevalence estimates are between 0.4% to 0.7% for schizophrenia [31] and 0.8% to 1% for bipolar disorder – type I [32-34]. The median incidence rate of schizophrenia was calculated to be 15.2 per 100, 000 people per year (80% confidence interval: 7.7-43) [31]. Schizophrenia is more common in males than females with a ratio of 1.4:1 [31] but this difference is not seen in bipolar disorder [32]. Few studies have estimated the prevalence of schizoaffective disorder, which may be in part due to the lack of diagnostic stability over time [35]. The existing data suggests lifetime prevalence of schizoaffective disorder is between 0.2% and 1.1% [35, 36].

The World Health Organisation’s Global Burden of Disease Study identified schizophrenia and bipolar disorder, along with depression, amongst the top ten leading causes of disease burden in young people (ages 15- to 44- years old) [37,

38]. Gore et al. [37] evaluated disability-adjusted life years (DALYs) in 10- to 24-year olds using data from the Global Burden of Disease Study. One DALY corresponds to one year of life lost in a population due to disability and premature mortality. Schizophrenia and bipolar disorder accounted for 4.1% and 3.8% of total DALYs. Further, neuropsychiatric disorders overall accounted for 45% of years lost due to premature mortality in this age group. Findings from the Global Burden of Diseases, Injuries and Risk Factors Study 2010 indicated that the burden of disease associated with schizophrenia and bipolar disorder (as measured by DALYs) was greatest between the ages of 25 and 50 years [39].

The age of onset of schizophrenia and bipolar disorder is typically around late adolescence and early adulthood [40-42]. In schizophrenia, there is a slight sex difference with a peak in cases in males between the ages of 20 to 25 years old but a less marked and slightly older peak in females [41, 43]. After the age of 35 years, the number of males developing schizophrenia drops markedly but there is a second peak for women around age 45 [41]. One proposed explanation for this is that oestrogen levels may act as a protective factor before menopause, as oestrogen reduces sensitivity of D₂ dopamine receptors [40]. This gender difference in age of onset is not seen in bipolar disorder [44, 45], although the first episode of mania may occur earlier in males than females [46].

Schizophrenia and bipolar disorder are associated with elevated risk of premature death. Standardized mortality ratios (SMR) for all-cause mortality in schizophrenia populations indicate that risk of death is two to three times greater than the general population (matched by age and sex) [31] and the life expectancy of patients is reduced by up to 20 years [47]. Risk of death from all causes is lower in bipolar disorder than schizophrenia and a long term follow up study of participants with affective disorders found an overall SMR of 1.58 for bipolar disorder [48]. Patients with bipolar disorder have a reduced life expectancy of between 12 and 15 years [49, 50].

1.4 Aetiology

Neither genetic nor environmental risk alone can account for risk of schizophrenia or bipolar disorder. The aetiology of these disorders is a complex mix of genetics and environment. The risk factors for schizophrenia and bipolar disorder are outlined in the following sections.

1.4.1 Genetic risk

Both schizophrenia and bipolar disorder have been shown to have substantial heritability. Heritability estimates are around 80% for schizophrenia [51, 52] and 60-80% for bipolar disorder [53-55]. Family studies have estimated that risk of schizophrenia is around 10% in first-degree relatives of patients with schizophrenia [53]. The risk of bipolar disorder in the first-degree relatives of individuals with bipolar disorder is around 8-9% [53, 55]. The risk of being admitted to hospital for a psychotic or affective disorder is substantially higher when both parents have a history of either schizophrenia (incidence rate of admission was 39%) or bipolar disorder (incidence rate of 25%) [56]. Adoption and twin studies have attempted to disentangle the effects of genetics and environment. Adopted offspring, whose biological parents had schizophrenia, have been shown to have around seven-fold risk of developing schizophrenia [53]. Adopted offspring, whose biological parents had bipolar disorder, have around four-fold risk of developing bipolar disorder [53]. In twin studies, concordance rates of schizophrenia in monozygotic twins have been estimated to be 40-65% compared to 2-30% in same-sex dizygotic twins [52]. In bipolar disorder, concordance rates are approximately 45-65% in monozygotic twins and 4-10% in dizygotic twins [55]. The fact that concordance rates are less than 100% in monozygotic twins indicates that environmental risk factors also contribute to the development of schizophrenia and bipolar disorder.

Family studies have demonstrated that schizophrenia and bipolar disorder have shared genetic aetiology. A study of Swedish registry data showed that relative risk (RR) of schizophrenia is 2.4-3.9 for first-degree relatives of patients with bipolar disorder, whilst relative risk of bipolar disorder is 3.7-5.2 for first-degree relatives of patients with schizophrenia [53]. A Danish registry study also found that relative risk of schizoaffective disorder was increased for those with a first degree relative with schizophrenia (RR=2.6), bipolar disorder (RR=3.2) or schizoaffective disorder

(RR=1.9) [57]. This suggests that schizoaffective disorder is genetically related to both disorders.

Advances in molecular genetics technology have provided new insights into the aetiology of psychiatric disorders. Genetic studies of schizophrenia indicate that both common variants with small effects and rare mutations with large effects are associated with increased risk of schizophrenia. A genome-wide association study (GWAS) of participants with schizophrenia conducted by the Schizophrenia Working Group of the Psychiatric Genomics Consortium (PGC) identified 128 independent single nucleotide polymorphisms (SNPs) at 108 loci that exceeded genome-wide significance [58]. The 108 loci included protein-encoding genes such as DRD2 that encodes dopamine receptor D₂ and genes involved in glutamate transmission, synaptic plasticity and calcium signalling. In the largest genetic study of participants with schizophrenia to date, Pardiñas et al. [59] identified 50 novel loci associated with schizophrenia and 179 genome-wide significant SNPs at 145 loci in total. The authors quantified that 64% of these variants were within gene boundaries and these were more likely to be mutation-intolerant genes, including genes that are important for the function of the central nervous system. Common genetic variation accounts for approximately one-third of genetic liability for schizophrenia [60].

In addition to common genetic variants, it is increasingly recognised that certain rare variants also increase risk of developing schizophrenia. Copy number variants (CNVs) are deletions or duplications of sections of DNA greater than 1 kilobase (kb) in size [61]. Several rare CNVs greater than 500kb have been associated with increased risk of schizophrenia. One of the largest identified genetic risk factors for the development of schizophrenia is 22q11.2 deletion syndrome (also known as DiGeorge, velo-cardial-facial or Shprintzen syndrome) [62, 63]. Patients with this genetic syndrome have up to 30% risk of developing schizophrenia or related disorders [62, 63]. Deletions within the neurexin 1 gene that intersect exons also substantially increase risk of schizophrenia (OR=8.97) [64]. This gene encodes a pre-synaptic cell adhesion protein. More recently, 12 CNVs in 11 loci were shown to be risk factors for schizophrenia [65, 66]. These CNVs are also associated with intellectual disability, autism spectrum disorders and congenital malformations [65, 66].

There has been less progress in identifying genetic risk variants for bipolar disorder than in schizophrenia research. As is the case for schizophrenia, there is evidence that common variants with small effects increase risk of bipolar disorder. Work by the Psychiatric GWAS Consortium Bipolar Disorder Working Group and a subsequent replication have identified associations between risk of bipolar disorder and several regions, including CACNA1C, ODZ4, ANK3 and 15q14 [67, 68]. These studies consistently identify a role for calcium channels in genetic risk for bipolar disorder. In contrast to research of schizophrenia, there is little evidence for an increased burden of CNVs in those with bipolar disorder [69-72]. There is preliminary evidence that the burden of CNVs is higher in those with early onset bipolar disorder, although this requires replication in larger samples [70, 71].

The Cross-Disorder Group of the Psychiatric Genomics Consortium analysed data on over 30,000 cases with schizophrenia, bipolar disorder, major depressive disorder, autism spectrum disorder and attention deficit hyperactivity disorder to evaluate the genetic overlap between these disorders [73, 74]. They identified SNPs at four loci that exceeded genome-wide significance [74]. Polygenic risk scores for each disorder were calculated and these scores were examined in each of the five disorder groups. There was significant overlap of polygenic risk between schizophrenia, bipolar disorder and major depressive disorder. Polygenic risk for autism also overlapped with both schizophrenia and bipolar disorder, whilst risk for attention deficit hyperactivity disorder did not overlap with the other four disorders. Pathway analysis provided evidence of pleiotropic effects for calcium signalling genes. This suggests voltage-gated calcium signalling is an important biological process across disorders and may be a potential treatment target. In a further study, they examined genetic correlations between the five disorders [73]. The highest genetic correlation was between schizophrenia and bipolar disorder. Moderate correlations were observed between bipolar disorder and major depressive disorder, schizophrenia and major depressive disorder, and attention deficit hyperactivity disorder and major depressive disorder. There was a low but significant genetic correlation between schizophrenia and autism spectrum disorder. It should be noted that there were differences in sample sizes across the disorders and the autism spectrum sample was small compared to the other samples. Despite this, genetic correlations were detected between the disorders. Overall, their results provide

evidence of shared risk loci between schizophrenia and bipolar disorder, as well as other adult and childhood onset disorders.

1.4.2 Environmental risk

The studies described in the previous section identified genetic variants that increase the likelihood of developing schizophrenia or bipolar disorder but these variants do not wholly explain the occurrence of these disorders. As noted above, concordance rates among monozygotic twins have been reported to be 40-65% in studies of schizophrenia and studies of bipolar disorder. This indicates that environmental factors are also important in the development of schizophrenia and bipolar disorder. A number of environmental risk factors from pregnancy through to early adulthood have been identified for bipolar disorder and schizophrenia. However, there is variability in outcomes amongst people exposed to these risk factors, which may be partly explained by differences in vulnerability or resilience [75]. Thus, it is likely that the onset of schizophrenia or bipolar disorder arise from a complex interaction of genes and environment [75].

Pregnancy and birth complications may increase risk of schizophrenia. Perinatal complications that have been associated with risk of schizophrenia include low birth weight (less than 2500 grams) [76-78], shorter gestation (less than 37 weeks) [76, 77], asphyxia [79], use of resuscitation or incubator [77], forceps delivery [77], preeclampsia [80], caesarean section [81, 82], congenital malformations [80] and bleeding during pregnancy [78, 83]. It is currently unclear whether these complications are causal or are early indicators of a genetic predisposition or abnormal neurodevelopment. The evidence for an association between obstetric complications and risk of bipolar disorder is conflicting. Several small studies found an association between overall presence of obstetric complications and bipolar disorder [84, 85] but larger studies have not found evidence that obstetric complications increase risk of bipolar disorder [86, 87]. However, a Swedish registry study found evidence that a shorter gestation increases risk of bipolar disorder in young adults (aged 16 years) [88]. Advanced paternal age has also been identified as a risk factor for schizophrenia [89-91] and bipolar disorder [92]. This association was not explained by socioeconomic, maternal age, family history of psychiatric disorder or parental death [89, 91, 92]. Biological mechanisms that

have been proposed to explain how advanced paternal age increases risk of schizophrenia include an increased rate of de novo mutations or genomic imprinting [75, 91].

There is a seasonal birth pattern for patients with bipolar disorder, schizoaffective disorder and schizophrenia such that more patients were born in the winter and spring months [93]. A number of possible explanations have been proposed for this pattern, including seasonal variations in obstetric complications, procreational habits or exposure to light, toxins, nutrients, temperature, weather or infectious agents [93]. Seasonal changes in the rate of infectious agents may be a plausible explanation, as prenatal exposure to infections increases the risk of developing a number of psychiatric disorders including schizophrenia and bipolar disorder. Specifically, prenatal exposure to influenza has been associated with a four-fold increase in risk of bipolar disorder [94]. Exposure to influenza in the second trimester of pregnancy has been shown to increase risk of psychotic bipolar disorder but not bipolar disorder in general [95]. Prenatal infections including influenza, rubella and toxoplasmosis have been shown to increase of schizophrenia [96-98]. Prenatal exposure to infection has also been linked to autism [99] and cerebral palsy [100]. This suggests that prenatal exposure to infection increases vulnerability to brain disorders and provides support for bipolar disorder and schizophrenia as neurodevelopmental disorders.

Childhood adversity or trauma has been shown to increase risk of all DSM-IV categories of psychiatric disorder in the World Mental Health survey of 21 high, middle and low income countries [101]. These adversities include parental loss, parental divorce or separation, parental maladjustment, neglect, abuse, life-threatening illness or poverty before 18 years old [101]. The strongest predictors of psychiatric disorder were adversities associated with maladaptive family functioning, including parental maladjustment (parental mental illness, substance use disorder, criminality or family violence), physical abuse, sexual abuse and neglect. Patients with bipolar disorder are more likely to report experiencing severe child abuse, including neglect, emotional, physical and sexual abuse [102, 103]. Childhood neglect, abuse and bullying are also associated with increased risk of psychosis [104]. However, these studies have relied on self-report measures of childhood adversities and it has been shown that adult participants are likely to

under-report adversities during their childhood [105]. The relationship between child adversities and psychiatric disorder is complex and likely to be influenced by genetic factors as well as the environment [75]. For example, greater exposure to an adverse environment may be due to living with a parent or sibling who either has the disorder or exhibits poor social functioning or subclinical features of psychosis or mood instability, such as schizotypal traits [75]. In addition, people with high genetic risk may be more likely to experience adverse events, such as parental neglect or abuse or peer bullying, due to poor social functioning or personality traits [75]. Genetic factors may also influence vulnerability or resilience to developing psychiatric disorders following an adverse event [75].

First- and second-generation migrants are at increased risk of developing schizophrenia, particularly migrants from countries in the Caribbean and sub-Saharan Africa [106]. The high incidence of schizophrenia among first- and second-generation migrants from the Caribbean to the UK has been well documented [107-110]. This group is also at increased risk of mania [110]. These findings are not explained by misdiagnosis [111, 112], cannabis use [113] or high exposure to obstetric complications [114]. A study of participants with a first episode of schizophrenia in Jamaica reported an incidence rate of 1.16 per 10,000 [115], which is comparable to the overall incidence rate of 1.17 per 10,000 reported by the ÆSOP study across three cities in England (London, Nottingham and Bristol) [116]. This suggests that genetic factors do not fully account for the higher incidence reported amongst migrants in the UK. Another UK-based study reported that siblings of second-generation African-Caribbean patients with schizophrenia were at greater risk of schizophrenia than the siblings of White British-born probands, and first-generation African-Caribbean probands [108]. This finding provides further support for the role of environmental factors, as first-degree relatives of patients born in the Caribbean had similar risk of schizophrenia as first-degree relatives of white patients born in the UK. Social factors that may contribute to the high incidence of schizophrenia amongst African-Caribbean migrants include a greater number of adverse experiences and perceptions of discrimination [117, 118].

There is a higher incidence of schizophrenia in urban areas compared to rural areas [119]. It is estimated that this risk factor can account for approximately 30% of

schizophrenia cases [120, 121]. It has been proposed that individuals with genetic liability for schizophrenia are more likely to move into urban areas, although it has been noted that increased risk of schizophrenia is associated with an urban upbringing and children or adolescents are unlikely to make decisions regarding where their family lives [75]. There is evidence of a gene-environment interaction between urban birth and genetic risk. The risk of schizophrenia is higher for individuals who were born in an urban area and have familial liability than individuals born in an urban area with no familial liability [122]. Another study found that people who live in rural areas during their first fifteen years of life had an elevated risk of schizophrenia if their sibling was born in an urban area compared to individuals whose siblings were also born in rural areas [123]. The effect of urban upbringing on risk of schizophrenia is not fully explained by cognitive functioning [124], air pollution [125] or obstetric complications [126].

Excessive use of cannabis has been associated with schizophrenia [127]. A study of over 50,000 Swedish conscripts found cannabis use increases the risk of developing schizophrenia by 30% [127]. There was a linear trend for frequency of use and risk of schizophrenia. This risk was evident when participants who had used other substances were excluded and after controlling for low IQ, urban upbringing, cigarette smoking, poor social integration and disturbed behaviour. However, this association between cannabis and schizophrenia does not imply causation. It is possible that patients use cannabis during the prodromal phase of schizophrenia to combat psychological distress of early symptoms [127]. Gage et al. [128] used Mendelian randomisation to examine whether there is a causal relationship between cannabis initiation and risk of schizophrenia. There was evidence of a small but significant causal effect of cannabis initiation on risk of schizophrenia, although it should be noted that none of the SNPs associated with cannabis initiation that were included in this study reached genome-wide significance in the original GWAS. There was stronger evidence that genetic risk for schizophrenia is associated with likelihood of cannabis initiation. However, cannabis use was recorded as a binary variable (never/ever) in the original GWAS and therefore the study did not consider frequency of cannabis use. Therefore, participants who had tried cannabis once were recorded as having a history of

cannabis use. This is an important consideration as more frequent cannabis use is associated with greater risk of schizophrenia [127].

There is conflicting evidence that cannabis use increases risk of mood disorders. One study found a modest association between cannabis use and risk of unipolar depression and a stronger association between cannabis use and risk of bipolar disorder, although the mean age of participants at baseline was 39 years old, older than the typical age of onset of bipolar disorder [129]. A second study found that weekly to daily use of cannabis was associated with increased incidence of bipolar disorder but not major depressive disorder [130]. However, the association between cannabis use and risk of bipolar disorder was not maintained after adjustment for potential confounders, including socio-demographic factors, alcohol and other substance use and diagnosis of other psychiatric disorders.

The use of cocaine [131], tranquilizers [132], stimulants [132], sedatives [132] or non-medical use of opioids [133, 134] has been associated with increased risk of bipolar disorder. However, it is unclear whether there is a direct relationship between substance use and bipolar disorder. Genetic and environmental factors may confer vulnerability for both bipolar disorder and drug use [134]. For example, childhood abuse has been associated with increased risk of bipolar disorder [102, 103] and substance use problems [135]. Evidence for an association between substance use (other than cannabis) and schizophrenia are scarce. In the study of Swedish conscripts, there was no association between stimulant use and risk of schizophrenia after adjustment for potential confounders [127]. However, a population study of inpatient admissions in California found a higher risk of schizophrenia amongst individuals who use methamphetamine compared to those who use cocaine or non-stimulant drugs, such as alcohol or opioids [136].

1.5 Course of illness and treatment

Early behavioural signs are apparent before the onset of schizophrenia. Prior to the onset of psychosis, patients often exhibit a decline in academic or occupational functioning and social withdrawal [137]. Schizophrenia is associated with a range of psychotic, negative and cognitive symptoms that can influence the course of the disorder. The course of schizophrenia can be broadly categorised as episodic with intermediate periods of partial or complete remission, complete and persistent

remission after one or more psychotic episodes or continuous psychotic symptoms with no remission. A review of longitudinal studies spanning almost a century found that up to 30-50% of participants with psychosis have a favourable outcome [138]. The International Study of Schizophrenia, co-ordinated by the World Health Organisation, examined 18 cohorts of participants recruited across the world with follow-up periods of up to 25 years [139]. At follow up, 43% of participants with schizophrenia and 62% of participants with other psychotic disorders had a favourable outcome, defined as no psychotic episodes in the last two years. Duration of psychosis during the first two years of illness was the strongest predictor of both symptom severity and level of disability at follow-up. The Schizophrenia Health Outcomes (SOHO) study recruited 5950 participants with schizophrenia across ten European countries to examine longitudinal course over a three-year period [140]. The SOHO study defined remission as either the absence of positive, negative and cognitive symptoms or the presence of only mild symptoms maintained for a period of six months or longer. Using these criteria, 46% of participants were considered to have achieved and maintained remission, 16% remitted but later relapsed and 39% had a continuous course of illness. Similar recovery rates were reported by the ÆSOP-10 study, a ten-year longitudinal study of 557 participants with a first episode of psychosis [141]. In this study, 77% of participants who were traced had met criteria for remission (absence of overt psychosis for at least six months) at least once during the follow-up period and 46% of participants met criteria for recovery (sustained remission for two or more years).

Whilst positive and disorganised symptoms have been shown to be less severe in older patients with schizophrenia, negative symptoms are not associated with age suggesting that these symptoms persist across the lifespan [142]. The presence of prominent and enduring negative symptoms, termed deficit syndrome [143], is associated with poorer outcomes in patients with schizophrenia. One 20-year longitudinal study showed that participants with deficit schizophrenia rarely recovered and had a much poorer outcome after 20 years than participants with non-deficit schizophrenia [142]. Only 13% of these participants met criteria for global recovery at any of the six follow-up assessments, compared to 63% of

participants with non-deficit schizophrenia and 76% of participants with non-psychotic depression.

The main treatment for schizophrenia is antipsychotic medication. Early antipsychotic medications (known as typical or first generation antipsychotics) showed a lack of efficacy in some patients, had negligible effects on negative symptoms and were associated with adverse side effects, particularly extrapyramidal side effects and tardive dyskinesia [144]. Second generation or atypical antipsychotic medications have fewer extrapyramidal side effects than typical antipsychotics, although there is limited evidence for greater efficacy of atypical antipsychotics in reducing symptoms [144-149]. Olanzapine and risperidone were found to be superior to other atypical antipsychotics for patients with non-treatment resistant schizophrenia in a meta-analysis [150]. Atypical antipsychotics are associated with small improvements in cognitive and negative symptoms [144, 151]. Up to one third of patients with schizophrenia do not respond after successive treatments of two or more antipsychotic medications (other than clozapine) [152]. Clozapine has been shown to be superior in treating patients with treatment-resistant schizophrenia [153, 154]. There is evidence that patients with a shorter duration of untreated psychosis have a better prognosis, including less severe positive and negative symptoms and better functioning [155]. This has led to the introduction of early intervention services. The National Institute for Health and Care Excellence (NICE) recommends that these services should be accessible to all people with a first presentation of psychosis and should offer a combination of antipsychotic medication and psychological interventions (family intervention and individual cognitive behavioural therapy (CBT)) [156]. Whilst antipsychotic medications are effective in treating patients' psychotic symptoms, psychosocial interventions and community support are important for improving patients' social and occupational outcomes [157]. A meta-analysis of the efficacy of CBT for reducing symptoms found small improvements in positive and negative symptoms following CBT (Hedges' g effect sizes were -0.25 and -0.13 respectively) [158]. However, the improvements in positive and negative symptoms were small and not significant (Hedges' g effect sizes were -0.08 and -0.04) in a sub-analysis of studies that had masked the treatment assignment from the researchers that administered outcome assessments.

The course of bipolar disorder is characterised by recurrent episodes of mania, hypomania, depression or mixed episodes. There is little evidence that nonpsychotic bipolar disorder is preceded by a decline in occupational and social functioning [159, 160], although some studies have found social impairments are present but to a milder extent than those seen in schizophrenia [161, 162]. Long-term (20-25 years) follow-up studies of participants with bipolar disorder indicate that the majority of participants recover from a mood episode within one year and episodes of depression are more frequent than episodes of mania [163, 164]. Depressive and mixed episodes have longer durations than mania or hypomania and are associated with a more chronic course of illness [163-165]. Episodes with psychotic features or severe psychosocial impairment have been associated with a lower probability of recovery [164].

Treatment of bipolar disorder usually involves a combination of mood stabilisers, antipsychotic and antidepressant medication [166]. Antipsychotics have been shown to be effective in treating acute mania, particularly olanzapine, risperidone and haloperidol [167, 168]. For long term maintenance, lithium or a combination of lithium and valproate remains the most effective treatment for bipolar disorder [168-171]. However, it is estimated that up to one third of patients do not respond to treatment [166, 172, 173]. As noted earlier, depressive symptoms are associated with a poorer prognosis in bipolar disorder but there is a lack of efficacious treatments for bipolar depression [166]. Anti-depressants are commonly prescribed but current evidence suggests that these medications are scarcely more effective than placebos in treating patients with bipolar disorder [174, 175]. There is some evidence that quetiapine or a combination of olanzapine and fluoxetine may be beneficial in treating bipolar depression [168, 176-178].

Participants with schizoaffective disorder are frequently grouped with participants with schizophrenia in longitudinal studies, although there is evidence that these participants may have better outcomes. A ten-year longitudinal study reported that participants with schizoaffective disorder had poorer global outcomes than participants with bipolar disorder and major depressive disorder but better outcomes than those with schizophrenia [179]. This study also found that participants with bipolar disorder or major depressive disorder who experienced mood-incongruent psychosis had worse outcomes than those with mood-congruent

psychosis. A 15-year study reported that participants with schizophrenia had more hospital admissions than participants with bipolar disorder and major depressive disorder, while those with schizoaffective disorder had an intermediate number of admissions [180]. Scores on the Global Functioning Scale increased from schizophrenia to schizoaffective disorder to bipolar disorder and major depressive disorder. Based on three measures of negative symptoms, 59-75% of participants with schizophrenia had negative symptoms compared with 53-74% of the schizoaffective group and 34-47% of the bipolar disorder and major depressive disorder group. It should be noted that these studies did not differentiate between the subtypes of schizoaffective disorder (bipolar and depressive). One study showed that participants with the depressive subtype of schizoaffective disorder displayed comparable levels of emotional blunting and negative symptoms to participants with schizophrenia, whilst participants with the bipolar subtype of schizoaffective disorder had fewer negative symptoms [181].

Despite advancements in the treatment of psychotic and manic symptoms, a substantial proportion of patients with schizophrenia and bipolar disorder continue to experience disability. Aside from negative and depressive symptoms, the presence of cognitive impairments limits patients' ability to maintain paid employment and function in the community. The number of studies into the nature and degree of these cognitive impairments has grown substantially in recent decades, as researchers attempt to identify the biological mechanisms that could be potential targets in the development of new treatments.

1.6 Cognition in schizophrenia and bipolar disorder

Deficits in cognitive ability have long been recognised as a key feature of schizophrenia but are increasingly recognised in patients with bipolar disorder. Cognitive impairments may be an important treatment target, as more severe impairments are linked to greater difficulties for patients in living and working independently. The nature and degree of these impairments across psychotic and affective disorders are not fully understood and there are currently no approved treatments for cognitive impairments.

Numerous studies have identified relationships between cognitive function and measures of functional outcomes in participants with schizophrenia and bipolar

disorder [182, 183]. One meta-analysis showed that both neurocognitive and social cognitive measures are associated with functional outcomes in participants with schizophrenia, accounting for 4% and 16% of the variance respectively [183]. Similar findings were reported in a meta-analysis of participants with bipolar disorder [182]. In this study, overall cognitive function was most strongly associated with performance-based measures of functional outcomes. It was not possible to determine the causality of these associations or measure the impact of changes in cognitive performance on functional outcomes in this meta-analysis due to the use of cross-sectional data. Longitudinal studies indicate that cognitive performance measured during or soon after the first episode of schizophrenia or bipolar disorder is associated with later social and occupational functioning [184, 185]. There is also evidence that a decline in cognitive function over a period of one to seven years is associated with greater functional disability [185, 186]. One study examined the association between cognitive function and overall disability in a cross-disorder sample of adolescents and young adults (aged 12-35 years) [186]. Participants were reassessed between 12 and 36 months after their initial assessment. Improved verbal memory and sustained attention between baseline and follow-up predicted greater reductions in overall disability, as measured by World Health Organisation's Disability Assessment Schedule. The authors performed a cluster analysis and identified three cognitive subtypes that were associated with functional outcomes. These clusters did not differ by diagnosis, which suggests that cognitive function predicts functional outcomes independently of diagnosis. This highlights the importance of examining cognitive function across disorders.

Another reason to examine cognitive function across disorders is that intelligence has been shown to be heritable. Therefore, the genetic overlap between bipolar disorder and schizophrenia may include genes that affect cognitive function. Identifying genetic variants associated with cognitive function may aid the discovery of biological pathways as new treatment targets. General intelligence has been shown to be heritable in twin studies of healthy individuals (heritability estimate: 0.47, [187]). Genetic studies indicate intelligence has a polygenic nature (SNP-based heritability: 0.20 [188]). The largest genome-wide association study of intelligence to date (N=78,308) implicated 52 genes through identification of genome-wide significant SNPs and gene-based analyses [188]. These included

genes previously identified as having a role in neuronal function (synapse formation, axon guidance, putamen volume, regulation of myogenic and neuronal differentiation) Genes implicated in cognitive function overlapped with genes implicated in schizophrenia [188]. The same study identified negative genetic correlations between general cognitive function and depressive symptoms and neuroticism. Another study reported negative genetic correlations between polygenic profile scores for higher cognitive ability or educational attainment, and schizophrenia, autism, bipolar disorder, Alzheimer's disease and major depressive disorder [189].

1.7 Cognition in schizophrenia

Cognitive impairments have been recognised as a central feature of schizophrenia since the disorder was first conceptualised in the nineteenth century [2, 3]. Morel, Kahlbaum and Kraepelin each described progressive deterioration in mental functions in their patients and considered schizophrenia to be a type of early onset dementia [2, 3]. However, by the second half of the twentieth century, focus had shifted towards the classification of psychosis and the treatment of these symptoms [1]. There has been a renewed interest in studying cognition in schizophrenia, due to the recognition that these impairments have a profound impact on functional outcomes [183] and advances in cognitive and neuroimaging approaches [1, 190]. The last three decades have seen a substantial increase in research studies examining cognitive impairments in participants with schizophrenia.

1.7.1 Nature of cognitive deficits

Heinrichs and Zakzanis [191] conducted the first meta-analysis of the studies comparing participants with schizophrenia to healthy controls. They calculated 22 effect sizes from 204 studies, including measures of verbal memory, nonverbal memory, motor performance, visual and auditory attention, general intelligence, spatial ability, executive function, language and tactile transfer. Cohen's *d* effect sizes ranged from 0.46 to 1.41 after correction for sample size and all domains were significant indicating that participants with schizophrenia exhibited general cognitive dysfunction compared to healthy controls. The worst affected cognitive ability was verbal memory. However, many of the studies in the meta-analysis included participants who were predominantly middle-aged and had been unwell

for long periods of time. There were several potential confounders, including antipsychotic medication use, symptoms and hospital admissions. The authors conducted a limited number of moderator analyses to examine the impact of these clinical variables but few studies had reported sufficient demographic and clinical data. Despite these limitations, the results of Heinrichs and Zakzanis's study have been consistently replicated by subsequent meta-analyses, which have demonstrated that participants with schizophrenia perform on average one to two standard deviations below healthy controls [192, 193]. A meta-analysis of studies examining antipsychotic-naïve participants with schizophrenia also demonstrated impairments in verbal memory, speed of processing, working memory, attention, visual memory and executive function (Cohen's d ranged from 0.74 to 1.03) [194].

One aspect of cognition that received little attention in these meta-analyses was processing speed. This is the speed with which relatively simple cognitive tasks can be completed. Typical measures of processing speed involve assessing how many trials of a simple task a participant can complete within a given time limit. Many higher order cognitive abilities are speed dependent. Dickinson et al. [195] conducted a meta-analysis of studies that assessed processing speed and compared the effect sizes to those obtained for other common measures of cognitive function. The largest effect size was for the processing speed task, Digit Symbol Coding (Hedge's $g = 1.57$), whilst effect sizes for the remaining tasks ranged between 0.52 and 1.41. Relatives of patients with schizophrenia also exhibited deficits on the Digit Symbol Coding task, as well as smaller deficits in measures of verbal learning, executive function and attention. Moderator analyses indicated that participants with a longer duration of illness and earlier age of onset had larger deficits in Digit Symbol Coding than younger participants or those who had been unwell for less than a year. A subsequent meta-analysis found a similarly large effect for Digit Symbol Coding (Hedge's $g = -1.50$) [196]. Meta-regression analyses indicated that part of the heterogeneity in effect sizes for this task could be explained by between-study differences in publication year, differences in IQ between cases and controls and chlorpromazine equivalent dose. However, their results still suggested a large deficit in performance on the Digit Symbol Coding task for the schizophrenia group.

Deficits in social cognition have also been identified in patients with schizophrenia. The term, “social cognition”, describes the mental processes involved in understanding and managing social situations, including interpreting the intentions or emotions of other people [197]. Examples of these processes include the ability to identify emotions in faces and theory of mind, which is the ability to attribute and understand the beliefs, desires and intentions of others. It has been posited that impairments in social cognition may play a role in the development and maintenance of delusions [197, 198]. Impairments in theory of mind have been identified in participants with schizophrenia at onset and throughout the course of the disorder, as well as in participants at high risk of developing psychosis [199]. Emotion perception has also been shown to be impaired in participants with schizophrenia [200]. Fett and colleagues [183] conducted a meta-analysis to examine the relationships between functional outcome and either neurocognitive performance or social cognitive performance. The social cognitive domains included theory of mind, emotion perception and processing and social perception and knowledge. Associations between the domains of social cognition and community functioning were stronger than those found for the neurocognitive domains and community functioning. This suggests that impairments in social cognition are another important target for interventions.

Whilst the results of these meta-analyses provided valuable insights into the nature and severity of cognitive impairments in schizophrenia, the studies included used a large variety of cognitive tasks. Therefore, the development and approval of cognitive-enhancing treatments was hampered by a lack of consensus on how to divide the specific cognitive processes affected in schizophrenia and the need for a standardised test battery to assess cognitive outcomes in schizophrenia. The National Institute of Mental Health (NIMH) in the United States launched the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative in response to the mounting evidence of cognitive impairments in schizophrenia. The purpose of the MATRICS initiative was to stimulate the development of treatments that would improve cognitive outcomes in patients with schizophrenia and related disorders [201]. One of the objectives of this initiative was to identify the domains of cognition affected and create a cognitive battery with good psychometric properties that could be used in research

of cognition, particularly clinical trials of cognition-enhancing therapies. In 2003, a subcommittee of the MATRICS initiative reviewed the available evidence for separable domains of cognition and made recommendations regarding which domains should be included in the cognitive battery [202]. Selection of these separable domains was based on factor analytic studies of cognitive performance in participants with schizophrenia, although relevant large studies of healthy participants were also considered [202]. The committee selected dimensions that were independent or only weakly correlated with other dimensions and had been replicated across several studies. They also considered whether these dimensions were likely to be sensitive to interventions. Six domains of cognition were identified from factor analytic studies: speed of processing, attention / vigilance, working memory, verbal learning and memory, visual learning and memory and reasoning and problem solving. The latter domain included measures of executive function but was labelled “reasoning and problem solving” to distinguish the domain from the executive processes of working memory. In 2003, research on social cognition in schizophrenia was in its infancy and so the factor analytic studies evaluated had not included measures of social cognition. However, it was concluded that social cognitive processes may represent an important treatment target in patients with schizophrenia and so social cognition was included as the seventh domain. The MATRICS committee later evaluated 90 nominated tasks and selected a beta battery of 20 tasks [203]. These tasks were evaluated for their psychometric properties, tolerability and relationship with functional outcome. The final MATRICS Consensus Cognitive Battery consisted of ten tasks that assessed the seven domains of interest. However, it should be noted that the evidence for separable cognitive deficits in schizophrenia is controversial and some researchers have argued that patients exhibit a generalised cognitive deficit.

1.7.2 General or specific cognitive deficits

Cognitive impairments in schizophrenia are widespread, affecting almost all domains from basic functions to higher order processes. This has led some researchers to argue that these widespread impairments may be the result of a generalised cognitive deficit. In healthy individuals, cognitive domains are at least moderately correlated and the structure of cognition is thought to be hierarchical with domains related to general cognitive ability, known as ‘g’ [204, 205]. This has

led researchers to examine whether the cognitive deficits are separable processes or the result of a unitary deficit. Dickinson et al. used confirmatory factor analysis to examine whether performance on seventeen tasks followed a hierarchical six-factor model [206]. The six factors were verbal comprehension, perceptual organisation, verbal learning and memory, visual learning and memory, information processing speed and executive / working memory. Each factor measures a separable ability but the hierarchical model specified that correlations between these six factors were caused by their relationship to a higher order factor, general ability ('g').

Confirmatory factor analysis supported this model for both the schizophrenia and healthy control groups. However, cognitive domains were more highly correlated in participants with schizophrenia than healthy individuals and there were higher loadings on the common factor, 'g'. This suggests that cognitive ability is more unitary in patients with schizophrenia than healthy populations. General cognitive ability accounts for approximately two-thirds of the difference in performance between participants with schizophrenia and healthy participants [207, 208].

However, 'g' does not fully account for differences in processing speed and verbal learning between patients and controls [207, 208]. These cognitive abilities may be disproportionately affected in patients with schizophrenia. An alternative explanation is that certain cognitive tasks, such as those tapping processing speed and verbal memory, may be more difficult and thus larger group differences are detected between patients and controls.

An important implication of these findings is that efforts to identify discrete neural mechanisms associated with specific cognitive deficits may be unproductive.

However, some researchers have questioned the concept of generalised cognitive deficits in schizophrenia. It has been argued that aspects of the disorder, such as reduced motivation or antipsychotic medication, may have a general "dulling" effect on cognitive performance [209]. Another possible explanation for the unitary nature of cognitive performance in schizophrenia is cognitive scaffolding.

Cognitive scaffolding is the process by which other cognitive processes compensate for deficits in specific areas of cognition and thus cognitive performance become less differentiated resulting in higher correlations between scores on tasks designed to measure different domains of cognition [210]. Other researchers have noted the relative non-specificity of cognitive assessments, which

tend to tap multiple abilities rather discrete processes [211]. There has been work to develop a battery of tasks that tap specific cognitive mechanisms. An example of this is the Cognitive Neuroscience-Based Approaches to Measuring and Improving Treatment Effects on Cognition in Schizophrenia (CNTRICS) initiative [212]. One of the aims of this initiative was to select a battery of tasks based on evidence from cognitive neuroscience studies. It is hoped that these tasks will be used to enhance translational research [212].

1.7.3 Course of cognitive impairments

Cognitive deficits are relatively stable over long periods suggesting the impairments are not the result of neurodegeneration [213]. Indeed, there is evidence that cognitive deficits are present before the onset of psychosis and during the first episode of psychosis supporting a neurodevelopmental origin of these impairments. In a 30-year follow-up study, more than 1000 children were assessed on their cognitive abilities at seven, nine, eleven and thirteen years old [214]. Children who went on to develop schizophrenia exhibited deficits in verbal comprehension and perceptual organisation at seven years old. These children also gradually fell behind their peers on measures of perceptual organisation and processing between the ages of seven and thirteen years old. A meta-analysis of 14 studies that assessed IQ in childhood or prior to the onset of schizophrenia found that full scale IQ was lower in participants who later developed schizophrenia [215]. The standardised mean difference between cases and controls was -0.43, which equated to a premorbid IQ of 93.6 in participants with schizophrenia. A one-point decrease in premorbid IQ was associated with an increase of 3.7% in the risk of developing schizophrenia. There was a weaker relationship between premorbid IQ and risk of schizophrenia in those with the highest IQ. The study examined the influence of age, gender and age at onset and found greater effect sizes for studies whose schizophrenia group had an earlier mean age of onset. There was insufficient data to examine other potential clinical or demographic confounders. In a study of Swedish conscripts, the association between low IQ and schizophrenia was maintained after accounting for history of other psychiatric illness, drug use, place of upbringing, paternal age, disturbed behaviour in childhood, family history of psychiatric illness and father's occupation [216].

Cognitive deficits have been demonstrated in participants at high familial or clinical risk of developing schizophrenia. In one study, neurocognitive profiles were compared between participants who were identified as showing clinical signs of an early prodromal state of psychosis, those considered in a late initial prodromal state, participants who were experiencing their first episode of psychosis and participants with a diagnosis of schizophrenia (multiple episodes of psychosis) [217]. Participants who were considered at risk of developing psychosis (early and late prodromal phase) exhibited deficits in executive function and verbal memory relative to controls, whilst the late prodromal phase group exhibited additional attentional deficits. The first episode group had greater impairments than the at-risk groups and the multiple episode schizophrenia group exhibited the most severe cognitive impairments. However, it is unclear how many of the participants in the at-risk groups went on to have a psychotic episode. Bora et al. [218] conducted a meta-analysis of studies examining cognitive impairment in youths who were either at high familial or clinical risk of developing psychosis. Familial high risk (FHR) was defined as having a parent or sibling with schizophrenia or at least two relatives with schizophrenia. Clinical high risk (termed ultra high risk, UHR) was defined as youths or young adults who have sought help and met one of the following criteria: i) recent onset or worsening of attenuated psychotic symptoms; ii) recent onset of clinically significant psychotic symptoms that were not sufficiently sustained to meet the criteria for a psychotic disorder; or iii) genetic risk of psychosis plus a deterioration in their functioning. The results indicated impairments on measures of current and premorbid IQ, verbal memory, visual memory, executive function, fluency, sustained attention, verbal and visuospatial working memory for both participants with FHR (Cohen's d ranged from 0.24 to 0.81) and UHR (Cohen's d ranged from 0.34 to 0.71). Participants with both high clinical and familial risk had worse cognitive scores than the other groups. Amongst the UHR participants, those who went on to develop psychosis were more impaired than those who did not but there was substantial overlap in cognitive scores between the two groups. This suggests that cognition may have limited utility on its own as a predictor of who will develop psychosis. However, a five-year longitudinal study of UHR participants found that combined performance on measures of executive function, working memory, visual memory and theory of mind predicted conversion to psychosis [219]. Another study reported that a

predictive model including scores on verbal learning and processing speed tasks at baseline correctly reclassified 77% of participants as converting or not converting to psychosis [220]. However, it should be noted that in this study the group that converted to psychosis exhibited significantly higher levels of prodromal psychotic and negative symptoms at baseline, as assessed by scores on the Positive and Negative Syndrome Scale (PANSS) and number of participants experiencing brief limited intermittent psychotic symptoms.

Numerous studies of participants admitted for a first episode of psychosis have identified deficits in executive function, verbal and visual memory, processing speed and working memory [217, 221-223]. The severity of these impairments has been shown to be associated with later severity of negative symptoms and poorer functional outcome [222, 224]. A meta-analysis of first episode studies indicated medium to large deficits in verbal memory, nonverbal memory, processing speed, language functions, visuospatial abilities, executive function, working memory, social cognition, attention and motor skills (Cohen's *d* ranged from -0.64 to -1.20) [225]. The degree of impairment found was comparable to those reported in meta-analyses of chronic patients [191-193]. This suggests that cognitive deficits are present at onset of the first episode of psychosis and remain stable thereafter. An issue with studies of first episode psychosis is that most participants are assessed following administration of antipsychotic medication and potentially other psychiatric medications. There are clear ethical difficulties in administering cognitive assessments for research before patients are given treatment for their psychotic symptoms and therefore few studies have examined cognitive deficits in antipsychotic-naïve patients. As noted earlier, one meta-analysis identified similar cognitive impairments in antipsychotic-naïve participants compared to healthy controls [194].

Meta-analyses of clinical trials of antipsychotic medication have found moderate improvements in cognitive function when patients are treated with atypical antipsychotics [226, 227]. The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study was one of the largest and most comprehensive independent clinical trials of antipsychotic medication ever conducted [151]. The study found small improvements in neurocognitive performance for participants treated with olanzapine, quetiapine, risperidone or perphenazine after two months.

Similar improvements were found at six months. By 18 months, cognitive improvement was greater for the perphenazine group than the olanzapine and risperidone groups. This finding was in contrast to studies showing that atypical antipsychotics are superior in improving cognitive function to typical antipsychotics [226, 227]. However, it should be noted that participants in the CATIE study were chronic patients and 75% were already taking antipsychotic medication at baseline. In a study of 104 participants with a first episode of psychosis, olanzapine and risperidone were associated with improvement in cognitive function at six and sixteen weeks [228]. However, the improvements were small and only two cognitive tests (Wechsler Memory Scale – Visual Reproduction subtest and Trail Making Test) showed greater improvements in cases compared to a healthy control group. This suggests that improvements reported over a small period of follow-up may be due to practice or placebo effects. Practice effects occur due to the participant’s familiarity with the specific task, as the participant may memorise the stimuli, develop strategies to complete the task or due to procedural learning [229]. Placebo effects are the result of the participant’s experience of taking part in the study and occur due to factors such as increased motivation, decreased anxiety about participating in the study or expectation bias [229]. The results of a study by Keefe et al. [230] provided further evidence of practice or placebo effects in a clinical trial of 250 participants with schizophrenia or schizoaffective disorder. Participants were stabilised on a second-generation antipsychotic and administered either donepezil (an acetylcholinesterase inhibitor) or placebo. Similar moderate cognitive improvements were observed in both groups (donepezil and placebo). Practice or placebo effects were observed across cognitive domains including when tasks used alternative forms at baseline and follow-up [229, 230]. The impact of long-term antipsychotic medication use on cognitive function remains unclear.

In addition to clinical trials examining the effects of antipsychotic medication on cognition, numerous studies have examined the longitudinal course of cognitive impairments in participants with schizophrenia. A meta-analysis of these studies indicated slight improvements in scores on assessments of memory, executive function, attention and processing speed [231]. However, the mean follow-up period of the included studies was just 12 months and comparisons with data from

healthy controls suggested the slight improvements observed were due to practice effects. Studies that have followed up participants for longer periods (five to ten years) have had small sample sizes. A study of 54 participants with first episode or recent onset schizophrenia found that performance on the majority of cognitive tasks remained stable after five years, except that performance IQ and full-scale IQ improved [232]. Improvements in negative symptoms were associated with improvements in full scale IQ. Finger-tapping speed was found to be slower after five years. One ten-year longitudinal study found significant cognitive decline in participants with schizophrenia on three of the nine tasks administered [233]. These tasks were the picture completion and object assembly subtests of the Wechsler Adult Intelligence Scale and the Memory-For-Design test. However, only 24 participants had completed the same cognitive battery at both time points and the effects were small. Another small study followed up participants and administered neurocognitive assessments five and ten years after their first episode of psychosis [234, 235]. The authors did not find evidence of cognitive decline after ten years but participants with schizophrenia showed less improvement in tasks assessing verbal and nonverbal recall and cognitive inhibition compared to controls.

In conclusion, current evidence suggests that cognitive impairments are apparent in patients before the onset of their first episode of psychosis. These deficits remain stable up to ten years after the onset of the disorder. These findings support a neurodevelopmental origin of these impairments rather than deficits resulting from neurodegenerative processes. There are currently no approved treatments for cognitive deficits in patients with schizophrenia and at best, current antipsychotic medications only marginally improve these deficits [236].

1.8 Cognition in bipolar disorder

Early conceptualisations of bipolar disorder described a mood disorder with remitting course, not typically associated with cognitive deterioration [4]. However, it has recently been recognised that cognitive impairments are present in patients with bipolar disorder and persist outside of mood episodes [237-240]. This research is less mature than studies of cognitive deficits in schizophrenia with the number of studies growing over the last 15 years.

1.8.1 Nature of cognitive deficits

Five meta-analyses of studies of euthymic participants with bipolar disorder have been carried out to examine the nature and extent of cognitive deficits [237-241]. The results of these meta-analyses indicated deficits in executive function, verbal learning, visual learning, attention and processing speed (Cohen's *d* effect sizes ranged from 0.28 to 1.09 across the meta-analyses). Findings across the meta-analyses have been largely consistent particularly regarding the most and least impaired cognitive domains. The largest impairments were observed in executive function and verbal learning across all the meta-analyses. The smallest effect sizes were seen for forward digit span [237-239] and sustained attention [237-239]. One exception was Torres et al. [240] who reported one of their largest effect sizes for the continuous performance test but the measure was total hits, which does not account for false positive responses and therefore should be viewed with caution. Only the most recent meta-analysis [241] had sufficient data to conduct meta-regressions with clinical variables. Their findings indicated that a younger age of illness onset and higher proportion of participants taking antipsychotic and antidepressant medications were associated with the larger effect sizes. None of the meta-analyses found significant effect sizes for premorbid IQ, as estimated using the National Adult Reading Test (NART), Wide Range Achievement Test (WRAT) or Wechsler Adult Intelligence Scale (WAIS) Vocabulary subtest [237-240]. Performance on visual copy tests was not impaired in participants with bipolar disorder in two meta-analyses [237, 241].

Measures of executive function are consistently identified as showing the greatest impairment in participants with bipolar disorder. However, some aspects of executive function are more impaired than others. Within the executive function domain of each meta-analysis, the largest effect sizes were reported for Trail Making Test – part B [237-239], Wisconsin Card Sorting Task [237, 240] and the Stroop test [240]. This suggests that participants with bipolar disorder are particularly impaired on measures of cognitive flexibility and response inhibition. Relatives of patients with bipolar disorder also demonstrate poorer performance on these three measures compared to controls [237, 241].

In response to increasing recognition of cognitive impairments in bipolar disorder, the International Society for Bipolar Disorder (ISBD) established a committee to identify domains of impairment in bipolar disorder, evaluate the suitability of the MATRICS Consensus Cognitive Battery (MCCB) for research of bipolar disorder and propose a preliminary cognitive battery [242]. Their findings indicated that the majority of the MCCB tasks would be suitable for measurement of impairments in bipolar disorder. However, the authors concluded that more complex measures of executive function should be included in a cognitive battery for bipolar disorder.

Few studies have examined social cognitive abilities in participants with bipolar disorder, although there is some evidence of mild to moderate deficits. A meta-analysis of these studies examined three social cognitive abilities: emotion processing, theory of mind and decision-making [243]. Participants with bipolar disorder exhibited moderate deficits in both simple and complex theory of mind tasks (Cohen's d ranged from 0.5 to 0.58). Milder deficits were found in emotion processing ($d = 0.35$), whilst decision-making skills were relatively preserved ($d = 0.15$). The number of studies included in each meta-analysis was small; the maximum number of studies included in a single analysis was nine. This limited the number of potential moderators that could be examined. None of the moderators examined (age, sex, years of education, duration of illness or medication use) influenced the size of the effects reported in the studies.

1.8.2 Subtypes of bipolar disorder

The majority of studies examining cognitive dysfunction in bipolar disorder has focused on bipolar disorder – type I. There is evidence of differences in cognitive function between patients with bipolar I disorder and bipolar II disorder, as well as differences within subgroups of bipolar I disorder.

Participants with bipolar II disorder exhibit significant cognitive impairments based on the findings of one meta-analysis [244]. These impairments were smaller in magnitude than those seen in bipolar I disorder. Specifically, participants with bipolar I disorder had more extensive impairments in verbal memory, visual memory and semantic fluency than participants with bipolar II disorder. These findings were not influenced by duration of illness, age of onset, depressive or manic symptoms, proportion of participants with a history of psychosis or

antipsychotic medication use. One study also found that 16% of participants with bipolar II disorder and 21% of participants with bipolar I disorder had clinically significant impairments in their attention and executive function, defined as performance one and a half standard deviations below the average of the healthy control group [245]. However, only 7% of participants with bipolar II disorder had clinically significant impairments in their verbal memory compared to 25% of participants with bipolar I disorder. This suggests that impairments in verbal memory may be more specific to bipolar I disorder.

Patients with bipolar disorder who have a history of psychosis have worse cognitive outcomes than patients who do not have a history of psychosis. A meta-analysis showed that participants with bipolar disorder and psychosis performed significantly worse than participants without psychosis on measures of planning and reasoning, working memory, verbal memory and processing speed, although effect sizes were modest [241]. These differences were not explained by between-group differences in duration of illness, age of onset, proportion of participants taking antipsychotic medication or number of inpatient admissions. Only number of manic episodes was associated with between-group differences in global cognition. It has been proposed that patients with bipolar disorder with more severe cognitive impairments and history of psychosis may represent a subtype of bipolar disorder that is genetically similar to schizophrenia [246].

1.8.3 Course of cognitive impairments

In contrast to patients with schizophrenia, there is little evidence of early cognitive deficits in individuals who later develop bipolar disorder. Premorbid IQ was not associated with risk of developing bipolar disorder in two population studies of conscripts [159, 216], although a third study of Finnish conscripts did find an association [247]. Evidence from the New England Family Studies indicated that IQ at seven years old was significantly lower in participants who went on to develop schizophrenia but was only marginally lower in those who developed bipolar disorder [248]. The study indicated that 42% of the schizophrenia group and 23% of the bipolar disorder group were cognitively impaired at seven years old, defined as IQ in the 10th percentile, compared to 7% of the control group. However, it should be noted that the bipolar group consisted of participants diagnosed with

bipolar disorder with psychosis and schizoaffective disorder – bipolar type. These participants exhibit more severe cognitive impairments than those with bipolar disorder and no history of psychosis [241].

There is evidence that higher than average intelligence is associated with increased risk of developing bipolar disorder. The study of Finnish conscripts showed that lower performance on a visuospatial reasoning test or higher performance on an arithmetic reasoning test at 20 years old was associated with greater risk of developing bipolar disorder [247]. Individuals with the highest scores in arithmetic reasoning had almost a 12-fold risk of bipolar disorder. A population study of educational attainment at 15 to 16 years in Sweden found that students with the highest grades were almost four times more likely to be admitted to hospital for bipolar disorder in adulthood than students with average performance [249]. The study also found modestly increased risk of bipolar disorder in the poorest performing students (hazard ratio = 1.86). These risks were maintained after adjustment for parental education, socioeconomic status, advanced parental age, parental education and season of birth. A study of four population-based cohorts also found high performance in cognitive tests in those who went on to develop bipolar disorder [250]. The bipolar disorder group outperformed population norms on all tasks at ages 13 and 18 years, although there was only a non-significant trend between better verbal ability at 18 years old and increased risk of bipolar disorder. Overall, these studies suggest a complex relationship between premorbid IQ and risk of bipolar disorder with both higher and lower than average premorbid IQ associated with increased risk.

There is evidence that deficits are present in participants with high genetic risk of bipolar disorder. A meta-analysis of 18 studies examining cognition in youth at familial high risk of bipolar disorder found significant deficits in general cognition (Cohen's $d=0.29$) and social cognition (Cohen's $d=0.23$) [251]. The social cognition domain included measures of theory of mind and emotion recognition. Deficits in neurocognition were modest and limited to visual memory, verbal memory, sustained attention and processing speed. Executive functions and working memory were not significantly impaired in the high-risk participants. Within studies that reported data on psychiatric disorders in the high-risk group, up to 30% of participants had a depressive disorder and up to 36% had attention

deficit hyperactivity disorder (ADHD). However, the proportions of participants with depression or ADHD did not account for the magnitude of the effect sizes. There was insufficient data to examine the impact of substance use, medication or current clinical or subclinical depressive or manic symptoms. It is unknown how many of the participants went on to develop bipolar disorder, as the meta-analysis included cross-sectional studies.

Few studies have examined whether participants at clinical high risk of bipolar disorder exhibit cognitive deficits. Two studies of participants at clinical high risk for psychosis have reported data on those participants who went on to develop bipolar disorder, although the group sizes in both studies were small [252, 253]. Neither study found differences in neurocognitive performance between high-risk participants who developed bipolar disorder and high-risk participants who did not develop either bipolar disorder or a psychotic disorder. The first of these studies found similar cognitive performance between high-risk groups that developed bipolar disorder or schizophrenia [252]. The second study found lower verbal IQ, performance IQ and full scale IQ in the bipolar disorder group than a healthy control group [253].

There are difficulties in conducting first episode studies with participants with bipolar disorder due to the nature of the diagnosis. Patients must have had multiple episodes before they meet ICD-10 criteria for bipolar disorder and may have had episodes of depression before their first manic episode. Even if a patient's first recorded episode is a manic episode, they may have had untreated depressive episodes in the past. In addition, if their first episode is accompanied by prominent psychosis then they may be initially diagnosed with a psychotic disorder rather than a mood disorder. Therefore, identifying potential participants for a first episode study is difficult. Current evidence indicates that cognitive impairments are present at onset of the first manic episode suggesting that these impairments occur early in the course of the disorder. A recent meta-analysis of 15 studies that compared participants with a first episode of mania and healthy controls identified deficits in processing speed, verbal memory, visual memory, attention, reasoning, working memory and verbal fluency (Cohen's *d* ranged from 0.31 to 0.8) [254]. Deficits in processing speed, verbal fluency, verbal memory and working memory were less pronounced in participants with first episode mania than those seen in

participants with first episode psychosis. Meta-regression analyses indicated that gender, education, age, clinical state (euthymic or non-euthymic) and drug use had no significant effects on differences in global cognition.

A meta-analysis of longitudinal studies of cognitive deficits in bipolar disorder indicated that patient performance on 14 cognitive measures remained stable over a mean follow-up period of 4.62 years [255]. However, the follow-up periods of the included studies were relatively short, the majority being between two and five years. The authors were also unable to account for the impact of medication use or mood states. There are few longitudinal studies of cognitive deficits in bipolar disorder with follow-up periods of greater than five years. One study showed that overall cognitive impairments remained relatively stable six years after initial assessment [256]. However, performance of the bipolar disorder group had declined after six years for specific tasks, including measures of executive function, working memory and verbal memory. Cognitive change between baseline and six years on the Trail Making Test – Part B was strongly correlated with scores on the Functioning Assessment Short Test, which assesses occupational, cognitive and social outcomes.

Bipolar disorder has a remitting course and there is some evidence that cognitive impairments are more severe when patients are experiencing mood symptoms than during remission [257, 258]. One study of participants with bipolar disorder (type I or type II) did not identify differences in cognitive performance between participants in depressed, manic or euthymic states with the exception of more impaired verbal fluency in the depressed group [257]. Another study found that residual manic or depressive symptoms were associated with poorer executive function in a group of stabilised participants with bipolar I disorder [258]. However, these studies examined cognitive function in participants in different illness states (depressed, manic or euthymic) rather than examining how mood changes are related to cognitive function. Another study found that an increase in depressive symptoms over three months was associated with poorer performance on a measure of verbal fluency [259]. Overall, there is some evidence to suggest that cognitive function, in particular verbal fluency and executive function, is more impaired during mood episodes but it is clear that cognitive impairments persist during euthymic periods.

In conclusion, studies examining premorbid IQ and risk of bipolar disorder indicate both higher and lower than average IQ increases risk of developing bipolar disorder. It has been proposed that patients with poor premorbid IQ comprise a subtype of bipolar disorder that is more genetically similar to schizophrenia with higher rates of psychosis [246]. This is based on evidence of shared genetic risk for schizophrenia and bipolar disorder [73, 74] and worse cognitive outcomes in patients with psychotic bipolar disorder [241]. Cognitive impairments are evident in patients at the onset of bipolar disorder and remain stable for at least several years, although longitudinal studies with longer follow-up periods are needed to determine whether cognitive performance declines after a decade or more of illness. Like schizophrenia, there are no approved treatments for cognitive impairment in bipolar disorder and few studies have examined the efficacy of current medications in improving cognitive function [260]. Lithium has not been shown to enhance cognitive function and has been associated with mild deficits in immediate verbal memory and psychomotor performance [261, 262].

1.9 Comparing cognition in schizophrenia and bipolar disorder

Studies comparing cognitive performance between participants with schizophrenia and bipolar disorder can provide important insights into the nosology of these disorders and have the potential to identify overlapping and distinguishable neurobiological pathways. A meta-analysis of participants with schizophrenia and participants with a diagnosis of either schizoaffective disorder or affective psychosis revealed poorer performance in the schizophrenia group in six domains of cognition [263]. These domains included immediate verbal memory, full scale IQ, verbal working memory, delayed verbal memory, mental speed and executive function. However, the differences observed were small and could be explained by a higher percentage of males, more severe negative symptoms and younger ages at onset in the schizophrenia samples. The meta-analysis revealed large variation in the direction and size of these effects across the studies. Larger effect sizes were observed in a quantitative review of 31 studies, which revealed more severe impairment across nine cognitive domains in participants with schizophrenia compared to participants with bipolar disorder (including euthymic and acute participants) [264]. These domains were verbal fluency, verbal working memory, executive control, visual memory, mental speed, immediate verbal memory, IQ,

delayed verbal memory and concept formation. Again, there was substantial heterogeneity in the effect sizes reported across the studies included. However, similar results were observed when the analysis was limited to participants matched on clinical and demographic characteristics. A recent meta-analysis found that participants with schizophrenia are also more impaired on measures of emotion recognition ($d = 0.39$) and theory of mind ($d = 0.57$) than participants with bipolar disorder [265]. Effect sizes were comparable for social cognition and neurocognition measures in this meta-analysis.

In conclusion, cognitive impairments are characteristic of both schizophrenia and bipolar disorder but these impairments appear to be more severe in patients with schizophrenia. However, the areas of cognition affected overlap; both disorders are associated with deficits in verbal and visual memory, attention, executive function, processing speed and working memory. Therefore, it has been hypothesised that cognitive deficits are a dimensional phenotype that cross diagnostic boundaries. The severity of these deficits may be a consequence of quantitative rather than qualitative differences in the underlying neurobiology of the disorders.

1.10 Cognition in schizoaffective disorder

Few studies have examined cognitive impairment in schizoaffective disorder as a separate diagnosis from either schizophrenia or bipolar disorder. The meta-analysis by Bora et al. [263] described in the previous section reported marginally larger effect sizes for comparisons between schizophrenia and psychotic mood disorders than differences between schizophrenia and schizoaffective disorder. This suggests that cognitive deficits associated with schizoaffective disorder are closer in severity to schizophrenia than those associated with mood disorders. However, the authors did not directly compare cognition between schizoaffective disorder and psychotic mood disorders.

As described earlier in the chapter, there are efforts to examine dimensional approaches to psychiatric classification. Cognitive performance can be considered one such dimension and the advantages of studying cognition rather than clinical symptoms include i) reliable and valid measurements of cognitive performance exist, ii) the relative stability of cognitive impairments over the course of illness and iii) the relationship between cognitive performance and functional outcome

means that impairments are an important treatment target. It has been proposed that schizophrenia, schizoaffective disorder and bipolar disorder lie on a gradient of neurodevelopmental impairment such that cognitive deficits increase in severity from bipolar disorder to schizoaffective disorder to schizophrenia [24, 26, 27]. However, there are few large cognitive studies of all three disorders. One such study is the Bipolar and Schizophrenia Network on Intermediate Phenotypes, which aims to identify potential physiological and cognitive biomarkers of these disorders. This study found support for a gradient of cognitive impairment demonstrating that performance in participants with schizoaffective disorder is intermediate between those with bipolar disorder and schizophrenia [266]. This study also showed that the severity of cognitive impairments is associated with the predominance of psychotic symptoms. However, there are few sufficiently large studies to replicate and expand on these findings.

1.11 Online cognitive testing

Cross-disorder samples may have greater power to examine how certain genetic variants or neurobiological markers contribute to the development of complex phenotypes, such as cognitive impairments. One barrier to examining the environmental and genetic factors that contribute to the development of cognitive impairments in psychiatric disorders is the lack of sufficiently large datasets. With the exception of a few large cross-diagnostic studies, researchers have relied on meta-analyses to generate these large numbers of participants but combining studies with different methodologies, particularly different cognitive tasks, is problematic.

The rise in internet use over the past few decades has presented researchers with new opportunities to collect large datasets. Internet use is widespread in the United Kingdom (UK). In 2017, 80% of adults accessed the internet every day and 90% of households had an internet connection [267]. The rate of internet use on mobile phones has also doubled since 2011 [267]. Therefore, researchers are increasingly interested in utilising the internet to recruit very large samples of participants. Early preconceptions about internet studies included that samples would be less diverse and would be over-represented by younger people [268]. However, the number of older adults using the internet is increasing; the most recent data from the UK's

Office for National Statistics suggests that 78% of adults aged 65 to 74 years had used the internet in the last three months, which has increased by 26% since 2011 [269]. Current evidence suggests that people with mental health disorders are less likely to access the internet, although this is improving over time [270]. A study of 241 participants with either psychosis or depression indicated that the majority of participants had at least some access to the internet in 2016. Participants with psychosis were less likely to have access to the internet than participants with depression and this group were also less confident using the internet. However, only 18% of participants with psychosis were considered “digitally excluded” in 2016, defined as lacking access to any internet-enabled device or lacking confidence in using an internet-enabled device [270]. The proportion of digitally excluded participants with psychosis had decreased since 2011 (30% of participants were defined as digitally excluded) [270]. The most common barrier to using the internet was concerns about security. Other barriers included lack of money, knowledge or places to access the internet. However, the majority of participants wanted to use the internet with only 16% reporting that they did not want to use it. It should be noted that the study was conducted in London, which has higher internet use than other parts of the UK and is unlikely to be representative of internet use amongst patients in remote regions [267]. Another study examined internet use amongst 337 participants with a wide range of psychiatric disorders, including affective disorders, schizophrenia, anxiety disorders, organic mental disorders, personality disorders and substance use disorders [271]. Approximately 80% of the participants were classified as internet users, defined as use of the internet at least once. Of these participants, 33% reported medium internet use (defined as 3.5-12.5 hours a week) and 32% of participants reported high internet use (defined as over 12.5 hours of internet use weekly). Participants who were older were less likely to use the internet frequently. There was no relationship between internet use and either diagnosis or illness severity.

Another concern for online studies is the quality of the data collected. This is a particular concern for cognitive data, especially tasks that measure response time or those that use complex stimuli. In an unsupervised environment, the motivation of the participant is unknown and they may be distracted or request outside help

completing the tasks [272, 273]. Other considerations include the technical skills of the participant, the hardware they are using to complete the tasks and the quality of their internet connection [272]. Despite these concerns, there are a rising number of research projects utilising online cognitive assessments. The Twins Early Development Study (TEDS) recruited a sample of several thousand twins born in the United Kingdom between 1994 and 1996. The study developed online tasks to assess reading, language, mathematics and general cognitive ability in children aged between ten and twelve years old [274]. The battery had good internal and test-retest reliability. Fifteen pairs of twins also completed these tasks in person with a researcher within three months of completing the tasks online. The online tasks were highly correlated with both offline versions of the same task (correlation coefficients ranged between 0.52 and 0.92) and classroom assessments of reading and mathematics. Another study used iPads to administer a cognitive battery to participants in their homes unsupervised [275]. This battery showed good test-retest reliability and was associated with the same battery administered in the clinic ($r^2=0.51$). However, a disadvantage of this approach is the use of iPads, which needed to be delivered to and then collected from participants thus limiting the number of participants that can be assessed at once. This is less practical than hosting the cognitive tasks on a website that participants can access from their own devices.

The website “TestMyBrain.org” was developed at Harvard University to collect large samples of cognitive data from around the world [273]. The website includes a number of experiments, each consisting of cognitive tasks and questionnaires, and provides individual feedback on the participant’s performance to encourage engagement in the research. The tests are taken from published research and are well validated. More than one and a half million people have completed tasks on the website since 2008, generating one of the largest datasets of cognitive performance in the world. In 2012, analyses of data from this project showed few systematic differences between web-based and laboratory-based samples on mean performance, performance variance and internal reliability [273]. These tests included online versions of the Cambridge Face Memory Test, Reading the Mind in the Eyes, Abstract Art Memory, Verbal Paired Associates Memory and WAIS: Forward Digit Span. A small proportion of the participants reported technical

problems or using strategies that could be considered cheating (3-5% across the tasks).

An advantage of online cognitive assessments is the relative ease with which researchers can collect longitudinal data to measure cognitive trajectories. The Melbourne Community Screening Study utilised online cognitive testing to repeatedly assess the cognitive functions of older adults in a community setting [276]. Participants aged 50 or older completed monthly unsupervised cognitive assessments over a 12-month period. This study used the CogState battery, which was designed specifically for repeated testing to measure subtle changes in cognition over time [277, 278]. The tasks included measures of reaction time, visual learning, working memory, episodic memory and executive function. The test-retest reliability of the battery was shown to be high with intra-class correlation coefficients for each task ranging between 0.72 and 0.93. The retention rate of the study by 12-month follow-up was 43%. The majority of the tasks were demonstrated to be suitable for online testing based on reports of technical issues and integrity checks. However, the assessments of executive function and episodic memory were identified as potentially unsuitable for unsupervised testing due to 9% of participants reporting technical difficulties. A limitation of this study was that all of the participants were experienced in using the computerised cognitive battery in a supervised setting and may not be representative of a typical internet-based sample.

The Nutrinet-Santé study is an online prospective study that aims to examine the relationship between nutrition, mortality and health outcomes [279]. Part of this study involved the development of four online cognitive tasks, including measures of processing speed, executive function, working memory and visual memory. These measures were administered to 189 participants in both supervised and unsupervised settings. Correlations between the supervised and unsupervised version of the tasks ranged between 0.42 and 0.73. Correlations were higher among participants with higher educational attainment and those with better knowledge of the internet.

There are a number of online cognitive batteries and testing platforms that have been designed for use in psychiatric research. The details of four cognitive testing

tools are summarised in Table 1-4: Cogstate, Penn Computerised Neurocognitive Battery, Cambridge Neuropsychological Test Automated Battery (CANTAB) and TestMyBrain. Cogstate is a commercial company that develops cognitive tests for clinical trials, academic research and healthcare [276, 278]. They have created a range of cognitive batteries for studies of specific populations, including people with schizophrenia, Alzheimer's disease, depression and multiple sclerosis. These batteries can be hosted online but the researcher needs to design and build their own website. Researchers at the University of Pennsylvania's Brain Behaviour Laboratory designed the Penn Computerised Neurocognitive Battery (CNB) [280, 281]. The CNB is an extensive battery that assesses nine domains of cognition and can be hosted online. Task selection was driven by evidence from neuroscience and neuroimaging studies. However, the measure of processing speed included in the CNB relies on motor skills, which may be compromised in older individuals or those with extrapyramidal side effects. It is important to include a measure of processing speed in a battery that will be used to assess cognition in schizophrenia, as patients with schizophrenia show large deficits in this domain [195]. The CNB is also designed for laptop and desktop computers but not touchscreen devices and is expensive due to ongoing costs for support, training, data validation and access to normative data. The CANTAB is a gold standard cognitive assessment designed by a leading neuroscience company in the UK, Cambridge Cognition. The tests have been used in over 2000 peer-reviewed publications. At the time of writing (March 2017), Cambridge Cognition had recently released their new web-based testing platform, CANTAB Connect. The system was still under development so not all tasks were available to be hosted online and the tasks were suitable for desktop and laptop computers but not touchscreen devices. The cost of CANTAB is also calculated per participants, which is prohibitive for studies collecting very large samples. The TestMyBrain cognitive testing platform was developed by researchers at Harvard University and is hosted by the not-for-profit organisation, The Many Brains Project, Inc. Researchers can create a unique cognitive battery by selecting tasks from an extensive list. The Many Brains Project will create and host the website on their server so the set-up is simple and cost effective. The tests are taken from peer-reviewed studies and the available tasks include some from the MATRICS Consensus Cognitive Battery. There is an option to provide feedback to

participants to encourage engagement with the study. The tasks can be programmed to run on a wide-range of devices to meet the needs of the researcher.

In conclusion, the internet may be a useful resource for conducting large-scale studies of cognitive function among participants with psychiatric diagnoses. Current evidence suggests that online cognitive measures are comparable to offline equivalents. However, at the time of writing, no published studies had investigated the use of online cognitive assessments in research of mental health disorders.

Table 1-4 Summary of available online cognitive assessments

	Cogstate	Penn Computerised Neurocognitive Battery	CANTAB Connect	TestMyBrain
Duration	15 to 40 minutes depending on which battery is selected	Approximately one hour	Can create customised batteries so duration varies	Can create customised batteries so duration varies
Domains of cognition tested	<ol style="list-style-type: none"> 1. Visual motor function 2. Executive function / spatial problem solving 3. Psychomotor function / speed of processing 4. Visual attention / vigilance 5. Visual learning and memory 6. Verbal learning and memory 7. Attention / working memory 8. Social cognition 	<ol style="list-style-type: none"> 1. Abstraction and mental flexibility 2. Attention 3. Working memory 4. Episodic memory 5. Language reasoning 6. Spatial processing 7. Sensorimotor processing speed 8. Motor speed 9. Emotion identification 	<ol style="list-style-type: none"> 1. Attention 2. Memory 3. Executive function 4. Emotion / social cognition 5. Psychomotor speed 	<ol style="list-style-type: none"> 1. Verbal memory 2. Visual memory 3. Reasoning 4. Processing speed 5. Working memory 6. Attention 7. Emotion recognition 8. Decision making 9. Crystallised intelligence

CANTAB: Cambridge Neuropsychological Test Automated Battery

Table 1-4 Summary of available online cognitive assessments

	Cogstate	Penn Computerised Neurocognitive Battery	CANTAB Connect	TestMyBrain
Features	<ol style="list-style-type: none"> 1. Language and culture independent 2. Brief administration time 3. Algorithms that evaluate performance to identify “suboptimal” performance 4. Repeatable with minimal practice effects 5. Battery based on MATRICS domains is available 	<ol style="list-style-type: none"> 1. Evidence-driven approach to task selection based on the findings of neuroscience and neuroimaging studies 2. Can be customised based on the age and language of the participants (15 languages available) 	<ol style="list-style-type: none"> 1. Tests have been published in over 2000 peer-reviewed papers 2. Language and culture independent 3. Tests have been shown to be sensitive in a wide-range of participant groups, from participants at high risk of mental disorders to chronic schizophrenia. 4. 30 languages supported 	<ol style="list-style-type: none"> 1. Batteries are completely customisable and the service includes set up of the study website. 2. Tests can be run on desktop and laptop computers, as well as touchscreen devices 3. Tests taken from published peer-reviewed studies and include tasks from the MCCB 4. Option to provide feedback to participants
Limitations	<ol style="list-style-type: none"> 1. Website to host the tasks must be built separately so additional costs, design and maintenance are required 2. Tasks were purpose built by Cogstate so have not been utilised in as many published studies 	<ol style="list-style-type: none"> 1. Measures some but not all domains outlined by the MATRICS initiative 2. Does not run on touchscreen devices 3. Ongoing costs for support, training, data validation and access to normative data 	<ol style="list-style-type: none"> 1. At the time of writing, the system was still under development so not all tasks were available 2. Cost is calculated per participant 3. Available for laptops and desktop computers only 	<ol style="list-style-type: none"> 1. Developed by researchers at Harvard University so graphics are basic. Therefore, it is not as visually appealing as other systems designed by commercial companies.

CANTAB: Cambridge Neuropsychological Test Automated Battery; MATRICS: Measurement and Treatment Research to Improve Cognition in Schizophrenia; MCCB: MATRICS Consensus Cognitive Battery

1.12 Aim and objectives

The aims of this PhD are to examine cognition across the bipolar / schizophrenia diagnostic spectrum and to develop a new online cognitive battery for use in large-scale studies of mental health disorders.

The objectives of the PhD are:

1. **To conduct a systematic review and meta-analysis of studies comparing cognitive performance in participants with schizoaffective disorder to participants with bipolar disorder and schizophrenia.** Many of the existing studies that examine cognition in schizoaffective disorder are small and there is conflicting evidence regarding the nature and extent of impairments. This will be the first meta-analysis comparing cognitive function between participants with schizoaffective disorder and bipolar disorder. Meta-analyses will be conducted for seven cognitive variables. Further meta-analyses will be conducted to examine cognitive performance in the subtypes of schizoaffective disorder: bipolar or depressive.
2. **To examine cognitive impairment across the bipolar / schizophrenia diagnostic spectrum using existing data from a large well-characterised dataset.** This data will be taken from the Cognition in Mood, Psychosis and Schizophrenia Study (CoMPaSS), a large UK-based cohort of participants with psychotic and affective disorders. This study aimed to test the hypothesis that there is a spectrum of increasing cognitive impairment from bipolar disorder through schizoaffective disorder – bipolar type to schizoaffective disorder – depressive type and schizophrenia. Cognitive performance will be compared between patient groups. Follow-up analyses will examine the relative contributions of demographic variables, clinical symptoms and antipsychotic medication. Ordinal logistic regression modelling will be used to examine whether there is a linear trend of increasing cognitive impairment from bipolar disorder to schizophrenia. The associations between cognition and lifetime symptoms domains will be explored across disorders.
3. **To develop an online cognitive battery for use in mental health research.** This battery will be developed based on the recommendations of

the NIMH-MATRICES initiative. The battery will be piloted in a sample of participants with major depressive disorder, bipolar disorder and schizophrenia. Performance on the new battery will be compared to the MATRICES Consensus Cognitive Battery to determine validity.

4. **To roll out the online cognitive battery to participants who have previously taken part in large genetic studies within the Medical Research Council Centre for Neuropsychiatric Genetics and Genomics.** Participants from CoMPaSS and the National Centre for Mental Health (NCMH) will be invited to complete the online cognitive study. Participants had a variety of mental health problems, including but not limited to psychotic disorders, mood disorders, anxiety disorders, autism spectrum disorders and posttraumatic stress disorder. The aim of this chapter will be to determine whether online cognitive testing is a suitable method for mental health research. The response rates, demographic and clinical characteristics of the sample and completion rates will be examined. The structure of the cognitive battery and the relationships between each task and general cognitive ability will also be examined.
5. **To examine clinical predictors of cognitive function and the relationship between cognition and functional outcome in a cross-disorder sample.** This study will utilise the data collected using the online battery to examine cognitive function in participants with major depressive disorder, bipolar disorder and schizophrenia. This study will examine whether a set of clinical variables are associated with cognitive function both within and across disorders. A further aim of the study will be to test the hypothesis that cognitive function is associated with functional outcome both within and across disorders.

Chapter 2: Cognitive Functioning in Schizoaffective Disorder: A Quantitative Review

2.1 Introduction

Schizophrenia and bipolar disorder have traditionally been considered to be discrete categories in diagnostic classification. In contrast, studies examining clinical features, genetic risk and neuroimaging data suggest there are overlaps between these disorders. The intermediate diagnosis, “schizoaffective disorder” was introduced due to the observation that some patients exhibit symptoms of schizophrenia and mood disturbance [20]. Schizoaffective disorder can be divided into subtypes based on whether the mood disturbance consists of depressive episodes only (depressive type) or manic episodes (known as bipolar type in DSM-5 and manic or mixed type in ICD-10) [7, 8]. However, the relationship between schizoaffective disorder and schizophrenia or bipolar disorder remains unclear (see Chapter 1 for a more extensive overview of the diagnostic concepts). Investigating the nature and degree of the cognitive impairments associated with schizoaffective disorder may further elucidate the relationship between these disorders.

It is well established that cognition is impaired in a large number of patients with schizophrenia [191]. These impairments are evident across a broad range of domains including visual and verbal memory, attention and executive function and are important predictors of outcome in patients [202]. Cognitive performance in affective disorders such as schizoaffective disorder and bipolar disorder is less clear. There are fewer studies that examine cognitive performance in schizoaffective disorder and bipolar disorder though there is evidence of cognitive impairments, albeit milder than in schizophrenia [263, 264, 282, 283]. The two meta-analyses conducted to date have detected heterogeneity of effect sizes between studies examining this question [263, 264].

More recent reviews have attempted to reduce this heterogeneity by comparing specific diagnoses and subgroups [284-287]. These reviews have concluded that participants with schizophrenia who have limited mood symptoms or prominent negative symptoms exhibit the most severe cognitive deficits [284-286].

Participants with bipolar disorder and no history of psychosis have the least severe cognitive deficits [284-286]. The cognitive performance of participants with either bipolar disorder and psychosis or schizoaffective disorder appears to be intermediate between bipolar disorder without psychosis and schizophrenia [284, 286]. Bora et al. [284] concluded that participants who were experiencing psychotic symptoms during assessment exhibited similar cognitive impairments irrespective of diagnosis. However, Madre et al. [287] suggest that the degree of cognitive impairments in schizoaffective disorder is closer to that of schizophrenia than bipolar disorder and schizoaffective disorder may represent a subtype of schizophrenia. Whilst there is some agreement across these reviews, to date there have been no attempts to aggregate the existing data into a meta-analysis. In addition, no reviews have examined the subtypes of schizoaffective disorder. This is an important consideration, as there is evidence to suggest that the depressive subtype of schizoaffective disorder may be associated with cognitive impairment closer to that of schizophrenia, whilst those with the bipolar subtype are less impaired [266]. This suggests that the proportion of each subtype included in schizoaffective disorder samples could bias study results.

2.2 Chapter aims and hypotheses

The aim of this chapter was to review studies that compared cognitive performance in participants with schizoaffective disorder to those with schizophrenia or bipolar disorder. To date, no meta-analyses have been conducted comparing schizoaffective disorder and bipolar disorder. Studies that compared the subtypes of schizoaffective disorder to schizophrenia and bipolar disorder were also reviewed. The main hypothesis was that cognitive impairments in schizoaffective disorder would be intermediate between those observed in bipolar disorder and schizophrenia. A further hypothesis was that the depressive subtype of schizoaffective disorder would be associated with more severe cognitive impairments similar to schizophrenia, whilst impairments in the bipolar subtype would be less severe than those of schizophrenia but more impaired than those of bipolar disorder.

2.3 Method

2.3.1 Study selection

This review was conducted following guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [288]. Searches were conducted using the following databases: PubMed, PsycINFO, Web of Science and EMBASE. The period covered was between January 1980 and January 2018. The keywords, “schizophrenia”, “schizoaffective” and “bipolar” were combined with “cogniti*”, “neurocogniti*” and “neuropsycholog*”. The latter terms were also replaced with key words and phrases to describe cognitive domains (memory, attention and executive function). In addition to database searches, the bibliographies of previous reviews, meta-analyses and studies that met inclusion criteria were checked for additional studies. Another member of the research team conducted an independent search using the same strategy. The articles meeting inclusion criteria were selected based on the consensus of both reviewers. There was a high level of agreement between the reviewers. Discrepancies between the two independent reviews of the papers were resolved through discussion with a third researcher until consensus was reached.

The inclusion criteria included all full text publications that:

1. Directly compared participants with schizoaffective disorder to those with schizophrenia, bipolar disorder or both disorders but did not combine different diagnoses into a single group (e.g. affective psychosis).
2. Included adults (aged 16 years or over) diagnosed using versions of DSM, ICD or Research Diagnostic Criteria (RDC).
3. Included published assessments of cognition for the following domains: executive function, speed of processing, working memory, immediate verbal memory, immediate visual memory or verbal fluency.
4. Reported independent data. When studies with overlapping samples were identified and both met inclusion criteria, the study with the largest sample was selected.

Studies were excluded if they:

1. Compared children or adolescent participants.

2. Compared participants in their first episode of psychiatric illness.
3. Were not available in the English language.

Recorded variables were:

1. Name of the first author and year of publication
2. Number of participants in each diagnostic group and proportion of subtypes for schizoaffective disorder
3. Sample characteristics (inpatients or outpatients, diagnostic criteria used) and status of patients (acute, stabilised, in remission) where defined
4. Cognitive test or battery results. Authors were contacted for missing data.
5. Demographic and clinical variables for groups, including age, sex, education, duration of illness, age of onset and medication dose.

2.3.2 Cognitive variables

The a priori primary study outcome was general cognitive performance measure, which allowed comparisons across studies. Composite cognition effect sizes and 95% confidence intervals were calculated using the mean and standard error of the effect sizes of the individual tests or domains. This included all tests reported in each paper in order to maximise the number of studies included. Composite scores were only calculated for studies with three or more tests available, as has been done in previous studies [289].

In addition to general cognitive function, domains were selected based on the Measurement in Assessment and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative [202], which is consistent with the approach taken by our research team in our previous work [290]. The tasks or domain scores included are listed in Table 2-1. Social cognition was not included as social cognition can be separated into multiple domains, which is beyond the scope of the current review. Attention was not included due to an insufficient number of studies. The executive function domain was expanded beyond the reasoning and problem-solving domain described by the MATRICS to include other higher-level cognitive processes such as inhibitory control and cognitive flexibility. Verbal fluency was included as a separate domain given that the majority of studies included a specific measure of verbal fluency. Tasks were assigned to domains based on the

MATRICES and previous reviews [263, 286], as well as discussions within the study team. If a study included more than one task for a single domain, the effect sizes were averaged to create a single domain score. For tasks with multiple outcome measures, the most common outcome measure used across the studies was included.

Table 2-1 Tasks included in each domain

Verbal Learning	Visuospatial Learning	Executive Function	Speed of Processing	Verbal Fluency	Working Memory
BACS: List Learning	BVRT	CANTAB: Stockings of Cambridge	BACS: Symbol Coding	BACS: Verbal Fluency	BACS: Digit sequencing
CVLT	CANTAB: Paired Associates Learning	BACS: Tower of London	d2 Test	Category Fluency: Animal Naming	WAIS-R: Digit Span
HVLT-R	WMS-R: Figural Memory	BADS: Composite Score	CNTRICS: Dot Probe Expectancy	COWAT	WAIS-III: Digit Span
RAVLT	WMS-III: Visual Memory	CCST (perseverative sorts)	SDMT	DKEFS: Verbal Fluency	WAIS-R: Block Span
VLMT		DKEFS: Colour-Word Interference	TMT A (time taken)	Letter Fluency	WAIS-III: Block Span
WMS-III: Logical Memory		SCWT	WAIS-III: Symbol Search		WAIS-III: Letter-Number Sequencing
		TMT B (time taken)	WAIS-R: Digit Symbol Substitution		WM-MA 2-back
		WAIS-R: Block Design			WMS-R: Digit Span
		WAIS-III: Matrix Reasoning			WMS-R: Visual Span
		WCST (perseverative errors)			WMS-III: Letter-Number Sequencing

Abbreviations: BACS, Brief Assessment of Cognition in Schizophrenia; BADS, Behavioural Assessment of the Dysexecutive Syndrome; BVRT, Benton Visual Retention Test; CANTAB, Cambridge Neuropsychological Test Automated Battery; CCST, California Card Sorting Test; CNTRICS, Cognitive Neuroscience Test Reliability and Clinical Applications for Schizophrenia; COWAT, Controlled Oral Word Association Test; CVLT, California Verbal Learning Test; D-KEFS, Delis-Kaplan Executive Function System; HVLT-R, Hopkins Verbal Learning Test – Revised; RAVLT, Rey Auditory Verbal Learning Test; SCWT, Stroop Colour-Word Test; SDMT, Symbol Digits Modalities Test; TMT, Trail Making Test; VLMT, Verbal Learning & Retention Test; WAIS-III, Wechsler Adult Intelligence Scale - Third Edition; WAIS-R, Wechsler Adult Intelligence Scale – Revised Edition; WCST, Wisconsin Card Sorting Test; WM-MA, Working Memory – Mental Arithmetic Test; WMS-III, Wechsler Memory Scale – Third Edition; WMS-R, Wechsler Memory Scale – Revised Edition.

2.3.3 Statistical analyses

Meta-analyses were conducted to compare general cognitive performance and domain-specific cognition between the following diagnoses:

1. Schizoaffective disorder and schizophrenia (N=20)
2. Schizoaffective disorder and bipolar disorder (N=8)
3. Schizoaffective disorder – depressive type and schizophrenia (N=3)
4. Schizoaffective disorder – depressive type and bipolar disorder (N=2)
5. Schizoaffective disorder – bipolar type and schizophrenia (N=2)
6. Schizoaffective disorder – bipolar type and bipolar disorder (N=3)

Hedges' g effect sizes were calculated for each pair of comparisons using the formulas described by Rosnow and Rosenthal [291] and Rosnow, Rosenthal and Rubin [292] (for formulas see Appendix A). Hedge's correction for bias was used due to uneven group sizes to calculate the pooled standard deviation [293]. All effect sizes were calculated such that a positive effect size would indicate that the schizoaffective disorder group had performed better than the comparison group. Where papers had reported the subtypes of disorders separately (for example, paranoid and undifferentiated types of schizophrenia), the means and standard deviations were pooled to create a single diagnostic group.

Meta-analyses were conducted using the package, "meta" in R v3.3.1. A random effects model was used (DerSimonian-Laird estimate [294]). Effect sizes were weighted using the inverse variance method. Homogeneity of the effect sizes was tested using the Q-test. Funnel plots and Egger's test were used to assess reporting bias. Homogeneity statistics Q_{bet} were calculated to compare the pooled effect sizes between the subtypes of schizoaffective disorder (i.e. the results of the schizoaffective bipolar/schizophrenia meta-analysis were compared with the schizoaffective depressive/schizophrenia meta-analysis and this was repeated for bipolar disorder).

Two sets of sensitivity analyses were performed. Firstly, the meta-analysis comparing bipolar disorder and schizoaffective disorder was repeated excluding papers that included bipolar disorder - type II in their sample. Secondly, the

analyses were repeated excluding two studies that had samples with a mean age between 58 and 65 years.

Meta-regression analyses were conducted to investigate the influence of five variables on the composite cognition findings. These variables were age, sex, age of onset, duration of illness and education. These variables have been shown to be associated with cognitive function and have been examined in previous meta-analyses of cognitive function in schizophrenia and bipolar disorder [263, 264]. There were an insufficient number of studies to investigate the influence of antipsychotic dose. Only three studies comparing schizophrenia and schizoaffective disorder reported medication dose, whilst none of the bipolar disorder studies had included this data. Meta-regression analyses were performed with a random effects model using the restricted-information maximum likelihood method.

2.4 Results

2.4.1 Retrieved studies

One hundred and seventy-seven records were identified from the initial searches and the abstracts screened for inclusion. Initially, 130 studies were excluded as either duplicates or not meeting inclusion criteria. A further 17 articles were excluded after examination of the full texts, mainly because these studies had combined diagnostic groups and thus we were unable to calculate separate effect sizes. This resulted in 30 studies being included in the systematic review and 29 in the meta-analysis (summary statistics or effect sizes were not available for one study). In total, there were 1462 participants with schizoaffective disorder, 2845 participants with schizophrenia and 1054 participants with bipolar disorder. Figure 2-1 shows the PRISMA flowchart illustrating the process of filtering potential studies. The final studies included are shown in Table 2-2. Not all the studies included in this chapter provided information on the subtypes of schizophrenia, schizoaffective disorder or bipolar disorder included in their sample. Information on subtypes was included if this information was provided in the paper.

The results are presented in three main sections:

1. Comparisons between schizoaffective disorder and schizophrenia (22 studies)
2. Comparisons between schizoaffective disorder and bipolar disorder (8 studies)
3. Comparisons of all three disorders. This final section summarises the results of 11 studies (out of the 30 studies above) that compared all three disorders.

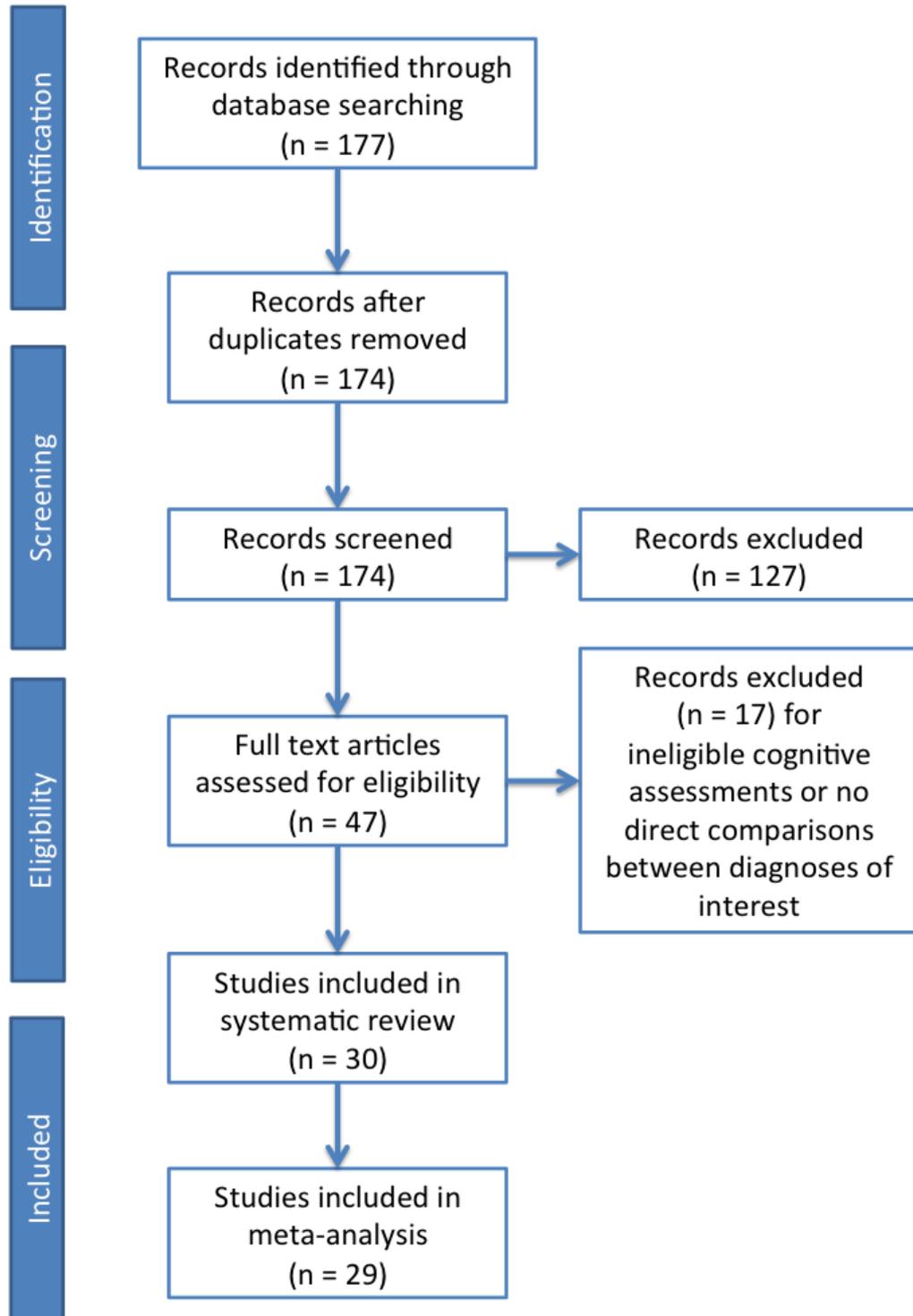


Figure 2-1 PRISMA flowchart illustrating the methodological process of filtering potential studies

The records excluded at the screening phase (n=127) included 22 reviews and meta-analyses, 88 studies that compared schizophrenia and bipolar disorder but not schizoaffective disorder and 17 studies that did not fit the aims of this reviews. Full text articles were excluded due to combining diagnoses (n=10), children or adolescent participants (n=2), studies with unsuitable cognitive assessments (n=3) or studies reported proportion of participants impaired or not impaired (n=2).

Table 2-2 Summary of studies included in systematic review

Study	Sample	Sample Characteristics	Cognitive Assessment	Hedge's g	
				SA vs. SZ	SA vs. BD
Amann et al. [295]	26 SA (bipolar)	Acutely unwell inpatients	WMS-III Verbal Memory	0.37	0.16
	45 SZ	DSM-IV	WMS-III Working Memory	0.02	0.05
	51 BD	Schizoaffective group also	WMS-III Visual Memory	0.26	-0.07
	65 HC	met RDC	BADS Total	-0.12	0.12
Beatty et al. [296]	11 SA	Outpatients	CCST free sorting (perseverative sorts)	0.26	
	10 SZ (3 paranoid, 7 undifferentiated)	DSM-III-R			
Birindelli et al. [297]	40 SA	Outpatients	CVLT (trials 1-5)	0.56	
	64 SZ	DSM-IV-TR	TMT A	0.08	
		In remission	TMT B	0.21	
			WCST (perseverative errors)	0.43	
Bornstein et al. [298]	18 SA	Primarily outpatients	WAIS-R Verbal IQ	0.29	
	55 SZ (28 paranoid, 27 non-paranoid)	DSM-III-R	WAIS-R Performance IQ	0.11	
	52 HC		HRB Category Test (no of errors)	0.11	
			WCST (perseverative errors)	0.66	
			VCAT	0.90	
			Verbal Fluency	-0.26	
			Verbal WMS-R	0.42	
			Spatial WMS-R	-0.01	
			HRB TPT Time	0.24	
			HRB TPT Memory	-0.55	
			HRB TPT Location	0.47	
			HRB Speech Perception	0.22	
			HRB Seashore Rhythm	0.17	
		HRB TMT A	0.13		
		HRB TMT B	0.47		

Table 2-2 (cont.) Summary of studies included in systematic review

Study	Sample	Sample Characteristics	Cognitive Assessment	Hedge's g	
				SA vs. SZ	SA vs. BD
Bornstein et al. [298] (cont.)	18 SA 55 SZ (28 paranoid, 27 non-paranoid) 52 HC	Primarily outpatients DSM-III-R	HRB Finger Tap (right)	0.19	
			HRB Finger Tap (left)	0.34	
			HRB Grooved Peg (right)	0.40	
			HRB Grooved Peg (left)	0.05	
			HRB Finger Agnosia (right)	0.54	
			HRB Finger Agnosia (left)	0.35	
			HRB Graphesthesia (right)	0.42	
			HRB Graphesthesia (left)	0.29	
DeRosse et al. [299]	129 SA 595 SZ (224 with mood, 371 without mood) 269 BD (Type-I with psychosis)	Inpatients and outpatients DSM-IV	WAIS-R Digit Span	0.004	-0.27
			CVLT	0.33	-0.23
			COWAT	-0.02	-0.06
			Verbal Fluency: Animal Naming	0.08	-0.28
			TMT A	0.10	-0.08
			TMT B	0.04	-0.38
Evans et al. [300]	24 SA (depressive and bipolar subtypes) 115 SZ	Outpatients, including veterans DSM-III-R	Verbal Ability	-0.02	
			<i>Aphasia Screening Test</i>		
			<i>WAIS-R Vocabulary</i>		
			<i>Boston Naming Test</i>		
			<i>WAIS-R Similarities</i>		
			<i>Thurstone Written Fluency</i>		
			<i>COWAT (FAS)</i>		

Table 2-2 (cont.) Summary of studies included in systematic review

Study	Sample	Sample Characteristics	Cognitive Assessment	Hedge's g		
				SA vs. SZ	SA vs. BD	
Evans et al. [300] (cont.)	24 SA (depressive and bipolar subtypes) 115 SZ	Outpatients, including veterans DSM-III-R	Psychomotor Speed	-0.16		
			<i>TMT A</i>			
			<i>WAIS-R Object Assembly</i>			
			<i>WAIS-R Digit Symbol</i>			
			<i>WAIS-R Block Design</i>			
			<i>TPT</i>			
			<i>Digit Vigilance Test (time)</i>			
			Abstraction / Cognitive Flexibility			-0.34
			<i>Booklet Category Test</i>			
			<i>TMT B</i>			
			<i>WCST</i>			
			Attention			-0.18
			<i>WAIS-R Digit Span</i>			
<i>Digit Vigilance Test (errors)</i>						
Learning and Incidental Memory	-0.38					
<i>CVLT (trials 1-5)</i>						
<i>Figure Memory Test (learning)</i>						
<i>Story Memory Test (learning)</i>						
Retention	-0.32					
<i>CVLT (long delay recall)</i>						
<i>Figure Memory Test (delayed)</i>						
<i>Story Memory Test (delayed)</i>						

Table 2-2 (cont.) Summary of studies included in systematic review

Study	Sample	Sample Characteristics	Cognitive Assessment	Hedge's g	
				SA vs. SZ	SA vs. BD
Evans et al. [300] (cont.)	24 SA (depressive and bipolar subtypes) 115 SZ	Outpatients, including veterans DSM-III-R	Motor <i>Finger Tapping Test</i> <i>Grooved Pegboard Test</i> <i>Hand dynamometer</i>	-0.07	
Fiszdon et al. [301]	73 SA 199 SZ	Outpatients DSM-IV	WCST (% conceptual level) WAIS-III Digit Symbol WAIS-III Digit Span WMS-R Logical Memory I HVLТ-R WMS-R Figural Memory	0.05 0.21 0.16 0.34 0.14 0.31	
Gilvarry et al. [302]	296 SA 223 SZ	Outpatients RDC	TMT A TMT B	0.02 -0.17	
Glahn et al. [303]	15 SA (depressive) 15 SZ 26 BD (11 with history of psychosis, 15 without psychosis) 32 HC	Outpatients DSM-IV Mixture of symptomatic and remitted patients	WAIS-III Forward Digit Span WAIS-III Backward Digit Span	0.20 -0.08	-0.27 -0.38

Table 2-2 (cont.) Summary of studies included in systematic review

Study	Sample	Sample Characteristics	Cognitive Assessment	Hedge's g	
				SA vs. SZ	SA vs. BD
Goldstein et al. [304]	20 SA 63 SZ (29 undifferentiated, 20 paranoid, 14 residual)	Male veterans Stabilised inpatients DSM-III-R	HRB Category Test	0.72	
			HRB TPT	0.31	
			TMT B	0.56	
			WCST (errors)	0.14	
			WAIS-R Information	0.27	
			WAIS-R Digit Span	-0.11	
			WAIS-R Vocabulary	0.85	
			WAIS-R Arithmetic	0.77	
			WAIS-R Comprehension	1.05	
			WAIS-R Similarities	0.17	
			WAIS-R Picture Completion	0.55	
			WAIS-R Picture Arrangement	0.21	
			WAIS-R Block Design	0.42	
			WAIS-R Object Assembly	0.23	
WAIS-R Digit Symbol	0.35				
Gooding & Tallent [305]	23 SA (19 bipolar, 4 depressive) 34 SZ (15 paranoid, 12 residual, 6 undifferentiated, 1 disorganised) 30 HC	Outpatients RDC	WCST (perseverative errors)	-0.18	

Table 2-2 (cont.) Summary of studies included in systematic review

Study	Sample	Sample Characteristics	Cognitive Assessment	Hedge's g	
				SA vs. SZ	SA vs. BD
Heinrichs et al. [306]	48 SA	Outpatients	WAIS-III Vocabulary	0.70	
	103 SZ	DSM-IV	WAIS-III Matrix Reasoning	0.50	
	72 HC		WAIS-III Letter-Number	0.53	
			WAIS-III Symbol Search	0.63	
			CVLT (trials 1-5)	0.65	
			COWAT	0.46	
			WRAT-3 Reading	0.44	
Hill et al. [266]	165 SA (55 depressive, 110 bipolar)	Outpatients DSM-IV	BACS Verbal Memory	0.05	-0.37
	293 SZ		BACS Tower of London	0.38	-0.24
	227 BD (all with history of psychosis)		BACS Symbol Coding	0.33	-0.17
	295 HC		BACS Verbal Fluency	0.14	-0.32
			BACS Digit Sequencing	0.10	-0.37
Leposavic et al. [307]	30 SA	Stabilised inpatients	VITI Information	-0.23	
	31 SZ (paranoid)	ICD-10	VITI Digit Span	-0.31	
	30 HC		VITI Vocabulary	-0.17	
			VITI Arithmetic	-0.65	
			VITI Comprehension	-0.38	
			VITI Similarities	-0.08	
			VITI Picture Completion	-0.19	
			VITI Picture Arrangement	-0.07	
			VITI Block Design	-0.90	

Table 2-2 (cont.) Summary of studies included in systematic review

Study	Sample	Sample Characteristics	Cognitive Assessment	Hedge's g				
				SA vs. SZ	SA vs. BD			
Leposavic et al. [307] (cont.)	30 SA 31 SZ (paranoid) 30 HC	Stabilised inpatients ICD-10	VITI Object Assembly	-0.85				
			VITI Digit Symbol	-0.44				
			MMSE	-2.42				
			TMT A	0.16				
			TMT B	-0.22				
			HVOT	0.42				
			RCF (delayed recall)	-0.34				
			RAVLT (total words)	0.22				
			WCST (perseverative errors)	-0.77				
Lewandowski et al. [308]	29 SA (all bipolar type) 25 SZ 31 BD (all with history of psychosis) 20 HC	Stabilised inpatients and outpatients DSM-IV-TR	TMT B	0.69	-0.07			
			Maj [309]	16 SA (all depressive type) 20 SZ 20 HC	Inpatients and outpatients RDC	LNNB Motor	0.31	
						LNNB Rhythm	0.23	
						LNNB Tactile	0.13	
LNNB Visual	0.31							
LNNB Receptive Speech	0.32							
LNNB Expressive Speech	0.43							
LNNB Writing	0.35							
LNNB Reading	0.41							
LNNB Arithmetic	0.14							
LNNB Memory	0.24							
LNNB Intellectual Processes	0.18							
LNNB Pathognomic	0.36							

Table 2-2 (cont.) Summary of studies included in systematic review

Study	Sample	Sample Characteristics	Cognitive Assessment	Hedge's g	
				SA vs. SZ	SA vs. BD
Maj [309] (cont.)	16 SA (all depressive type) 20 SZ 20 HC	Inpatients and outpatients RDC	LNNB Left Hemisphere	0.27	
			LNNB Right Hemisphere	0.23	
Miller et al. [310]	26 SA (9 bipolar, 17 depressive) 26 SZ (8 paranoid, 3 undifferentiated, 4 residual, 1 disorganised)	Male veterans Inpatients RDC	LNNB Motor	-0.35	
			LNNB Rhythm	0.02	
			LNNB Tactile	0.05	
			LNNB Visual	-0.15	
			LNNB Receptive Speech	0.01	
			LNNB Expressive Speech	-0.44	
			LNNB Writing	-0.31	
			LNNB Reading	-0.18	
			LNNB Arithmetic	-0.51	
			LNNB Memory	-0.36	
			LNNB Intellectual Processes	-0.08	
			LNNB Pathognomic	0.05	
			LNNB Left Hemisphere	0.03	
			LNNB Right Hemisphere	-0.08	
BVRT	-0.53				
RAVLT (trials 1-5)	-0.09				
WAIS-R Verbal IQ	-0.24				
WAIS-R Performance IQ	-0.21				

Table 2-2 (cont.) Summary of studies included in systematic review

Study	Sample	Sample Characteristics	Cognitive Assessment	Hedge's g		
				SA vs. SZ	SA vs. BD	
Mueser et al. [311]	52 SA 51 SZ 36 BD	Outpatients aged 50 or older DSM-IV	Administered the DKEFS battery and derived factor scores (domains) using principal components analysis:			
				Memory	0.01	-0.04
				Verbal Fluency	0.01	-0.03
				Psychomotor Speed	0.01	-0.05
				Executive Functioning	0.02	-0.04
Owoso et al. [312]	63 SA 188 SZ 268 HC	Outpatients DSM-IV-TR	CNTRICS: Dot Probe Expectancy	-0.07		
Pinna et al. [313]	66 SA 46 SZ	Outpatients DSM-IV-TR	MMSE	0.05		
			BACS Verbal Memory	0.21		
			BACS Working Memory	0.02		
			BACS Letter Fluency	0.28		
			BACS Semantic Fluency	0.18		
			BACS Symbol Coding	-0.07		
			BACS Tower of London	0.03		
Reichenberg et al. [314]*	78 BD (all with history of psychosis) 15 SA 94 SZ	Longitudinal study – tasks administered at 24 month follow-up from first admission DSM-IV	WAIS-R Vocabulary			
			WAIS-R Information			
			WMS-R Verbal Paired Associates			
			WMS-R Visual Reproduction			
			SCWT			
			TMT A TMT B			

Table 2-2 (cont.) Summary of studies included in systematic review

Study	Sample	Sample Characteristics	Cognitive Assessment	Hedge's g	
				SA vs. SZ	SA vs. BD
Reichenberg et al. [314] (cont.)*	78 BD (all with history of psychosis) 15 SA 94 SZ	Longitudinal study – tasks administered at 24 month follow-up from first admission DSM-IV	WAIS-R Picture Completion SDMT WAIS-R Digit Symbol Coding Letter Fluency Test Sentence Repetition Test		
Savage et al. [315]	20 SA 41 SZ (20 paranoid, 21 undifferentiated)	Outpatients DSM-IV	SDMT Anomalous Sentences Repetition Test TMT A TMT B COWAT	0.45 0.15 0.67 0.24 0.51	
Simonsen et al. [316]	27 SA 102 SZ 136 BD (75 with history of psychosis & 61 without / 80 Type-I & 56 Type-II) 280 HC	Inpatients and outpatients DSM-IV	WMS-III Logical Memory CVLT WAIS-III Digit Symbol WAIS-III Backward Digit Span WM-MA 2-back D-KEFS Phonetic Fluency D-KEFS Semantic Fluency D-KEFS Set Shifting D-KEFS Colour-Word Interference	0.26 0.12 0.07 0.10 -0.04 0.10 -0.13 -0.08 -0.08	-0.27 -0.62 -0.58 -0.27 -0.40 -0.15 -0.53 -0.51 -0.60
Stip et al. [317]	13 SA 44 SZ	Outpatients DSM-IV	CANTAB Motor Screening CANTAB Reaction Time CANTAB Stockings of Cambridge CANTAB Paired Associates Learning	0.67 -0.02 -0.20 0.40	

Table 2-2 (cont.) Summary of studies included in systematic review

Study	Sample	Sample Characteristics	Cognitive Assessment	Hedge's g	
				SA vs. SZ	SA vs. BD
Studentkowski et al. [318]	28 SA	DSM-IV	d2 Test (concentration)		-0.14
	32 BD	Outpatients	TMT A		-0.63
			TMT B		-0.48
			WAIS Forward Digit Span		-0.59
			WAIS Backward Digit Span		-0.25
			WAIS Forward Block Span		0.72
			WAIS Backward Block Span		-0.64
			VLMT		-0.73
Szoke et al. [319]	25 SA	Inpatients (recruited prior to discharge)	WCST	0.27	-0.65
	48 SZ				
	92 BD (52 with history of psychosis & 40 without)	DSM-IV			
	48 HC				
Torniainen et al. [320]	62 SA (52 bipolar, 10 depressive)	Outpatients	WAIS-R: Vocabulary	0.44	
		DSM-IV	WAIS-R: Digit Symbol	0.42	
	218 SZ		TMT A	0.34	
	123 HC		TMT B	0.03	
			WMS-R: Forward Digit Span	0	
			WMS-R: Backward Digit Span	0.19	
			WMS-R: Forward Visual Span	0.22	
			WMS-R Backward Visual Span	0.32	
			CVLT	0.60	

Table 2-2 (cont.) Summary of studies included in systematic review

Study	Sample	Sample Characteristics	Cognitive Assessment	Hedge's g	
				SA vs. SZ	SA vs. BD
Torrent et al. [321]	34 SA (bipolar) 41 BD (16 Type – I, 25 Type – II, no psychosis) 35 HC	Outpatients DSM-IV	WCST		-0.11
			SCWT		0.11
			WAIS Forward Digit Span		-0.13
			WAIS Backward Digit Span		0.06
			TMT A		-0.31
			TMT B		-0.54
			COWAT (FAS)		-0.38
			Category Fluency: Animal Naming		-0.48
		CVLT		-0.84	
Van Rheenen et al. [322]	33 SA 49 SZ 35 BD (all Type-I; 26 with psychosis, 9 without)	Outpatients DSM-IV-TR	Processing Speed	0.24	-0.20
			<i>Digit Symbol Coding</i>		
			<i>TMT A</i>		
			<i>DKEFS Colour-Word</i>		
			<i>Interference (word reading and colour naming)</i>		
			Immediate Memory	0.92	0.51
			<i>BVMT-R (trial 1)</i>		
			<i>HVLT-R (trial 1)</i>		
			Learning	0.24	-0.07
			<i>BVMT-R (trials 1-3)</i>		
<i>HVLT-R (trials 1-3)</i>					
Semantic Memory	0.59	-0.67			
		<i>Category Fluency: Animal Naming</i>			

Table 2-2 (cont.) Summary of studies included in systematic review

Study	Sample	Sample Characteristics	Cognitive Assessment	Hedge's g	
				SA vs. SZ	SA vs. BD
Van Rheenen et al. [322] (cont.)	33 SA	Outpatients	Attention / Vigilance	0.19	0.05
	49 SZ	DSM-IV-TR	<i>CPT-IP</i>		
	35 BD (all Type-I; 26 with psychosis, 9 without)		Working Memory <i>Letter-Number Span</i> <i>WMS: Spatial Span (backwards)</i>	0.01	-0.03
			Executive Function <i>NAB Mazes</i> <i>DKEFS Colour-Word Interference (interference / switching blocks)</i>	0.18	0.26
Varma et al. [323]	35 SA	Outpatients	WCST (perseverative errors)	0.10	
	48 SZ	DSM-IV	SCWT	-0.03	
	48 HC		VMPT	-0.28	

*Study not included in meta-analysis, as summary data and effect sizes were not reported. *Abbreviations:* BD, Bipolar Disorder; SA, Schizoaffective Disorder; SZ, Schizophrenia; BACS, Brief Assessment of Cognition in Schizophrenia; BADS, Behavioural Assessment of the Dysexecutive Syndrome; BVRT, Benton Visual Retention Test; CANTAB, Cambridge Neuropsychological Test Automated Battery; CCST, California Card Sorting Test; CNTRICS, Cognitive Neuroscience Test Reliability and Clinical Applications for Schizophrenia; COWAT, Controlled Oral Word Association Test; CPT-IP, Continuous Performance Test – Identical Pairs; CVLT, California Verbal Learning Test; D-KEFS, Delis-Kaplan Executive Function System; HRB, Halstead-Reitan Neuropsychological Battery; HVLN-R, Hopkins Verbal Learning Test – Revised; HVOT, Hooper Visual Organisation Test, LNNB, Luria-Nebraska Neuropsychological Battery; RAVLT, Rey Auditory Verbal Learning Test; RCF, Rey Complex Figure Test; SCWT, Stroop Colour-Word Test; SDMT, Symbol Digits Modalities Test; TMT, Trail Making Test; TPT, Tactual Performance Test; VCAT, Verbal Concept Attainment Test; VITI, Wechsler's Individual Test of Intelligence, Serbian translation of WAIS; VLMT, Verbal Learning & Retention Test; WAIS-III, Wechsler Adult Intelligence Scale - Third Edition; WAIS-R, Wechsler Adult Intelligence Scale – Revised Edition; WCST, Wisconsin Card Sorting Test; WM-MA, Working Memory – Mental Arithmetic Test; WMS-III, Wechsler Memory Scale – Third Edition; WMS-R, Wechsler Memory Scale – Revised Edition; WRAT, Wide Range Achievement Test.

2.4.2 Schizophrenia and schizoaffective disorder

Meta-analysis

Composite cognition effect sizes were calculated for 20 studies comparing schizoaffective disorder (n=928) and schizophrenia (n=2246). Participants with schizoaffective disorder performed better than participants with schizophrenia based on composite cognition scores ($g=0.16$, $p=0.0004$, see Figure 2-2). Effect size distributions were homogeneous ($T^2=0.007$; $Q=22.81$, $p=0.25$) and there was no evidence of publication bias (Egger: bias = -0.33). When the two studies with older samples were excluded, the effect size was slightly larger ($g=0.20$, see Appendix B).

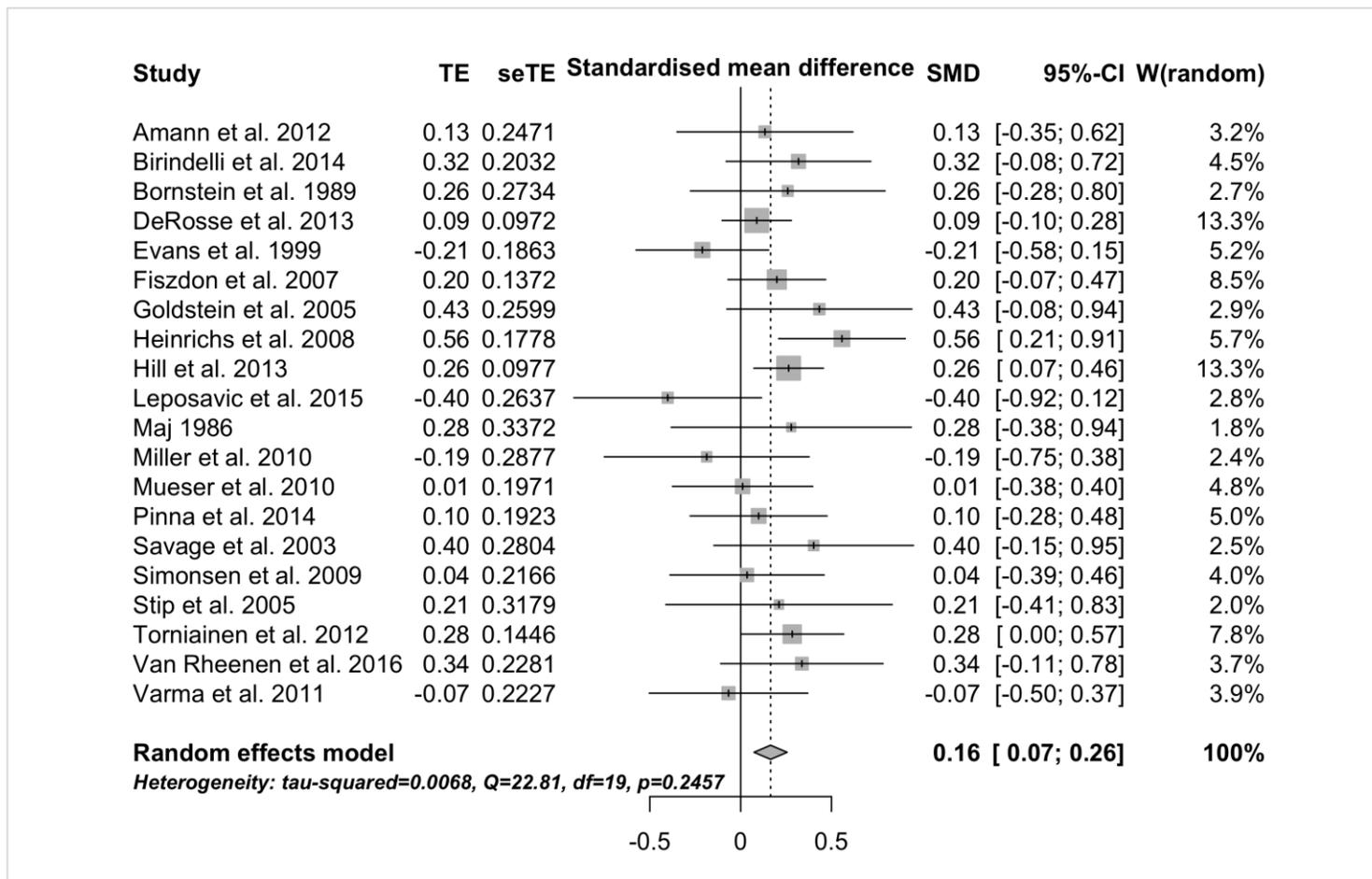


Figure 2-2 Forest plot of individual and pooled random effect estimates of mean differences between schizophrenia and schizoaffective disorder

Positive effect sizes indicate better performance in the schizoaffective disorder group.

Cognitive domains

In analyses examining individual cognitive domains, the schizoaffective group outperformed the schizophrenia group in verbal learning ($g=0.27$) and speed of processing ($g=0.18$), although there was evidence of heterogeneity (*verbal learning*: $Q=33.91$, $p=0.01$; *speed of processing*: $Q=22.11$, $p=0.05$, see Table 2-3).

Table 2-3 Pooled effect sizes for comparisons between schizoaffective disorder and schizophrenia

Domain	Studies (N)	SZ (N)	SA (N)	g	95% CI	Z	P	Q-test P	Bias
Verbal learning	13	1825	745	0.27	0.12 - 0.41	3.65	0.0003	0.01	0.17
Visuospatial learning	5	369	156	0.14	-0.14 - 0.42	1.00	0.32	0.15	-1.93
Executive function	19	2135	1132	0.12	-0.01 - 0.26	1.77	0.08	0.001	0.63
Speed of processing	14	2268	1106	0.18	0.08 - 0.29	3.33	0.001	0.05	0.82
Verbal fluency	6	1243	486	0.16	-0.003 - 0.33	1.93	0.05	0.08	0.74
Working memory	11	1710	661	0.10	-0.01 - 0.20	1.84	0.07	0.37	-0.27

SA, schizoaffective disorder; SZ, schizophrenia. Positive effect sizes indicate better performance in the schizoaffective disorder group.

Schizoaffective disorder subtypes

The meta-analyses were repeated for the separate subtypes of schizoaffective disorder: schizoaffective bipolar type and schizoaffective depressive type (see Figure 2-3 for results). Only a small number of studies had reported separate statistics for the subtypes of schizoaffective disorder or only included one subtype in their sample. There was no significant difference between participants with schizophrenia and participants with schizoaffective disorder – depressive type ($g=0.16$, $p=0.22$). Participants with schizoaffective disorder – bipolar type outperformed participants with schizophrenia ($g=0.22$, $p=0.03$). The results of the Q-test and Egger's test indicated that there was little evidence of heterogeneity or publication bias but these tests have low power when there is only a small number of studies included. The Q_{bet} test was not significant for differences in the effect sizes between schizophrenia/schizoaffective depressive and schizophrenia/schizoaffective bipolar comparisons ($p=0.67$).

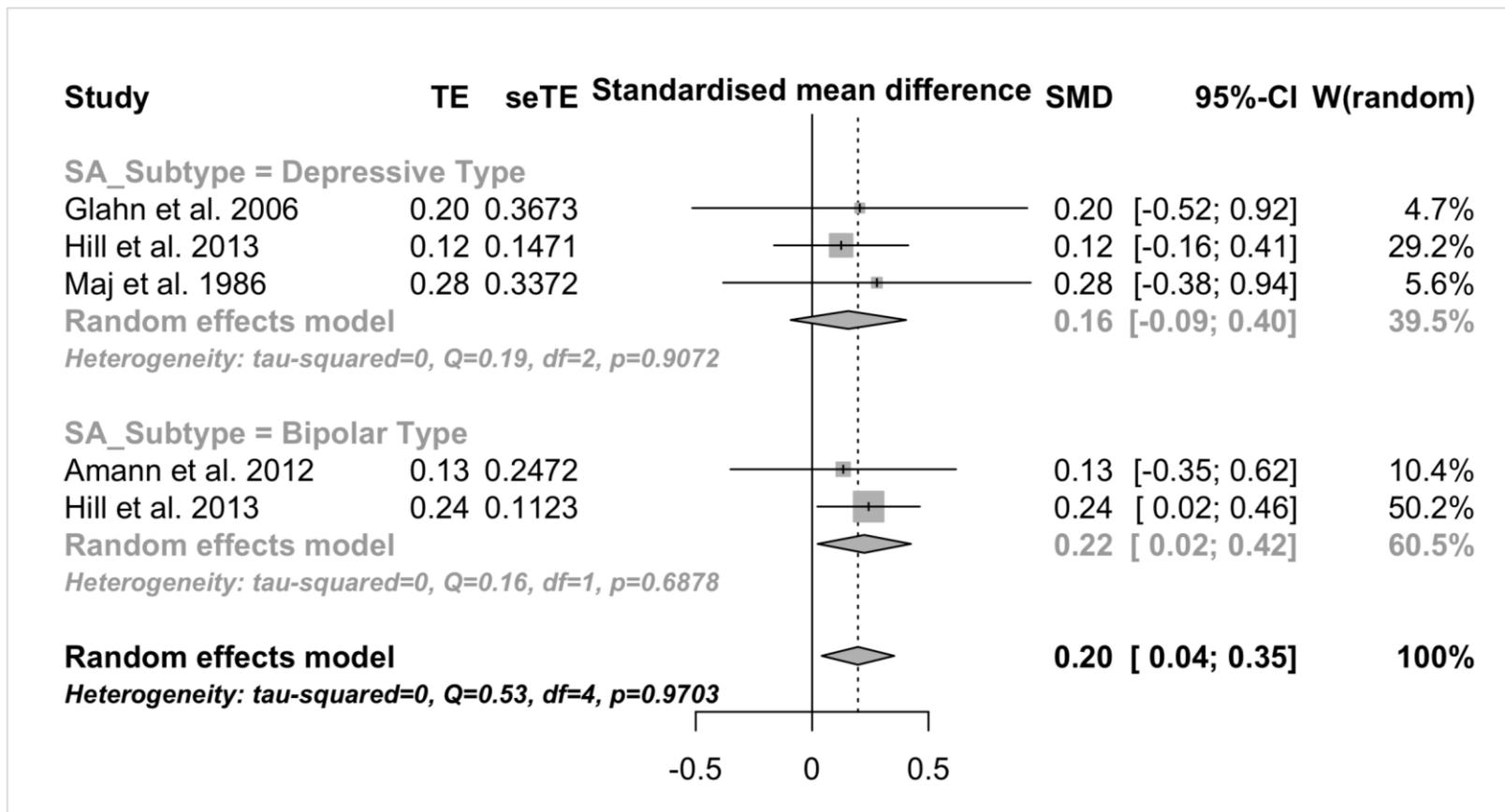


Figure 2-3 Forest plot of individual and pooled random effect estimates of mean differences between subtypes of schizoaffective disorder and schizophrenia

Schizoaffective disorder – depressive type (participant N=86) vs. schizophrenia (participant N=328) comparison: Egger’s test bias = 0.57. Egger’s bias cannot be calculated for the schizoaffective disorder – bipolar type (participant N=136) vs. schizophrenia (participant N=272) comparison. Positive effect sizes indicate better performance in the schizoaffective disorder group.

Meta-regression analyses

Meta-regression analyses were conducted to investigate the influence of five variables on the composite cognition findings. These variables were age, sex, age of onset, duration of illness and education. Meta-regression analyses were not significant for any of the variables examined (see Table 2-4).

Table 2-4 Results of meta-regression analyses

	N	B	95% CIs	p
Age	20	-0.06	-0.52 – 0.41	0.81
Age of Onset	8	0.69	-0.11 – 1.49	0.09
Duration of Illness	11	0.21	-0.23 – 0.65	0.36
Years in Education	13	0.12	-0.08 – 0.31	0.24
Sex	15	-0.002	-0.15 – 0.14	0.98

Summary

Twenty-two studies directly compared cognitive function between participants with schizophrenia and schizoaffective disorder. There is evidence to suggest that those with schizophrenia are more impaired on measures of verbal memory [297, 298, 306, 320], executive function [297, 298, 306], working memory [306, 320], verbal fluency [306], processing speed [298, 306, 315, 320] and visuospatial memory [317]. Hill et al. [266] reported greater overall impairment in the schizophrenia group compared to the schizoaffective disorder group.

Negative symptoms were strongly associated with cognitive performance in one study [320] and lower cognitive abilities were demonstrated in those with non-paranoid subtypes of schizophrenia such as undifferentiated type compared to paranoid schizophrenia and schizoaffective disorder [298, 304, 315]. This suggests that severity of cognitive impairments may be differentiated on the basis of the presence of negative symptoms rather than diagnosis. When Heinrichs et al. [306] entered cognitive scores into a regression model, performance correctly classified 91% of participants as being diagnosed with schizophrenia but 65% of participants with schizoaffective disorder were misclassified as having schizophrenia

suggesting there is a large overlap in cognitive function. This is supported by a number of studies that did not report differences between schizophrenia and schizoaffective disorder [296, 300-302, 305, 310, 312, 313, 323]. In addition, one study reported better performance of participants with paranoid schizophrenia compared to schizoaffective disorder [307].

Five studies reported information regarding the subtypes of schizoaffective disorder included in their sample [266, 305, 309, 310, 320]. Two studies included higher proportions of participants with the bipolar subtype than participants with the depressive subtype (Gooding and Tallent [305]: 83% bipolar; Torniainen et al. [320]: 84% bipolar). Gooding and Tallent [305] did not find differences between schizophrenia and schizoaffective disorder on the WCST. Torniainen et al. [320] reported greater impairment in the schizophrenia group, which was associated with more symptomatology and higher doses of antipsychotic medication. Miller et al. [310] reported no differences between participants with schizophrenia and schizoaffective disorder on the Luria-Nebraska Neuropsychological Battery in their sample of 17 participants with the depressive subtype and 9 with the bipolar subtype. Only one study reported comparisons between schizophrenia and a subtype of schizoaffective disorder [309]. Maj et al. [309] included participants with the depressive subtype only and reported no differences between schizophrenia and schizoaffective disorder on the Luria-Nebraska Neuropsychological Battery. Finally, three studies compared performance between the subtypes of schizoaffective disorder and did not find significant differences [266, 310, 312].

Overall, studies have reported conflicting findings regarding whether differences in cognitive function exist between schizoaffective disorder and schizophrenia. However, the balance of evidence suggests that cognitive performance does not differentiate those with schizophrenia and those with schizoaffective disorder, particularly after accounting for clinical features. There was a lack of evidence suggesting differences between the subtypes of schizoaffective disorder but few studies had examined this and sample sizes were small. To date, only one study has compared participants with a specific subtype of schizoaffective disorder to participants with schizophrenia.

2.4.3 Bipolar disorder and schizoaffective disorder

Meta-analysis

Composite cognition effect sizes were calculated for 8 studies comparing schizoaffective disorder (n=494) and bipolar disorder (n=827). Participants with schizoaffective disorder performed worse than participants with bipolar disorder ($g=-0.27$, $p<0.0001$, see Figure 2-4). Effect size distributions were homogeneous ($T^2<0.0001$; $Q=6.81$, $p=0.45$) and there was no evidence of publication bias (Egger: bias = 1.11). These results did not change when the analysis was repeated including participants with bipolar disorder – type I only ($g=-0.27$, see Appendix B). When the two studies with older samples were excluded, the effect size was slightly larger ($g=-0.28$, see Appendix B).

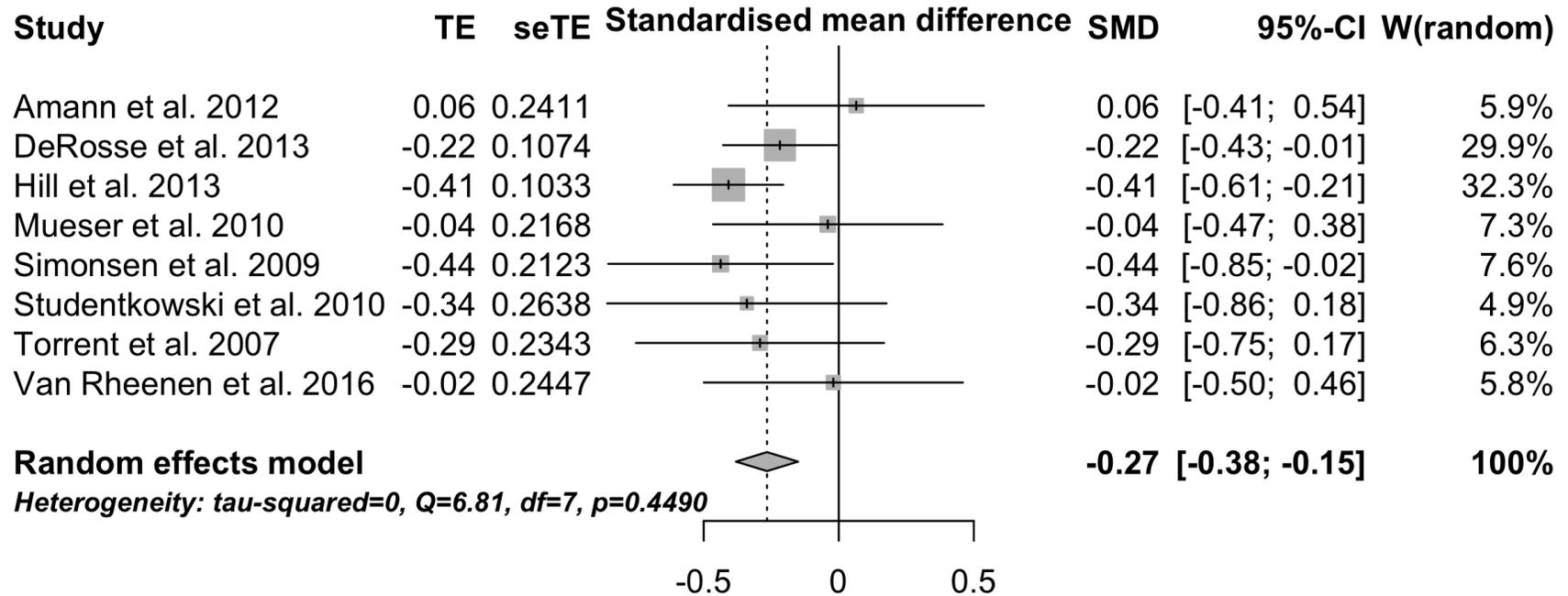


Figure 2-4 Forest plot of individual and pooled random effect estimates of mean differences between schizoaffective disorder and bipolar disorder

Positive effect sizes indicate better performance in the schizoaffective disorder group.

Cognitive domains

In analyses examining individual cognitive domains, performance in the schizoaffective group was worse than bipolar disorder in verbal learning ($g=-0.41$), executive function ($g=-0.32$), speed of processing ($g=-0.27$), verbal fluency ($g=-0.31$) and working memory ($g=-0.28$, see Table 2-5). Data comparing visuospatial learning between bipolar disorder and schizoaffective disorder were not available. There was evidence of heterogeneity in the effect sizes for verbal learning ($Q=13.41$, $p=0.02$).

Table 2-5 Pooled effect sizes for comparisons between schizoaffective disorder and bipolar disorder

Domain	Studies (N)	BD (N)	SA (N)	g	95% CI	Z	P	Q-test P	Bias
Verbal learning	6	750	408	-0.41	-0.64 to -0.18	-3.48	0.005	0.02	-1.47
Executive function	8	877	463	-0.32	-0.46 to -0.17	-4.21	<0.0001	0.22	0.02
Speed of processing	5	705	383	-0.27	-0.47 to -0.06	-2.55	0.01	0.10	-2.54
Verbal fluency	5	708	388	-0.31	-0.44 to -0.18	-4.63	<0.0001	0.39	-1.91
Working memory	6	756	409	-0.28	-0.40 to -0.15	-4.30	<0.0001	0.42	0.75

BD, bipolar disorder; SA, schizoaffective disorder. Positive effect sizes indicate better performance in the schizoaffective disorder group.

Schizoaffective disorder subtypes

The meta-analyses were repeated for the separate subtypes of schizoaffective disorder: schizoaffective bipolar type and schizoaffective depressive type (see Figure 2-5 for results). Only a small number of studies had reported separate statistics for the subtypes of schizoaffective disorder or only included one subtype in their sample. The schizoaffective bipolar group had lower overall cognitive scores than bipolar disorder ($g=-0.22$, $p=0.02$). The schizoaffective depressive group were more impaired than those with bipolar disorder ($g=-0.37$, $p=0.007$). The results of the Q-test and Egger's test indicated that there was little evidence of heterogeneity or publication bias but these tests have low power when there is only a small number of studies included. The Q_{bet} test was not significant for differences in the effect sizes between bipolar disorder/schizoaffective depressive and bipolar disorder/schizoaffective bipolar comparisons ($p=0.36$).

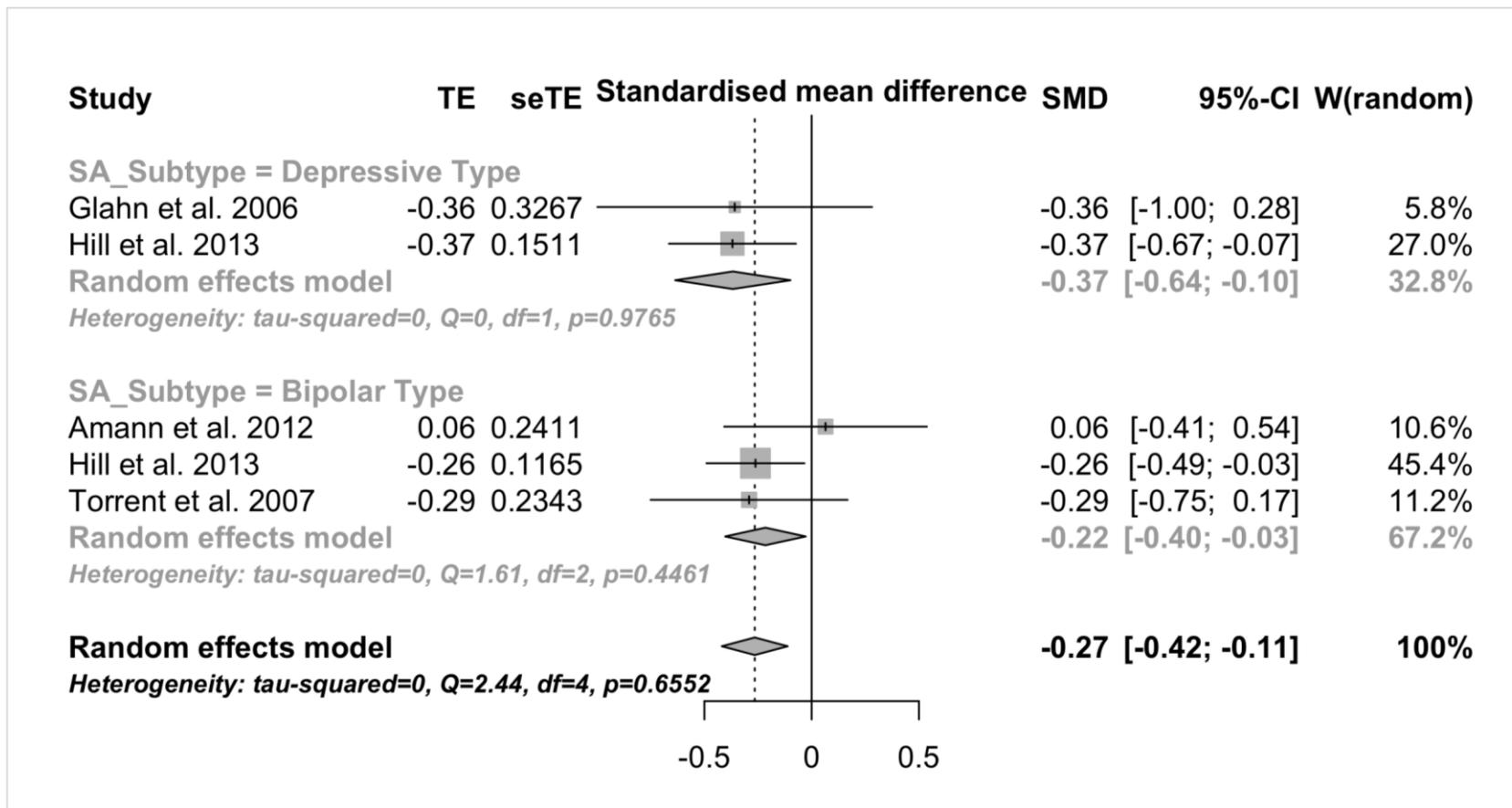


Figure 2-5 Forest plot of individual and pooled random effect estimates of mean differences between subtypes of schizoaffective disorder and bipolar disorder

Schizoaffective disorder – bipolar type (participant N=170) vs. bipolar disorder (participant N=385) comparison: Egger’s test bias = 1.24. Egger’s bias cannot be calculated for the schizoaffective disorder – depressive type (participant N=70) vs. bipolar disorder (participant N=238) comparison. Positive effect sizes indicate better performance in the schizoaffective disorder group.

Meta-regression analyses

There was insufficient data to examine the influence of age of onset and years in education for studies comparing bipolar disorder and schizoaffective disorder. Meta-regression analyses were not significant for any of the variables examined (see Table 2-6).

Table 2-6 Results of meta-regression analyses

	N	B	95% CIs	p
Age	8	0.38	-0.50 – 1.26	0.40
Duration of Illness	6	0.01	-0.55 – 0.56	0.99
Sex	8	0.02	-0.20 – 0.25	0.83

Summary

Six studies directly compared cognitive functioning between participants with schizoaffective disorder and bipolar disorder. The other two studies included in the meta-analysis reported suitable data but did not directly compare the groups. There were no differences between participants with schizoaffective disorder and bipolar disorder in a study of acutely unwell inpatients [295]. In a study of inpatients and outpatients, participants with schizoaffective disorder and bipolar disorder with a history of psychosis had similar cognitive performance [324]. However, both groups were more impaired on measures of verbal memory and verbal fluency than participants with bipolar disorder who did not have a history of psychosis [318, 324].

The remaining four studies included samples of euthymic outpatients [266, 311, 321]. One of these studies only included participants without a history of psychosis in the bipolar disorder group and participants with the bipolar subtype in the schizoaffective disorder group [321]. The study included participants with bipolar disorder – type I and type II [321]. Hill et al. [266] included participants with both subtypes of schizoaffective disorder but did not compare these subtypes separately to participants with psychotic bipolar disorder. Lifetime history of psychosis, bipolar disorder type and schizoaffective subtype was not stated in the remaining

two studies [311, 318]. In these studies, participants with schizoaffective disorder were more impaired on measures of psychomotor speed [318], verbal memory [318, 321], executive function [321] and global cognitive function [266, 311].

2.4.4 All three diagnostic groups

Of the studies included in this review, there were 11 studies comparing all three disorders. Studies that have limited their bipolar disorder group to those with a lifetime history of psychosis have primarily reported no significant differences in global cognitive function between the three disorders [295, 308, 314, 316].

Simonsen et al. [316] found severity of cognitive impairments in the bipolar with psychosis group was similar to those with a diagnosis of schizophrenia or schizoaffective disorder across measures of verbal learning and memory, working memory and executive function, whereas the performance of the bipolar without psychosis group was more comparable to the healthy control group. Two studies included only the bipolar subtype of schizoaffective disorder and reported no differences between this subtype and schizophrenia or psychotic bipolar disorder, although in both studies the participants were highly symptomatic at the time of testing [295, 308].

In the largest study to date, the cognitive profiles across the three disorders were similar but the severity of impairments increased from psychotic bipolar disorder to schizoaffective disorder to schizophrenia [266]. The authors were able to separate the subtypes of schizoaffective disorder and demonstrated lower cognitive performance in the depressive group than the bipolar group, although the differences were not significant. Two studies included participants with and without a history of psychosis in their bipolar group. These studies also found evidence of increasing impairment from bipolar disorder to schizoaffective disorder to schizophrenia on measures of executive function [319] and working memory [303]. This pattern was not consistent with the studies reporting differential patterns of performance using tasks designed to measure the same domain [303, 319]).

Whilst the studies described above have compared average cognitive performance between diagnoses, other studies have taken different approaches. DeRosse et al. [299] used a regression model to estimate cognitive decline based on performance

on measures of premorbid IQ and current cognitive function. Their results suggested that cognitive decline in schizoaffective disorder is greater than bipolar disorder. Reichenberg et al. [314] categorised participants as cognitively impaired according to three separate criteria and demonstrated higher rates of cognitive impairment in the schizophrenia and schizoaffective disorder groups compared to psychotic bipolar disorder, although average performance did not differ between groups. Van Rheenen et al. [322] used discriminant function analysis to determine if performance on cognitive tasks could separate disorders. A high proportion of those with schizoaffective disorder were misclassified as having schizophrenia or bipolar disorder, which does not provide validity for schizoaffective disorder as an independent diagnostic entity. Finally, Mueser et al. [311] showed that overall cognitive performance in males with schizoaffective disorder and females with schizophrenia was more impaired than males with bipolar disorder.

2.5 Discussion

The aim of this work described in this chapter was to compare cognitive outcomes of schizoaffective disorder with schizophrenia and bipolar disorder. This is the first meta-analysis to compare cognitive performance of participants with schizoaffective disorder and bipolar disorder. It is also the first review that has attempted to examine whether the subtypes of schizoaffective disorder differ in cognitive outcomes compared to schizophrenia and bipolar disorder.

There were three main findings:

1. Participants with schizoaffective disorder performed worse than those with bipolar disorder on global cognition and all domains.
2. Participants with schizoaffective disorder performed better than those with schizophrenia on global cognition, verbal learning, and speed of processing.
3. Cognitive impairments in participants with the depressive subtype of schizoaffective disorder are closer in severity to those seen in participants with schizophrenia, whereas participants with the bipolar subtype are more impaired than participants with bipolar disorder and less impaired than those with schizophrenia. This result was largely driven by Hill et al.'s study of 980 participants.

2.5.1 Comparisons between schizoaffective disorder and bipolar disorder

The schizoaffective disorder group exhibited worse performance across all cognitive domains compared to the bipolar disorder group. This supports the conclusions of a review by Madre et al. [287] who suggested that cognitive impairments are more severe in schizoaffective disorder than in bipolar disorder. Other reviews have concluded that bipolar disorder and psychosis is associated with similar cognitive impairments to those seen in schizoaffective disorder [284], whilst participants with bipolar disorder and no history of psychosis have less severe deficits [284-286]. Consistent with this, the current review found four studies that had identified milder or no cognitive impairments in bipolar disorder without psychosis compared to the other diagnoses [303, 316, 319, 321]. This suggests that a lifetime history of psychosis is associated with greater cognitive impairments. Lifetime history of psychosis has been associated with poorer cognitive outcomes in bipolar disorder in a meta-analysis by Bora et al. [241]. However, the exact relationship between history of psychosis and cognition remains unclear. Bora et al. found a more severe illness course for those with a history of psychosis, including a higher number of admissions, younger age of illness onset and higher percentage of antipsychotic use but these factors did not explain the association between lifetime psychosis and cognitive function. Previous studies have rated lifetime history of psychosis as a binary measure (present or absent) so it is currently unknown whether a linear relationship exists between lifetime severity, duration or frequency of psychosis and severity of cognitive impairments.

Participants with bipolar disorder – type II were not analysed separately in this chapter. Bipolar disorder – type I has been shown to be associated with more widespread cognitive impairments than type II [244]. There were a sufficient number of studies that had reported data on bipolar disorder – type I only to conduct a sensitivity analysis. The results of this sensitivity analysis were comparable to the meta-analysis including both subtypes. However, it was not possible to compare bipolar disorder – type II and schizoaffective disorder, as only one study reported separate data for participants with type II.

2.5.2 Comparisons between schizoaffective disorder and schizophrenia

Participants with schizoaffective disorder were less cognitively impaired than participants with schizophrenia. This is consistent with the findings of an earlier meta-analysis [263]. The effect size reported in the current study ($g=0.16$) fell within the range of effect sizes reported by the earlier meta-analysis ($d=0.08-0.32$). The difference between schizoaffective disorder and schizophrenia was smaller than the effect size of the schizoaffective disorder and bipolar disorder analysis ($g=0.27$). This is consistent with the conclusions drawn in the review by Madre et al. [287], which suggested that the degree of cognitive impairments in schizoaffective disorder is closer to that of schizophrenia than bipolar disorder.

The schizoaffective disorder and schizophrenia groups differed on processing speed ($g=0.18$) and verbal learning ($g=0.27$). Comparable effect sizes were reported in the meta-analysis by Bora et al. [263], which found the schizophrenia group were more impaired than the schizoaffective disorder group on verbal memory ($d=0.23$), Wisconsin Card Sorting Test ($d=0.21$) and processing speed ($d=0.24$). This is an interesting finding as previous studies have shown that most of the impairments in specific cognitive domains seen in patients with schizophrenia can be accounted for by a general intelligence factor (g). However, g does not fully account for deficits in processing speed and verbal learning [207, 208]. This suggests that these abilities may be disproportionately affected in patients with schizophrenia.

2.5.3 Cognition across the three disorders

The results of the meta-analysis indicated that cognitive performance in schizoaffective disorder was better than schizophrenia but worse than bipolar disorder. This suggests that cognitive impairments increase in severity from bipolar disorder to schizoaffective disorder to schizophrenia. However, the effect sizes were small particularly between schizoaffective disorder and schizophrenia. The magnitudes of the effect sizes across the studies were not influenced by age, sex, age of onset, duration of illness or years in education.

It has been hypothesised that schizoaffective disorder may represent the midpoint in a bipolar-schizophrenia diagnostic spectrum [325]. This spectrum ranges from bipolar disorder without psychosis at one end and schizophrenia without affective

symptoms at the other with patients with features of both disorders falling at some point in the middle [24, 325, 326]. Researchers from the B-SNIP study have created a dimension to assess lifetime psychosis and mood symptoms (the Schizo-Bipolar Scale) and examined the distribution of scores in their sample of participants diagnosed with schizophrenia, schizoaffective disorder and bipolar disorder [327]. Their findings provided support for the bipolar-schizophrenia spectrum by demonstrating that participants with schizoaffective disorder scored across the middle range of the scale and overlapped with both schizophrenia and bipolar disorder. The distribution of scores was not consistent with a clear-cut divide between schizophrenia and bipolar disorder. Higher scores on this scale (indicating more prominent psychosis and less prominent mood) have been shown to be associated with greater overall cognitive impairment [266]. Further support comes from evidence that the functional outcome of schizoaffective disorder is poorer than bipolar disorder but better than schizophrenia [179, 328]. The finding that the degree of cognitive impairment increases from bipolar disorder to schizoaffective to schizophrenia is consistent with this view.

2.5.4 Subtypes of schizoaffective disorder

Few studies reported the proportion of subtypes of schizoaffective disorder in their sample. Therefore, it is difficult to draw any firm conclusions about differences in cognitive performance between the subtypes and the results should be interpreted with caution. In the subgroup analysis, no difference in cognitive performance was detected between participants with the depressive subtype and schizophrenia, although performance was marginally better in the schizoaffective disorder - depressive type group. In contrast, participants with the bipolar type performed significantly better than participants with schizophrenia. Both subtypes were more impaired than bipolar disorder. These results suggest that the depressive subtype of schizoaffective disorder may have more severe cognitive impairments than those seen in the bipolar subtype and more closely resemble that of schizophrenia. However, the magnitude of the effect sizes did not differ between the subtypes of schizoaffective disorder.

These findings are likely driven by the results reported by Hill et al. whose sample (N=980) was much larger than any other study included in these subtype analyses.

The proportion of weight assigned to Hill et al.'s study was 79.4% in the schizophrenia comparison and 72.4% in the bipolar disorder comparison. Thus, the findings of this study had a significant impact on the results of the meta-analyses. Hill et al. reported greater impairment in the depressive subtype than the bipolar subtype but the differences between the subtypes were not significant [266]. Interestingly, this pattern of results is consistent with findings using the Schizo-Bipolar Scale. Participants with the depressive subtype had a distribution of scores on the Schizo-Bipolar Scale that were closer to those with schizophrenia, whilst the bipolar subtype scores were closer to bipolar disorder [327]. Overall, these results suggest that the depressive subtype of schizoaffective disorder may more closely resemble schizophrenia than the bipolar subtype. There is a need for more studies with sufficiently large sample sizes to compare the subtypes of schizoaffective disorder with schizophrenia and bipolar disorder.

2.5.5 Concluding statements and recommendations for future research

This meta-analysis was the first to compare schizoaffective disorder and bipolar disorder and examine the subtypes of schizoaffective disorder. These results indicate that the severity of cognitive impairments in schizoaffective disorder is intermediate between schizophrenia and bipolar disorder. There was initial evidence that participants with the subtypes of schizoaffective disorders may exhibit differing levels of impairment. However, effect sizes were small and the results of individual studies were not consistent.

Several limitations of this review should be noted. Only one large study reported separate data for the subtypes of schizoaffective disorder and was therefore assigned a large proportion of the weight in the subtype analyses (68-83%). Therefore, the results of the meta-analyses examining subtypes were driven by this single study. It would have been preferable to include multiple studies that included both subtypes but such studies have not been published. To maximise the data available, studies reporting data on a single subtype were included in the relevant meta-analysis. However, there may be differences between studies that examined the depressive subtype and studies that examined the bipolar subtype that cannot be accounted for in separate analyses and may influence the results. The studies included in this review employed different measures of cognition, which may

explain the heterogeneity in the distribution of effect sizes for some domains. However, there was little evidence of heterogeneity in the analyses of composite cognition scores. There were also differences in the inclusion of stabilised and symptomatic participants across studies and few included a definition of remission. It has been argued that cognitive impairment may be affected by illness state at the time of assessment. Meta-regression analyses were conducted to examine whether the results were influenced by between-study differences in age, sex, age of onset, duration of illness and education. However, few studies had reported data on these variables, particularly in studies comparing schizoaffective disorder and bipolar disorder, so the results of these analyses should be interpreted with caution.

This meta-analysis included studies from a wide range of countries and thus their methodologies differed on diagnostic criteria and cognitive assessments (both type and language). The use of different diagnostic criteria is particularly relevant in this meta-analysis, as criteria for schizoaffective disorder varies considerably between the Diagnostic and Statistical Manual (DSM), International Classification of Diseases (ICD) and Research Diagnostic Criteria (RDC). The majority of the studies (N=25) used DSM criteria so the diagnosis of schizoaffective disorder relied on mood symptoms being present for a substantial proportion of the total illness duration, with a period of at least two weeks of psychosis in the absence of mood. In contrast, ICD (utilised by one study) places an emphasis on first rank symptoms of schizophrenia for the diagnosis of schizoaffective disorder. Vollmer-Larsen et al. [329] demonstrated that using ICD-10 and DSM-IV to diagnose schizoaffective disorder results in a different set of patients. Four studies defined schizoaffective disorder according to the RDC. Schizoaffective disorder in RDC includes a broad range of patients including those with brief psychotic symptoms and chronic mood symptoms, and the converse [330]. Thus, participants diagnosed with RDC schizoaffective disorder are a broad, heterogeneous group. The results of this meta-analysis are most generalizable to patients diagnosed according to the DSM and the results of studies using ICD or RDC may differ from those presented here.

Several recommendations for future research can be made based on the findings of this chapter. Studies should report the clinical characteristics of their sample, including clinical status of participants (with defined remission criteria), measures

of mood and psychosis and classes and doses of psychiatric medication. These results also highlight the importance of considering heterogeneity within disorders. Combining the subtypes of schizoaffective disorder may produce conflicting results and hamper efforts to understand the relationship between this disorder and schizophrenia or bipolar disorder. There is a need for studies that are sufficiently large enough to separate the subtypes of schizoaffective disorder. As a minimum, studies should report the proportion of each subtype included in their sample. In addition to this, studies should report the proportion of their bipolar disorder group that have a lifetime history of psychosis. The current findings supported the findings of previous reviews, which have highlighted a poorer cognitive outcome for participants with bipolar disorder with psychosis compared to those without psychosis. Future work should attempt to explore this association further. This could include examining whether these associations are mediated by exposure to antipsychotic medication, prolonged hospitalisations or illness course and determining if severity of cognitive impairment is associated with severity, frequency or type of psychotic symptoms or episodes. This will enable a better understanding of cognitive impairments across these disorders, which have implications for treatment, diagnostic classification and informs investigations of the underlying aetiology.

Chapter 3: Examining Cognition Across the Bipolar / Schizophrenia Diagnostic Spectrum

3.1 Introduction

Cognitive impairments are a well-established feature of schizophrenia whilst there is ongoing debate about the nature and degree of impairment in schizoaffective disorder and bipolar disorder. It has been proposed that these disorders lie on a gradient of neurodevelopmental impairment with the severity of cognitive dysfunction increasing from bipolar disorder to schizophrenia [24, 26, 27].

Cognitive studies that provide support for a diagnostic spectrum have demonstrated increasing severity of impairment from bipolar disorder to schizoaffective disorder to schizophrenia, although these differences were not always significant [266, 303, 314, 319] (for a comprehensive review of these studies, see Chapter 2). In one of the largest studies to date, Hill et al. [266] showed an association between ratings on the Schizo-Bipolar scale [327] and composite cognition scores with more severe impairments amongst those with prominent psychosis and fewer affective symptoms. However, findings from cognitive studies of these three disorders have been inconsistent with some studies indicating that performance in schizoaffective disorder is similar to schizophrenia [300] and others indicating no differences between diagnostic groups [295, 308, 316].

There are a number of potential explanations for the conflicting findings between studies including differences in the use of covariates and the phase of illness of the study participants. Studies of symptomatic participants with schizophrenia, schizoaffective disorder and bipolar disorder have reported similar levels of impairment [295, 308]. It has been argued that cognitive impairments are state dependent in bipolar disorder and therefore improve during periods of remission. However, more recent research has demonstrated that cognitive impairments are present in euthymic bipolar disorder [238]. Lifetime history of psychosis in bipolar disorder has been identified as another important factor that may influence cognitive function. Studies do not consistently report the proportion of participants with bipolar disorder who have a lifetime history of psychosis despite evidence that the presence or absence of lifetime psychosis differentiates participants with

cognitive impairments from those without impairments [316]. Finally, studies often consider schizoaffective disorder as a single group despite evidence that cognitive impairment in the depressive subtype is closer in severity to schizophrenia than the bipolar subtype [266] (see meta-analytic findings of Chapter 2). This suggests amalgamation of both subtypes of schizoaffective disorder as a single group may obscure findings. At the time of writing, there have been no published studies that have compared the subtypes of schizoaffective disorder individually to schizophrenia and bipolar disorder in a single cohort.

3.2 Chapter aims and hypotheses

This chapter examines cognitive function in a large well-characterised sample of participants with bipolar disorder, schizoaffective disorder and schizophrenia. The sample was sufficiently large to separate schizoaffective disorder into its subtypes, bipolar and depressive. The main chapter hypothesis was that there is a spectrum of increasing cognitive impairment from bipolar disorder through schizoaffective disorder - bipolar type to schizoaffective disorder - depressive type and schizophrenia. It was also hypothesised that lifetime frequency and severity of psychotic symptoms (across and within diagnostic boundaries) would be associated with cognitive impairment. These hypotheses were tested in three ways. Firstly, cognitive performance was compared between the diagnostic groups. Secondly, ordinal logistic regression was used to examine whether there was a linear trend of increasing cognitive impairment from bipolar disorder through schizoaffective disorder - bipolar type to schizoaffective disorder - depressive type and schizophrenia. Thirdly, the associations between cognition and symptom domains were explored in a cross-disorder analysis.

3.3 Method

3.3.1 Sample

The data obtained for this study was taken from the Cognition in Mood, Psychosis and Schizophrenia Study (CoMPaSS) sample, an ongoing UK-based study that investigates genetic and environmental factors that contribute to susceptibility to psychosis and cognitive deficits. All participants gave written informed consent and were reimbursed for their participation. The study had UK multi-site NHS ethics approval.

Cases

Cases were recruited from the community via outpatient clinics, clozapine and depot clinics, and through the use of posters, leaflets, website and voluntary organisations. Participants were also referred to the study from other studies within the department including the National Centre for Mental Health (NCMH) and the Bipolar Disorder Research Network (BDRN). Most participants were outpatients at the time of assessment and inpatients were only recruited if they were deemed clinically well enough to give informed consent according to their clinical team. Inclusion criteria for the study included all persons aged 16 or over, who have been in contact with mental health services with a current diagnosis of schizophrenia, schizoaffective disorder, bipolar disorder or related psychotic illness. Exclusion criteria included all persons under 16 years old, unable to speak English, unable to give informed consent or suffering from a neurological or cognitive condition (i.e. dementia or amnesia), which in the opinion of the investigators was likely to impact on their ability to participate in the study. Those with signs or symptoms of current substance misuse or dependence were discussed beforehand to determine suitability and were asked to abstain for 24 hours before their participation if they were able to do so. Concerns regarding substance use, including risk to the researcher or risk of withdrawal symptoms for the patient, were discussed with their clinical team prior to participation in the study.

Participants were interviewed using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) [331]. This interview was reviewed along with available clinical records by trained raters to determine a consensus lifetime DSM-IV-TR diagnosis (inter-rater reliability Kappa statistics: schizophrenia=.83, schizoaffective

disorder – depressive type=.63, schizoaffective disorder – bipolar type=.72, bipolar disorder=.85) [332]. The final sample included 824 participants with a diagnosis of schizophrenia (N=558), schizoaffective disorder – depressive type (N=112), schizoaffective disorder – bipolar type (N=76) or bipolar disorder (N=78). The bipolar disorder group included all participants who met criteria for a diagnosis of bipolar disorder – type I (N=68) or type II (N=10), of which 59 had a lifetime history of psychosis according to scores on the Bipolar Affective Disorder Dimension Scale (BADDs) [333]. Further details of the BADDs ratings are provided in Section 3.3.2 but history of psychosis was defined as at least one psychotic symptom present during their course of illness (a score of at least 10 on the BADDs psychosis dimension).

Controls

One hundred and three control participants were recruited from the same communities through job centres, leisure centres and the use of adverts and leaflets. Participants completed a brief clinical interview (Mini-International Neuropsychiatric Interview (MINI) [334]) as a screen for mental disorders. Controls were excluded if they met criteria for schizophrenia or bipolar disorder or there was a family history of these conditions. None of the controls met criteria for any psychiatric disorder or reported taking psychiatric medication.

3.3.2 Measures

Cognitive assessment

Cognitive ability was assessed using the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB)[203]. This battery was designed specifically for use in schizophrenia research but has been shown to be a valid and reliable cognitive measure in bipolar disorder [335-337]. The MCCB assesses seven domains of cognition using ten tasks (for a summary see Table 3-1). The battery takes approximately one hour to complete.

Table 3-1 Description of the MCCB

Domain	Task	Task Description
Speed of Processing	Brief Assessment of Cognition in Schizophrenia: Symbol Coding	P uses the key to assign the correct numbers to a series of symbols
	Category Fluency: Animal Naming	P names as many animals as they can in 60 seconds
	Trail Making Test: Part A	P connects the numbered circles in ascending order
Working Memory	Wechsler Memory Scale III: Spatial Span	P must tap the blocks in the sequence they have just seen
	Letter-Number Span	P rearranges a string of numbers and letters into ascending numbers followed by letters alphabetically
Attention / Vigilance	Continuous Performance Test: Identical Pairs	P responds every time an identical pair of numbers flash on the screen consecutively
Verbal Learning	Hopkins Verbal Learning Test – Revised	P immediately recalls a list of 12 words
Visual Learning	Brief Visuospatial Memory Test – Revised	P immediately recalls the shape and location of 6 figures
Reasoning and Problem Solving	Neuropsychological Assessment Battery: Mazes	P draws a line through the maze from the start point to the finish point
Social Cognition	Mayer-Salovey-Caruso Emotional Intelligence Test: Managing Emotions	P presented with a social scenario and must judge a response on a scale of very ineffective to very effective.

Scoring and imputation

For each task, z scores were derived using the mean and standard deviation of the control sample (sample characteristics: 50% males, mean age = 41.7 years). As the Trail Making Test (TMT) scores were not normally distributed, the raw scores were log transformed before being converted. In addition to this, TMT scores had their sign reversed so that lower scores represented poorer performance and thus their direction was the same as the other tasks. Missing values were imputed using the formula described in the MCCB manual [338]. Imputed scores were only included in analyses of domains with more than one test and the composite scores. Domain and composite scores were calculated following the MCCB manual procedures. Composite scores were only calculated if a participant had completed 5 or more domains. Full details of the imputation methods including formulas can be found in Appendix C.

Premorbid IQ

Scores on the National Adult Reading Test (NART) were used to estimate premorbid IQ [339]. The NART is a widely used measure of premorbid IQ. The test consists of 50 irregularly spelled words that the participant must read aloud. These words cannot be guessed on the basis of their spelling and therefore performance is dependent on familiarity with the words. Reading ability is thought to be relatively preserved after the onset of psychiatric illness and is considered a valid method of estimating premorbid intelligence.

Clinical measures

Clinical measures were rated based on the SCAN interview [331] and available clinical records. In addition to the measures described below, participants were rated on current global functioning using the Global Assessment Scale (GAS)[340]. Intraclass correlation coefficients for the clinical variables ranged from 0.71 to 0.95.

Symptom dimensions

The following scales were used to record symptom severity and frequency: 1) Bipolar Affective Disorder Dimension Scale (BADDS) [333]; 2) Scale for the Assessment of Positive Symptoms (SAPS) [341] and 3) Scale for the Assessment of Negative Symptoms [342]. Trained raters determined scores on these scales following review of the SCAN interview and case notes. The BADDS comprises of four dimensions each rated on a scale of 0 to 100: mania, depression, psychosis and incongruence. Rating of the BADDS is based on the participant's lifetime history of each dimension. The Mania, Depression and Psychosis dimensions are designed to reflect the severity and frequency of clinical and subclinical episodes. Higher scores on these scales indicate more severe and frequent episodes. If psychosis is present during mania or depression, the minimum score that can be assigned for mania or depression dimension is 80. The psychosis dimension is rated based on the presence of psychotic symptoms as a proportion of the participant's overall duration of mental illness. The incongruence dimension is designed to measure the relationship between psychotic and affective symptoms and is based on current diagnostic criteria. This scale indicates the extent to which psychotic symptoms occur during or outside episodes of mood and is only rated if the participant has experienced at least one symptom of psychosis. Higher scores indicate more frequent psychosis outside of mood episodes.

Psychotic symptoms were also rated using the Scale for the Assessment of Positive Symptoms (SAPS) and negative symptoms were rated using the Scale for the Assessment of Negative Symptoms (SANS). The SAPS consists of symptoms and behaviours grouped into four domains, "Hallucinations", "Delusions", "Bizarre Behaviour" and "Formal Thought Disorder", which are rated from 0 to 5 based on severity. The SANS is also rated from 0 to 5 based on severity and symptoms are grouped into five domains, "Affective Flattening", "Alogia", "Avolition – Apathy",

“Anhedonia – Asociality” and “Attention”. The final domain of the SANS, “Attention”, was not rated in this study. Total scores for the SAPS and SANS were calculated by summing the global scores of each domain. SAPS and SANS were rated based on the participant’s presentation and report of the last two weeks (current SAPS and SANS) and across the lifetime using information from the SCAN interview and case notes (lifetime SAPS and SANS).

Antipsychotic medication

Doses of antipsychotic medication at time of assessment were calculated as olanzapine equivalents [343]. Lifetime antipsychotic exposure was rated as the total number of months a participant had taken antipsychotic medication, excluding self-reported periods of non-compliance or breaks in prescribed medication.

3.3.3 Statistical analysis

Comparing cognition between diagnostic groups

Statistical analyses to compare the groups were performed using R version 3.1.2. For each cognitive domain and across diagnostic groups, performance was compared using analysis of covariance (ANCOVA) with age and sex as covariates and followed up with Tukey’s HSD for pairwise comparisons. Pairwise comparisons were conducted between the following groups:

1. Healthy controls and bipolar disorder
2. Healthy controls and schizoaffective disorder – bipolar type
3. Healthy controls and schizoaffective disorder – depressive type
4. Healthy controls and schizophrenia
5. Bipolar disorder and schizoaffective disorder – bipolar type
6. Bipolar disorder and schizoaffective disorder – depressive type
7. Bipolar disorder and schizophrenia
8. Schizoaffective disorder – bipolar type and schizoaffective disorder – depressive type
9. Schizoaffective disorder – bipolar type and schizophrenia
10. Schizoaffective disorder – depressive type and schizophrenia

Bonferroni correction was used to adjust for multiple comparisons resulting in an alpha of 0.00625 (0.05/8, 7 domains and composite score). The alpha was not

corrected further for the number of pairwise comparisons, as Tukey's HSD is already a conservative test that corrects for family-wise error rate. Effect sizes were calculated by dividing mean group difference by the pooled standard deviation [344] (see Appendix A for formulas). Repeated measures analysis of variance was used to compare profiles of cognitive performance between groups. The within-subject factor was cognitive domain. This is consistent with the approach used in previous studies to compare cognitive profiles [266, 314].

The assumptions of ANCOVA include normal distribution of the data and homogeneity of variances across groups. Whilst the results of Shapiro-Wilk tests were significant for all domains (except speed of processing) indicating deviation from normality, visual inspection of Q-Q plots revealed overall normal distributions. Homogeneity of variance was assessed with Levene's test and by calculating the variance ratios (highest variance divided by lowest variance). The variances were homogeneous across the groups with no variance ratios exceeding a value of 2.

Secondary analyses

Sensitivity analyses were conducted excluding participants diagnosed with bipolar disorder – type II, as there is evidence that these individuals have better cognitive functioning than participants with bipolar disorder – type I [245, 345]. A sensitivity analysis was also conducted by conducting an ANCOVA that only included participants who were taking antipsychotic medication at the time of assessment, given evidence that participants with bipolar disorder who are taking antipsychotic medication have worse cognitive function [258, 346].

The effects of potential confounding variables were investigated by conducting five sets of ANCOVAs for the covariates of interest. Age and sex were included as covariates in all analyses. These analyses included cases only. The covariates included in each analysis are listed below:

1. Olanzapine equivalent dose
2. Duration of antipsychotic exposure
3. Current SAPS total score
4. Current SANS total score

5. Olanzapine equivalent dose, duration of antipsychotic exposure, current SAPS total score, current SANS total score and lifetime depression (BADDs depression dimension)

The final set of analyses examined whether differences in premorbid IQ could account for differences observed between the groups. NART scores, age and sex were entered as covariates in this model. This set of analyses included both cases and controls.

Variance inflation factors (VIF) were calculated to check the assumption of no collinearity between predictors. Age and duration of antipsychotic exposure were correlated, although variance inflation was low. Analyses were repeated using age-adjusted cognition scores (residuals taken from linear regressions of age against each cognitive domain). The results of the analyses using age-adjusted cognition scores were consistent with the original analyses and so the original analyses are presented here.

Examining cognition as a dimension across diagnostic groups

To test the hypothesis that cognition can be considered a dimensional phenotype showing increasing impairment from bipolar disorder to schizoaffective disorder - bipolar type to schizophrenia and schizoaffective disorder - depressive type, an ordinal regression analysis was conducted using SPSS version 22 with diagnosis as the outcome, composite cognition score as the predictor and age and sex as covariates. Schizophrenia and schizoaffective disorder - depressive type were combined given pre-existing data showing that their degree of impairment is comparable [266]. Diagnosis was coded on an ordinal scale combining schizoaffective disorder – depressive type and schizophrenia: 0 – schizoaffective disorder - depressive type and schizophrenia, 1 – schizoaffective disorder - bipolar type and 2 – bipolar disorder. The analysis was repeated including olanzapine equivalent dose, antipsychotic exposure in months and current negative symptoms as covariates in the model.

Two sets of follow-up analyses were conducted with diagnosis coded in the following ways:

1. Each diagnosis assigned to separate groups and coded as: 0 – schizophrenia, 1 – schizoaffective disorder - depressive type, 2 – schizoaffective disorder - bipolar type and 3 – bipolar disorder. These groups reflect those included in the analysis comparing cognition between diagnoses.
2. The subtypes of schizoaffective disorder combined into a single group: 0 – schizophrenia, 1 – schizoaffective disorder and 2 – bipolar disorder. This was done to mirror the groups included in previous studies, which have combined the subtypes of schizoaffective disorder.

The purpose of these follow-up analyses was to provide comparisons against the first model, using groupings that reflect current diagnostic categories and those used in previous studies of cognitive function across these disorders.

Ordinal regression outputs a single coefficient for the effect of the explanatory variable across all levels of the dependent variable since there is an assumption that the coefficients must be equal across all levels (known as the assumption of proportional odds). This assumption was tested using the test of parallel lines in SPSS and the results of this test for each ordinal regression are presented in the results.

Cross disorder symptom dimensions and cognitive performance

Linear regression analyses were conducted using R version 3.1.2 to determine if symptom dimensions were associated with cognitive performance. Each symptom dimensions (scores on each of the BADDs dimensions, SAPS and SANS) were entered into separate linear regressions as predictors with composite cognition score as the outcome and age and sex as covariates. This was initially conducted across the whole sample. However, scores on the BADDs dimensions are influenced by diagnosis. For example, participants with bipolar disorder or schizoaffective disorder – bipolar type would have high scores on the mania dimension, whilst participants with schizophrenia or schizoaffective disorder – depressive type would have scores of zero. This could result in an association between mania scores and cognitive performance. Therefore, the analyses were

repeated within two subgroups: 1) bipolar disorder and schizoaffective disorder - bipolar type as one group and 2) schizoaffective disorder - depressive type and schizophrenia as one group. Bonferroni correction was used to adjust for multiple comparisons resulting in an alpha of 0.00833 (0.05/6, 6 symptom dimensions). All linear regressions were then repeated including age, sex, current negative symptoms (total SANS scores), olanzapine equivalent dose and antipsychotic exposure in months as covariates.

Inspections of Q-Q plots confirmed that the residuals for all analyses were normally distributed. Residuals and standardized residuals were plotted against fitted values to ensure homoscedasticity of the errors. Standardized residuals were plotted against leverage to identify potential outliers. One outlier was identified when the additional covariates (negative symptoms, antipsychotic dose and exposure) were added so this individual was excluded from these analyses. Variance inflation factors were calculated to identify collinearity between the predictors. Lifetime and current SANS scores were highly correlated ($r=0.86$) so current SANS scores were removed as a covariate in the regressions examining the association between lifetime SANS scores and cognition.

3.4 Results

3.4.1 Sample size and completeness of data

Complete cognitive data was available for verbal learning, reasoning and problem solving, speed of processing and working memory resulting in a total of 927 participants (824 cases and 103 controls) for these analyses. Of the remaining domains, 4 participants failed to complete the BVMT-R, 20 did not complete the MSCEIT ME and 55 did not complete the CPT-IP. For participants with missing data, composite scores were imputed for participants who had completed at least five tasks. Therefore, it was possible to impute a composite score for all but one participant resulting in 926 participants with composite scores. There was no missing data for the control group. The number of available data points for each diagnostic group can be found in Appendix D.

3.4.2 Demographic variables

Demographic and clinical variables are displayed for each diagnostic group in Table 3-2. There were no differences in age between the groups. Groups differed on proportion of males ($\chi^2=61.39$, 1.48×10^{-12}) with more males observed in the schizophrenia group; therefore sex was used as a covariate in all analyses. There were differences in estimated premorbid IQ ($F=22.64$, $p<2.2 \times 10^{-16}$) and years in education ($F=14.19$, $p=5.12 \times 10^{-9}$), which were lower for those with schizophrenia and schizoaffective disorder - depressive type compared to those with bipolar disorder and schizoaffective disorder - bipolar type. Groups differed on current positive and negative symptoms (SAPS: $F=65.96$, $p=3.13 \times 10^{-14}$; SANS: $F=64.16$, $p=7.58 \times 10^{-14}$) with lower scores in those with bipolar disorder compared to all other groups. Measures of current global functioning (Global Assessment Scale) differed between groups ($F=4.99$, $p=0.002$) with higher scores observed in the bipolar disorder group.

Table 3-2 Clinical and demographic variables

DSM-IV Diagnosis	Healthy Controls	Bipolar Disorder	Schizoaffective Disorder – Bipolar Type	Schizoaffective Disorder – Depressive Type	Schizophrenia	Test Statistic	P Value
N	103	78	76	112	558		
Age	41.7 (16.1)	45.8 (10.6)	43.8 (10.6)	44.1 (10.1)	43.3 (11.9)	1.40	0.23
Sex (% males)	50	40	46	40	69	61.39	1.48 x 10 ⁻¹²
NART score	32.4 (7.1)	31.2 (10.6)	29.6 (10.2)	25.4 (9.6)	23.7 (11.3)	22.41	1.2 x 10 ⁻¹⁷
Years in Education	14.7 (3.2)	14.6 (3.3)	13.7 (3.0)	12.3 (2.3)	12.7 (2.7)	14.19	5.12 x 10 ⁻⁹
Taking Antipsychotic (%)		63	75	78	86	25.51	1.2 x 10 ⁻⁵
Olanzapine Equivalent Dose*		8 (12)	15 (10)	15 (13.5)	13.7 (13.7)	26.79	6.51 x 10 ⁻⁶
Antipsychotic exposure in months*		60 (102)	153 (181.5)	168 (164.5)	170 (168)	39.97	1.08 x 10 ⁻⁸
Current SAPS*		0 (0)	2 (5)	2 (5)	3 (6)	65.96	3.13 x 10 ⁻¹⁴
Current SANS*		0.5 (3)	4 (5)	6 (7)	5.5 (7)	64.16	7.58 x 10 ⁻¹⁴
GAS Past Week		70.8 (14.2)	60.1 (16.8)	58.6 (15.8)	60.2 (15.1)	4.99	0.002

Figures represent means and standard deviations, except for proportions and scores with non-normal distributions. *Medians and interquartile ranges are presented due to non-normal distribution. Test statistic is F value (ANOVA or Kruskal-Wallis Analysis of Variance) for continuous variables and X² for proportions. Current SAPS and SANS scores represent the sum of the global scores. SAPS: Scale for the Assessment of Positive Symptoms; SANS: Scale for the Assessment of Negative Symptoms; GAS: Global Assessment Scale; NS: Not Significant.

3.4.3 Comparison of cognition between diagnostic groups

There was a significant main effect of diagnosis for all domains of cognition (*composite cognition*: $F(4, 921) = 94.12$, $p < 0.00625$, see Table 3-3 for domain results). Figure 3-1 displays the marginal mean z scores (adjusted for age and sex) for each diagnostic group and the control group. Cognitive impairments increased in severity from bipolar disorder to schizoaffective disorder – bipolar type to schizophrenia and schizoaffective disorder – depressive type.

Effect sizes are displayed for each pairwise comparison in Figure 3-2. All diagnostic groups were impaired across cognitive domains compared to controls except for social cognition in those with bipolar disorder. The bipolar disorder group was the least impaired of the diagnostic groups, performing 0.5 to 1.25 standard deviations below the mean of the control group across domains (*composite cognition*: $g = 1.12$, $p < 0.001$). The schizoaffective disorder - bipolar type group was more impaired than the bipolar disorder group although this does not withstand correction for multiple testing (*composite cognition*: $g = 0.44$, $p = 0.02$). The schizophrenia and schizoaffective disorder - depressive type groups were the most cognitively impaired and did not differ on any cognitive variable (*composite cognition*: $g = 0.07$, $p = 0.90$) corroborating the *a priori* decision to amalgamate these groups for these analyses. These participants were more impaired than those with schizoaffective disorder - bipolar type (schizophrenia: $g = 0.52$, $p < 0.001$; schizoaffective disorder - depressive type: $g = 0.45$, $p = 0.01$) and those with bipolar disorder (schizophrenia: $g = 0.90$, $p < 0.001$; schizoaffective disorder - depressive type: $g = 0.83$, $p < 0.001$).

In contrast to other domains, levels of impairment in social cognition between schizoaffective disorder - bipolar type, schizoaffective disorder - depressive type and schizophrenia did not differ (Hedge's g ranged between 0.05 and 0.28). All three of these groups were more impaired than bipolar disorder on social cognition (Hedge's g ranged between 0.50 and 0.81). Given this pattern of results, composite scores were derived excluding social cognition and the analysis repeated. When social cognition was excluded, the difference in composite cognition between schizoaffective disorder - bipolar type and bipolar disorder was reduced ($g = 0.37$, $p = 0.06$) and the remaining pairwise comparisons did not change.

Table 3-3 Cognitive performance in each diagnostic group

Domain	Task	HC	BD	SAB	SAD	SZ	F^{df}	p	Partial η^2
Verbal Learning	HVLT-R	28.81 (3.89)	24.32 (5.76)	22.34 (5.36)	19.85 (6.27)	19.25 (6.11)	F ^{4, 922} =63.75	p<2.20 x 10 ⁻¹⁶	0.22
Reasoning & Problem Solving	NAB: Mazes	19.50 (5.56)	14.42 (6.87)	12.49 (7.12)	9.73 (7.02)	11.19 (7.22)	F ^{4, 922} =43.85	p<2.20 x 10 ⁻¹⁶	0.16
Visual Learning	BVMT-R	25.92 (6.62)	20.69 (7.50)	18.34 (7.56)	15.75 (8.53)	14.65 (8.29)	F ^{4, 918} =52.93	p<2.20 x 10 ⁻¹⁶	0.19
Social Cognition	MSCEIT: ME	95.14 (8.75)	93.23 (10.04)	87.40 (9.62)	87.96 (11.15)	85.06 (10.21)	F ^{4, 902} =25.07	p<2.20 x 10 ⁻¹⁶	0.10
Attention / Vigilance	CPT: IP	2.76 (0.66)	2.23 (0.81)	2.15 (0.78)	1.88 (0.78)	1.81 (0.80)	F ^{4, 867} =35.44	p<2.20 x 10 ⁻¹⁶	0.14
Speed of Processing	TMT A	28.30 (9.17)	37.32 (13.78)	43.36 (19.15)	49.04 (21.62)	51.03 (26.24)	F ^{4, 922} =82.52	p<2.20 x 10 ⁻¹⁶	0.26
	BACS: Symbol Coding	58.02 (11.26)	46.50 (11.87)	43.28 (12.63)	37.28 (12.26)	36.47 (12.84)			
	Category Fluency: Animal Naming	27.70 (7.68)	22.59 (6.59)	21.88 (6.01)	19.33 (6.05)	19.47 (5.96)			

Means (SDs) of raw scores are reported. All case-control comparisons were significant (p<.001), except for bipolar disorder on social cognition (not significant). Partial η^2 indicates the proportion of variance in cognitive scores that is associated with diagnosis. HC, healthy controls; BD, bipolar disorder; SAB, schizoaffective disorder – bipolar type; SAD, schizoaffective disorder – depressive type; SZ, schizophrenia; ANCOVA, analysis of covariance; HVLT-R, Hopkins Verbal Learning Test – Revised; NAB, Neuropsychological Assessment Battery; BVMT-R, Brief Visuospatial Memory Test – Revised; MSCEIT: ME, Mayer-Salovey-Caruso Emotional Intelligence Test: Managing Emotions; CPT: IP, Continuous Performance Test: Identical Pairs; TMT, Trail Making Test; BACS, Brief Assessment of Cognition in Schizophrenia; WMS III: SS, Wechsler Memory Scale III: Spatial Span; LNS, Letter Number Span

Table 3-3 (cont.) Cognitive performance in each diagnostic group

Domain	Task	HC	BD	SAB	SAD	SZ	F^{df}	p	Partial η^2
Working Memory	WMS III: SS	17.31 (3.10)	14.04 (3.12)	13.50 (3.08)	12.56 (3.45)	12.86 (3.70)	F ^{4, 922} =51.42	p<2.20 x 10 ⁻¹⁶	0.18
	LNS	15.80 (3.14)	13.31 (3.68)	12.34 (3.61)	10.76 (4.49)	10.58 (4.35)			
Composite Cognition Score							F ^{4, 921} =94.12	p<2.20 x 10 ⁻¹⁶	0.29
Composite Cognition Score without Social Domain							F ^{4, 921} =90.16	p<2.20 x 10 ⁻¹⁶	0.28

Means (SDs) of raw scores are reported. All case-control comparisons were significant (p<.001), except for bipolar disorder on social cognition (not significant). Partial η^2 indicates the proportion of variance in cognitive scores that is associated with diagnosis. HC, healthy controls; BD, bipolar disorder; SAB, schizoaffective disorder – bipolar type; SAD, schizoaffective disorder – depressive type; SZ, schizophrenia; ANCOVA, analysis of covariance; HVLTR, Hopkins Verbal Learning Test – Revised; NAB, Neuropsychological Assessment Battery; BVMT-R, Brief Visuospatial Memory Test – Revised; MSCEIT: ME, Mayer-Salovey-Caruso Emotional Intelligence Test: Managing Emotions; CPT: IP, Continuous Performance Test: Identical Pairs; TMT, Trail Making Test; BACS, Brief Assessment of Cognition in Schizophrenia; WMS III: SS, Wechsler Memory Scale III: Spatial Span; LNS, Letter Number Span

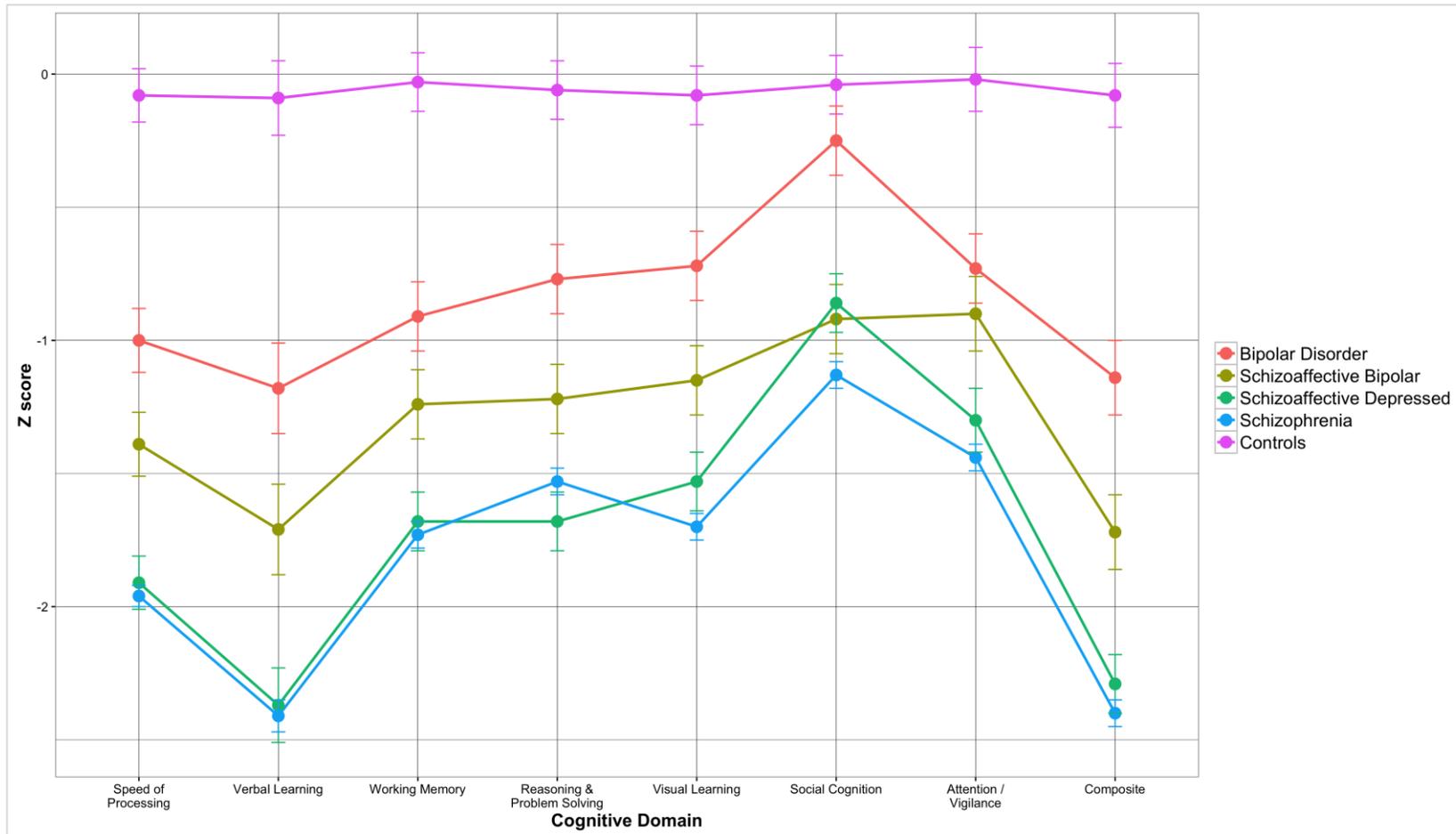


Figure 3-1 Cognitive profiles for participants with bipolar disorder, schizoaffective disorder - bipolar type, schizoaffective disorder - depressive type and schizophrenia

Error bars indicate ± 1 standard error

SAB	0.36	0.28	0.32				Verbal Learning	Reasoning & Problem Solving	Visual Learning
	0.60	0.10	0.32				Social Cognition	Attention / Vigilance	Speed of Processing
	0.25	0.44					Working Memory	Composite Cognition Score	
SAD	0.74	0.68	0.61	0.43	0.39	0.32			
	0.50	0.44	0.78	-0.05	0.35	0.47			
	0.61	0.83		0.39	0.45				
SZ	0.84	0.45	0.74	0.52	0.18	0.45	0.10	-0.20	0.14
	0.81	0.53	0.80	0.24	0.43	0.51	0.28	0.09	0.05
	0.54	0.90		0.33	0.52		-0.03	0.07	
	BD			SAB			SAD		

Figure 3-2 Pairwise comparisons

Each 3x3 section displays the Hedge's *g* effect sizes for the difference between two diagnostic groups for each domain of cognition. Positive effect sizes indicate that the group on the horizontal bottom row performed better than the group on the left-hand vertical column. Lighter shade $p < 0.05$, darker shade $p < 0.00625$.

When the control group were included, diagnostic group explained a significant proportion of the variance in cognition scores with partial η^2 ranging from 0.10 to 0.29. Given that the differences between cases and controls were highly significant, the analyses were repeated excluding controls to determine the proportion of variance explained by differences in diagnosis. These results are displayed in Table 3-4. Estimated variance explained by diagnosis ranged from 0.04 to 0.09 after excluding healthy controls.

Table 3-4 ANCOVA results excluding healthy control group

Domain	ANCOVA Results		
	F ^{df}	p	Partial η^2
Verbal Learning	F ^{3, 820} =17.84	3.2 x 10 ⁻¹¹	0.06
Reasoning & Problem Solving	F ^{3, 820} =12.03	1.0 x 10 ⁻⁷	0.04
Visual Learning	F ^{3, 816} =18.62	1.1 x 10 ⁻¹¹	0.06
Social Cognition	F ^{3, 800} =12.89	3.2 x 10 ⁻⁸	0.05
Attention / Vigilance	F ^{3, 765} =10.07	1.7 x 10 ⁻⁶	0.04
Speed of Processing	F ^{3, 820} =22.85	3.3 x 10 ⁻¹⁴	0.08
Working Memory	F ^{3, 820} =12.35	6.6 x 10 ⁻⁸	0.04
Composite Score	F ^{3, 819} =27.04	<2.2 x 10 ⁻¹⁶	0.09

Partial η^2 indicates the proportion of variance in cognitive scores that is associated with diagnosis.

Comparing cognitive profiles

In order to test whether between group differences were qualitative or merely quantitative, cognitive profiles were compared between diagnostic groups using repeated measures analysis of variance, with cognitive domain included as the within-subject factor. Mauchly's test indicated that the assumption of sphericity had been violated ($\chi^2(20)=360.23$, $p=3.5 \times 10^{-64}$) therefore degrees of freedom were corrected using Huynh-Feldt estimates of sphericity. The diagnosis-by-domain interaction was not significant ($F=1.62$, $df=15.50$, 3051.33 , $p=0.06$). The analysis was repeated excluding social cognition (given the quantitative differences in this domain) and the diagnosis-by-domain interaction was not significant ($F=1.604$, $df=1.60$, 2680.70 $p=0.07$) indicating that patterns of cognitive ability did not differ by diagnostic group but rather differed quantitatively.

Sensitivity analyses

Bipolar disorder type I and type II

Given that there is some evidence to suggest patients with bipolar disorder – type II are less cognitively impaired than those with bipolar disorder – type I [245, 345], the analysis was repeated including only participants with bipolar disorder – type I (N=68). This did not change the results or post hoc comparisons (see Table 3-5).

Table 3-5 Comparisons of cognitive performance when only bipolar disorder - type I was included

Domain	Effect of Diagnosis			Pairwise Comparisons
	F ^{df}	p	Partial η^2	
Verbal Learning	F ^{4, 912} =64.25	<2.2 x 10 ⁻¹⁶	0.22	SAD < BD ² SZ < BD ² SAD < SAB ¹ SZ < SAB ²
Reasoning & Problem Solving	F ^{4, 912} =43.74	<2.2 x 10 ⁻¹⁶	0.16	SAD < BD ² SZ < BD ² SAD < SAB ¹
Visual Learning	F ^{4, 912} =51.13	<2.2 x 10 ⁻¹⁶	0.18	SAD < BD ² SZ < BD ² SZ < SAB ²
Social Cognition	F ^{4, 892} =24.65	<2.2 x 10 ⁻¹⁶	0.10	SAB < BD ² SAD < BD ² SZ < BD ²
Attention / Vigilance	F ^{4, 857} =35.22	<2.2 x 10 ⁻¹⁶	0.14	SAD < BD ¹ SZ < BD ² SZ < SAB ²
Speed of Processing	F ^{4, 912} =81.39	<2.2 x 10 ⁻¹⁶	0.26	SAD < BD ² SZ < BD ² SAD < SAB ² SZ < SAB ²
Working Memory	F ^{4, 912} =49.91	<2.2 x 10 ⁻¹⁶	0.18	SAD < BD ² SZ < BD ² SZ < SAB ²
Composite Score	F ^{4, 911} =92.74	<2.2 x 10 ⁻¹⁶	0.29	SAB < BD ¹ SAD < BD ² SZ < BD ² SAD < SAB ¹ SZ < SAB ²

All case-control comparisons were significant (p<.001), except for bipolar disorder on social cognition (no significant difference). Partial η^2 indicates the proportion of variance in cognitive scores that is associated with diagnosis. BD, bipolar disorder; SA, schizoaffective disorder; SZ, schizophrenia; ¹p<.05, ²p<.00625 (Bonferroni-corrected)

Although the groups were small, cognitive performance was compared between participants with bipolar disorder – type I and bipolar disorder – type II. There were no significant differences between these groups (composite cognition: $g=0.07$, $p=0.83$, see Table 3-6).

Table 3-6 Comparison of cognitive performance in bipolar disorder type I and type II

Domain	Marginal Means		Hedge's g	p
	Bipolar I (N=68)	Bipolar II (N=10)		
Verbal learning	-1.14	-1.86	-0.479	0.146
Reasoning & Problem Solving	-0.81	-1.25	-0.335	0.313
Visual Learning	-0.88	-0.45	0.36	0.274
Social Cognition	-0.21	-0.36	-0.121	0.706
Attention	-0.76	-0.81	-0.039	0.908
Speed of Processing	-1.12	-1.06	0.054	0.859
Working Memory	-1.06	-0.66	0.356	0.292
Composite	-1.22	-1.31	-0.073	0.834

Participants taking antipsychotic medication only

Given evidence that participants with bipolar disorder who are taking antipsychotic medication have worse cognitive function [258, 346], the analyses were repeated only including participants who were taking antipsychotic medication at the time of the assessment (*bipolar disorder*: N=48; *schizoaffective disorder – bipolar type*: N=56; *schizoaffective disorder – depressive type*: N=80; *schizophrenia*: N=448). These results are displayed in Table 3-7. The effect of diagnosis persisted but none of the pairwise comparisons for attention were significant at the Bonferroni-corrected alpha value of 0.00625.

Table 3-7 Comparison of cognitive performance for cases currently taking antipsychotic medication only

Domain	F^{df}	p	Partial η^2	Pairwise Comparisons
Verbal Learning	F ^{3, 628} =7.98	3.2 x 10 ⁻⁵	0.04	SAD < BD ² SZ < BD ² SZ < SAB ¹
Reasoning & Problem Solving	F ^{3, 628} =7.13	0.0001	0.03	SAD < BD ² SZ < BD ² SAD < SAB ¹
Visual Learning	F ^{3, 624} =9.76	2.7 x 10 ⁻⁶	0.05	SAD < BD ² SZ < BD ² SZ < SAB ¹
Social Cognition	F ^{3, 614} =7.88	3.7 x 10 ⁻⁵	0.04	SAB < BD ¹ SAD < BD ¹ SZ < BD ²
Attention / Vigilance	F ^{3, 587} =4.31	0.005	0.02	SZ < BD ¹
Speed of Processing	F ^{3, 628} =14.27	5.3 x 10 ⁻⁹	0.06	SAD < BD ² SZ < BD ² SAD < SAB ¹ SZ < SAB ²
Working Memory	F ^{3, 628} =9.09	6.8 x 10 ⁻⁶	0.04	SAD < BD ² SZ < BD ² SZ < SAB ¹
Composite Score	F ^{3, 627} =15.25	1.4 x 10 ⁻⁹	0.07	SAD < BD ² SZ < BD ² SZ < SAB ²

Partial η^2 indicates the proportion of variance in cognitive scores that is associated with diagnosis. BD, bipolar disorder; SAB, schizoaffective disorder – bipolar type; SAD, schizoaffective disorder – depressive type; SZ, schizophrenia; ANCOVA, analysis of covariance. ¹p<0.05; ²p<0.00625 (Bonferroni-corrected)

Effects of clinical and demographic variables

Medication effects

The effects of both lifetime duration of antipsychotic medication and olanzapine equivalent dose were investigated. Duration of antipsychotic exposure was associated with all cognitive domains. The estimated proportion of variance in cognitive scores explained by duration of antipsychotic exposure ranged from 0.01 to 0.04 (see Table 3-8). The main effect of diagnostic group on cognitive scores remained significant after controlling for duration of antipsychotic exposure, although the proportion of variance explained by diagnosis was reduced (partial η^2 ranged from 0.02 to 0.06). Post hoc comparisons revealed a reduction in the magnitude of the differences between groups (see Table 3-8).

Olanzapine equivalent dose was associated with all cognitive domains, except social cognition, with the estimated proportion of variance explained ranging between 0.01 and 0.04 (see Table 3-9). The main effect of diagnostic group on cognitive scores remained significant after controlling for olanzapine equivalent dose, although the proportion of variance explained by diagnosis was reduced (partial η^2 ranged from 0.03 to 0.08). Post hoc comparisons revealed a reduction in the magnitude of the differences between groups (see Table 3-9).

Table 3-8 The effects of diagnostic group and duration of antipsychotic exposure on cognitive performance

Domain	Effect of Diagnosis			Effect of Duration of Antipsychotic Exposure			Pairwise Comparisons
	F ^{df}	p	Partial η^2	F ^{df}	p	Partial η^2	
Verbal Learning	F ^{3, 766} =8.84	9.2 x 10 ⁻⁶	0.03	F ^{1, 766} =28.50	1.2 x 10 ⁻⁷	0.04	SAD < BD ² SZ < BD ² SAD < SAB ¹ SZ < SAB ¹
Reasoning & Problem Solving	F ^{3, 766} =5.90	6.0 x 10 ⁻⁴	0.02	F ^{1, 766} =17.10	3.9 x 10 ⁻⁵	0.02	SAD < BD ² SZ < BD ¹ SAD < SAB ¹
Visual Learning	F ^{3, 762} =12.29	7.4 x 10 ⁻⁸	0.05	F ^{1, 762} =23.96	1.2 x 10 ⁻⁶	0.03	SAD < BD ² SZ < BD ² SZ < SAB ²
Social Cognition	F ^{3, 750} =8.48	1.5 x 10 ⁻⁵	0.03	F ^{1, 750} =8.57	0.004	0.01	SAB < BD ¹ SAD < BD ¹ SZ < BD ²
Attention / Vigilance	F ^{3, 715} =6.00	4.8 x 10 ⁻⁴	0.03	F ^{1, 715} =11.86	6.1 x 10 ⁻⁴	0.02	SZ < BD ² SZ < SAB ¹
Speed of Processing	F ^{3, 766} =14.57	3.1 x 10 ⁻⁹	0.05	F ^{1, 766} =12.71	3.9 x 10 ⁻⁴	0.02	SAD < BD ² SZ < BD ² SAD < SAB ² SZ < SAB ²
Working Memory	F ^{3, 766} =8.62	1.3 x 10 ⁻⁵	0.03	F ^{1, 766} =14.90	1.2 x 10 ⁻⁴	0.02	SAD < BD ² SZ < BD ² SZ < SAB ¹
Composite Score	F ^{3, 765} =16.18	3.4 x 10 ⁻¹⁰	0.06	F ^{1, 765} =33.69	9.5 x 10 ⁻⁹	0.04	SAD < BD ² SZ < BD ² SZ < SAB ² SAD < SAB ¹

Partial η^2 indicates the proportion of variance in cognitive scores that is associated with diagnosis. BD, bipolar disorder; SAB, schizoaffective disorder – bipolar type; SAD, schizoaffective disorder – depressive type; SZ, schizophrenia; ANCOVA, analysis of covariance; ¹p<0.05, ²p<0.00625 (Bonferroni-corrected)

Table 3-9 The effects of diagnosis and olanzapine equivalent dose on cognitive performance

Domain	Effect of Diagnosis			Effect of Olanzapine Equivalent Dose			Pairwise Comparisons
	F ^{df}	p	Partial η^2	F ^{df}	p	Partial η^2	
Verbal Learning	F ^{3, 774} =13.03	2.6 x 10 ⁻⁸	0.05	F ^{1, 774} =26.61	3.2 x 10 ⁻⁷	0.03	SAD < BD ² SZ < BD ² SAD < SAB ¹ SZ < SAB ²
Reasoning & Problem Solving	F ^{3, 774} =9.23	5.3 x 10 ⁻⁶	0.03	F ^{1, 774} =10.13	0.002	0.01	SAD < BD ² SZ < BD ² SAD < SAB ¹
Visual Learning	F ^{3, 770} =15.90	4.9 x 10 ⁻¹⁰	0.06	F ^{1, 770} =24.19	1.1 x 10 ⁻⁶	0.03	SAD < BD ² SZ < BD ² SZ < SAB ²
Social Cognition	F ^{3, 757} =9.72	2.7 x 10 ⁻⁶	0.04	F ^{1, 757} =4.22	0.04	0.01	SAB < BD ¹ SAD < BD ¹ SZ < BD ²
Attention / Vigilance	F ^{3, 722} =7.31	7.8 x 10 ⁻⁵	0.03	F ^{1, 722} =25.69	5.1 x 10 ⁻⁷	0.03	SZ < BD ² SZ < SAB ²
Speed of Processing	F ^{3, 774} =18.43	1.5 x 10 ⁻¹¹	0.07	F ^{1, 774} =12.83	3.6 x 10 ⁻⁴	0.02	SAD < BD ² SZ < BD ² SAD < SAB ¹ SZ < SAB ²
Working Memory	F ^{3, 774} =10.33	1.1 x 10 ⁻⁶	0.04	F ^{1, 774} =14.38	1.6 x 10 ⁻⁴	0.02	SAD < BD ² SZ < BD ² SZ < SAB ¹
Composite Score	F ^{3, 773} =21.42	2.5 x 10 ⁻¹³	0.08	F ^{1, 773} =31.85	2.3 x 10 ⁻⁸	0.04	SAD < BD ² SZ < BD ² SZ < SAB ² SAD < SAB ¹

Partial η^2 indicates the proportion of variance in cognitive scores that is associated with diagnosis. BD, bipolar disorder; SAB, schizoaffective disorder – bipolar type; SAD, schizoaffective disorder – depressive type; SZ, schizophrenia; ANCOVA, analysis of covariance; ¹p<0.05, ²p<0.00625 (Bonferroni-corrected)

Current positive and negative symptoms

Current positive symptoms were only associated with social cognition ($F(1,790)=5.31, p=0.02$, see Table 3-10 for full results), although explained a small proportion of the variance in performance on this domain (partial $\eta^2=0.01$). The effect of diagnosis on social cognition remained significant after adjusting for positive symptoms, although differences between schizoaffective disorder (both subtypes) and bipolar disorder were attenuated. Negative symptoms were significantly associated with all cognitive domains but the effect of diagnosis remained significant after adjusting for these symptoms (see Table 3-11). The estimated proportion of variance in cognitive scores explained by current negative symptoms ranged from 0.02 to 0.07. Differences between groups were attenuated for social cognition, attention, speed of processing and working memory after adjusting for negative symptoms.

Table 3-10 The effects of diagnosis and total SAPS scores on cognitive performance

Domain	Effect of Diagnosis			Effect of Current Positive Symptoms			Pairwise Comparisons
	F ^{df}	p	Partial η^2	F ^{df}	p	Partial η^2	
Verbal Learning	F ^{3, 807} =17.58	4.6 x 10 ⁻¹¹	0.06	F ^{1, 807} =1.29	0.26	0.002	SAD < BD ² SZ < BD ² SAD < SAB ¹ SZ < SAB ²
Reasoning & Problem Solving	F ^{3, 807} =12.06	9.9 x 10 ⁻⁸	0.04	F ^{1, 807} =1.51	0.22	0.002	SAD < BD ² SZ < BD ² SAD < SAB ¹
Visual Learning	F ^{3, 804} =18.61	1.1 x 10 ⁻¹¹	0.07	F ^{1, 804} =0.19	0.67	2.6 x 10 ⁻⁴	SAD < BD ² SZ < BD ² SZ < SAB ²
Social Cognition	F ^{3, 790} =9.90	2.1 x 10 ⁻⁶	0.04	F ^{1, 790} =5.31	0.02	0.01	SAB < BD ¹ SAD < BD ¹ SZ < BD ²
Attention / Vigilance	F ^{3, 755} =7.79	4.0 x 10 ⁻⁵	0.03	F ^{1, 755} =2.05	0.15	0.003	SZ < BD ² SZ < SAB ² SAD < BD ¹
Speed of Processing	F ^{3, 807} =19.55	3.1 x 10 ⁻¹²	0.07	F ^{1, 807} =2.17	0.14	0.003	SAD < BD ² SZ < BD ² SAD < SAB ² SZ < SAB ²
Working Memory	F ^{3, 807} =11.10	3.8 x 10 ⁻⁷	0.04	F ^{1, 807} =1.20	0.28	0.001	SAD < BD ² SZ < BD ² SZ < SAB ¹
Composite Score	F ^{3, 807} =24.52	3.4 x 10 ⁻¹⁵	0.08	F ^{1, 807} =0.46	0.50	4.8 x 10 ⁻⁴	SAB < BD ¹ SAD < BD ² SZ < BD ² SZ < SAB ² SAD < SAB ¹

Total SAPS were calculated by summing the global scores (hallucinations, delusions, bizarre behaviour and positive formal thought disorder). Partial η^2 indicates the proportion of variance in cognitive scores that is associated with diagnosis. BD, bipolar disorder; SAB, schizoaffective disorder – bipolar type; SAD, schizoaffective disorder – depressive type; SZ, schizophrenia; ¹p<0.05, ²p<0.00625 (Bonferroni-corrected)

Table 3-11 The effects of diagnosis and total SANS scores on cognitive performance

Domain	Effect of Diagnosis			Effect of Current Negative Symptoms			Pairwise Comparisons
	F ^{df}	p	Partial η^2	F ^{df}	p	Partial η^2	
Verbal Learning	F ^{3, 805} =10.88	5.2 x 10 ⁻⁷	0.04	F ^{1, 805} =35.82	3.3 x 10 ⁻⁹	0.04	SAD < BD ² SZ < BD ² SAD < SAB ¹ SZ < SAB ²
Reasoning & Problem Solving	F ^{3, 805} =6.09	4.2 x 10 ⁻⁴	0.02	F ^{1, 805} =29.74	6.6 x 10 ⁻⁸	0.04	SAD < BD ² SZ < BD ²
Visual Learning	F ^{3, 802} =13.86	8.1 x 10 ⁻⁹	0.05	F ^{1, 802} =14.89	1.2 x 10 ⁻⁴	0.02	SAD < BD ² SZ < BD ² SZ < SAB ²
Social Cognition	F ^{3, 789} =8.77	1.0 x 10 ⁻⁵	0.03	F ^{1, 789} =32.80	1.5 x 10 ⁻⁸	0.04	SAB < BD ¹ SAD < BD ¹ SZ < BD ²
Attention / Vigilance	F ^{3, 755} =5.49	9.8 x 10 ⁻⁴	0.02	F ^{1, 755} =28.20	1.5 x 10 ⁻⁷	0.04	SZ < BD ¹ SZ < SAB ¹
Speed of Processing	F ^{3, 805} =13.51	1.3 x 10 ⁻⁸	0.05	F ^{1, 805} =60.42	2.4 x 10 ⁻¹⁴	0.07	SAD < BD ² SZ < BD ² SAD < SAB ¹ SZ < SAB ²
Working Memory	F ^{3, 805} =7.16	9.5 x 10 ⁻⁵	0.03	F ^{1, 805} =33.60	9.7 x 10 ⁻⁹	0.04	SAD < BD ² SZ < BD ² SZ < SAB ¹
Composite Score	F ^{3, 805} =16.71	1.6 x 10 ⁻¹⁰	0.06	F ^{1, 805} =64.75	3.1 x 10 ⁻¹⁵	0.07	SAD < BD ² SZ < BD ² SZ < SAB ² SAD < SAB ¹

Total SANS were calculated by summing the global scores (affective flattening, alogia, avolition / apathy and anhedonia / asociality). Partial η^2 indicates the proportion of variance in cognitive scores that is associated with each variable. BD, bipolar disorder; SAB, schizoaffective disorder – bipolar type; SAD, schizoaffective disorder – depressive type; SZ, schizophrenia; ¹p<0.05, ²p<0.00625 (Bonferroni-corrected)

Modelling the contributions of clinical variables

Diagnosis, olanzapine equivalent dose, duration of antipsychotic exposure, total current SANS scores, total current SAPS scores, and lifetime depression (as measured by the BADDs depression dimension) were added as predictors into a single model. The main effect of diagnostic group on composite cognition remained significant ($F(3,694)=8.33$, $p=1.9 \times 10^{-5}$, see Table 3-12). After correction for multiple testing, there were significant differences in composite cognition between schizoaffective disorder - depressive type and bipolar disorder ($g=0.65$, $p<0.001$) and schizophrenia and bipolar disorder ($g=0.58$, $p<0.001$). The effect of diagnosis was not significant for the domains of reasoning and problem solving, social cognition or attention / vigilance at the Bonferroni-corrected alpha of 0.00625.

Table 3-12 Main effect of diagnostic group after accounting for all covariates

Domain	Effect of Diagnosis			Pairwise Comparisons
	F ^{df}	p	Partial η^2	
Verbal Learning	$F^{3, 694}=4.65$	0.003	0.02	SZ < BD ¹ SAD < BD ¹
Reasoning & Problem Solving	$F^{3, 694}=3.67$	0.01	0.02	SAD < BD ¹
Visual Learning	$F^{3, 691}=8.02$	2.9×10^{-5}	0.03	SAD < BD ² SZ < BD ² SZ < SAB ¹
Social Cognition	$F^{3, 683}=3.26$	0.02	0.01	SZ < BD ¹
Attention / Vigilance	$F^{3, 651}=2.24$	0.08	0.01	NS
Speed of Processing	$F^{3, 694}=7.58$	5.4×10^{-5}	0.03	SAD < BD ² SZ < BD ² SAD < SAB ¹ SZ < SAB ²
Working Memory	$F^{3, 694}=4.27$	0.005	0.02	SAD < BD ¹ SZ < BD ¹
Composite Score	$F^{3, 694}=8.33$	1.9×10^{-5}	0.04	SAD < BD ² SZ < BD ² SZ < SAB ¹ SAD < SAB ¹

Partial η^2 indicates the proportion of variance in cognitive scores that is associated with diagnosis. BD, bipolar disorder; SAB, schizoaffective disorder – bipolar type; SAD, schizoaffective disorder – depressive type; SZ, schizophrenia; ANCOVA, analysis of covariance; ¹ $p<.05$, ² $p<.00625$ (Bonferroni-corrected)

The effects of each predictor on composite cognition scores are shown in Table 3-13. Of the clinical variables, current negative symptoms explained the largest proportion of variance in cognitive scores ($F(1,694)=47.07$, $p=1.5 \times 10^{-11}$, partial $\eta^2=0.06$). This was followed by diagnosis (partial $\eta^2=0.04$). Olanzapine equivalent dose and antipsychotic exposure in months explained the same proportion of variance (partial $\eta^2=0.03$). Neither current positive symptoms nor lifetime depression scores were associated with cognitive performance.

Table 3-13 Effect of each variable on composite cognition

	F^{df}	p	Partial η^2
Diagnosis	$F^{3, 694}=8.33$	1.9×10^{-5}	0.04
Sex	$F^{1, 694} = 0.17$	0.68	2.5×10^{-4}
Age	$F^{1, 694} = 43.55$	8.3×10^{-11}	0.06
Olanzapine Equivalents	$F^{1, 694} = 18.74$	1.7×10^{-5}	0.03
Antipsychotic Exposure in Months	$F^{1, 694} = 19.29$	1.3×10^{-5}	0.03
Current SAPS Total	$F^{1, 694} = 0.33$	0.57	4.8×10^{-4}
Current SANS Total	$F^{1, 694} = 47.07$	1.5×10^{-11}	0.06
BADDs Depression	$F^{1, 694} = 1.05$	0.31	0.002

Partial η^2 indicates the proportion of variance in cognitive scores that is associated with diagnosis. BADDs, Bipolar Affective Disorder Dimension Scale; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms.

Premorbid IQ

Diagnostic group had significant effects on all domains of cognition when NART scores were entered as a covariate (see Table 3-14). However, post hoc comparisons between the groups in attention and working memory did not survive correction for multiple testing, except for all case-control comparisons. The differences between schizoaffective disorder – bipolar type and bipolar disorder were larger after accounting for premorbid IQ (composite cognition: $g=0.60$, $p=0.003$). The proportion of variance in cognitive performance explained by NART scores ranged between 0.06 and 0.32.

Table 3-14 The effects of diagnostic group and NART score on cognitive performance

Domain	Effect of Diagnosis			Effect of NART Score			Pairwise Comparisons
	F ^{df}	p	Partial η^2	F ^{df}	p	Partial η^2	
Verbal Learning	F ^{4, 876} = 40.18	<2.2 x 10 ⁻¹⁶	0.16	F ^{1, 876} = 197.45	<2.2 x 10 ⁻¹⁶	0.18	SAD < BD ² SZ < BD ²
Reasoning & Problem Solving	F ^{4, 876} = 27.79	<2.2 x 10 ⁻¹⁶	0.11	F ^{1, 876} = 88.99	<2.2 x 10 ⁻¹⁶	0.09	SAD < BD ² SZ < BD ²
Visual Learning	F ^{4, 872} = 28.82	<2.2 x 10 ⁻¹⁶	0.12	F ^{1, 872} = 192.47	<2.2 x 10 ⁻¹⁶	0.18	SAD < BD ² SZ < BD ²
Social Cognition	F ^{4, 859} = 13.45	1.2 x 10 ⁻¹⁰	0.06	F ^{1, 859} = 50.64	2.4 x 10 ⁻¹²	0.06	SAB < BD ² SZ < BD ²
Attention / Vigilance	F ^{4, 831} = 18.72	9.6 x 10 ⁻¹⁵	0.08	F ^{1, 831} = 160.11	<2.2 x 10 ⁻¹⁶	0.16	SZ < BD ¹
Speed of Processing	F ^{4, 876} = 56.75	<2.2 x 10 ⁻¹⁶	0.21	F ^{1, 876} = 168.77	<2.2 x 10 ⁻¹⁶	0.16	SAD < BD ² SZ < BD ²
Working Memory	F ^{4, 876} = 29.95	<2.2 x 10 ⁻¹⁶	0.12	F ^{1, 876} = 413.14	<2.2 x 10 ⁻¹⁶	0.32	SAD < BD ¹ SZ < BD ¹
Composite Score	F ^{4, 875} = 67.40	<2.2 x 10 ⁻¹⁶	0.24	F ^{1, 875} = 389.01	<2.2 x 10 ⁻¹⁶	0.31	SAB < BD ² SAD < BD ² SZ < BD ²

All cases were significantly impaired compared to controls, except for comparisons between the BD group and controls on social cognition and visual learning. Partial η^2 indicates the proportion of variance in cognitive scores that is associated with diagnosis. BD, bipolar disorder; SAB, schizoaffective disorder – bipolar type; SAD, schizoaffective disorder – depressive type; SZ, schizophrenia; ANCOVA, analysis of covariance. ¹p<0.05; ²p<0.00625 (Bonferroni-corrected)

3.4.4 Examining cognition as a dimension across diagnostic groups

Schizoaffective disorder – depressive type and schizophrenia as one group

Ordinal regression analyses were conducted to test the hypothesis that cognition can be considered a dimensional phenotype showing increasing impairment from bipolar disorder to schizoaffective disorder – depressive type / schizophrenia. Participants were assigned scores from 0 to 2 based on their diagnosis (0 = schizoaffective disorder - depressive type / schizophrenia, 1 = schizoaffective disorder - bipolar type and 2 = bipolar disorder). Diagnosis was entered as the outcome variable with composite cognition scores as the predictor and age and sex as covariates.

Ordinal regression analysis indicated that higher cognitive scores were associated with higher scores on the diagnostic scale supporting a spectrum of increasing impairment from bipolar disorder to schizoaffective disorder - bipolar type to schizophrenia/schizoaffective disorder - depressive type. An alternative way of interpreting this result is that among the clinical cases participants with a one standard deviation higher score in composite cognition were almost twice as likely to be diagnosed with schizoaffective disorder - bipolar type or bipolar disorder compared to schizophrenia (OR = 1.98, $p = 2.4 \times 10^{-16}$, see Table 3-15). The assumption of proportional odds was confirmed using the test of parallel lines ($\chi^2 = 4.97$, $df = 3$, $p = 0.174$) and by comparing the coefficients for binary regressions for each cut-off point in the scale (see Appendix E). The results were similar when social cognition was excluded from the composite score. The results of the ordinal regression did not change after adjustment for olanzapine equivalent dose, antipsychotic exposure in months and current negative symptoms (OR = 1.63, $p = 4.9 \times 10^{-7}$), although this result should be interpreted with caution given the proportional odds assumption was violated in this model ($\chi^2=26.98$, $p=1.5 \times 10^{-4}$).

The analysis was followed up with binary regressions between the diagnostic groups (*model 1*: BD and SAB; *model 2*: SAB and SAD/SZ) to compare the gradients from one diagnosis to the next on the scale. The resulting coefficients were equivalent for models 1 and 2. This confirmed that there is a gradient of increasing impairment from bipolar disorder to schizoaffective disorder - bipolar type to schizophrenia / schizoaffective disorder - depressive type.

Table 3-15 Ordinal regression results and post hoc comparisons

	Logistic Coefficient	Standard Error	Odds Ratio	95% Confidence Intervals	p value
Composite score ¹	0.69	0.08	1.98	1.68 to 2.33	2.4 x 10 ⁻¹⁶
Composite score without social cognition	0.67	0.08	1.96	1.67 to 2.27	8.2 x 10 ⁻¹⁶
With clinical covariates ²	0.49	0.10	1.63	1.35 to 1.97	4.9 x 10 ⁻⁷
<i>Post hoc tests</i>					
BD vs. SAB	0.50	0.16	1.65	1.20 to 2.26	0.002
SAB vs. SAD / SZ	0.45	0.11	1.56	1.27 to 1.92	2.6 x 10 ⁻⁵
BD vs. SAD / SZ	0.88	0.12	2.41	1.91 to 3.05	2.5 x 10 ⁻¹³

BD, Bipolar Disorder; SAB, Schizoaffective Disorder – Bipolar Type; SAD, Schizoaffective Disorder – Depressive Type; SZ, Schizophrenia. ¹Model fit: chi-square = 103.57 (p = 2.7 x 10⁻²²). Goodness of fit: i) Pearson chi-square = 1636.42 (p=0.527); ii) Deviance chi-square = 903.30 (p=1.00). ²Proportional odds assumption violated ($\chi^2=26.98$, p=1.5 x 10⁻⁴).

All groups

In the second ordinal model, participants were assigned scores from 0 to 3 based on their diagnosis (0 = schizophrenia, 1 = schizoaffective disorder – depressive type, 2 = schizoaffective disorder – bipolar type and 3 = bipolar disorder). These groups reflect those included in the analysis comparing cognition between diagnoses.

Ordinal regression analysis indicated that higher cognitive scores were associated with higher scores on the diagnostic scale (see Table 3-16). Participants with a one standard deviation higher score in composite cognition were 59% more likely to be grouped in a higher category on the scale compared to a lower category (OR = 1.59, p = 2.7 x 10⁻¹³). However, the test of parallel lines was significant indicating that the proportional odds assumption had been violated in this model ($\chi^2 = 27.61$, df = 6, p = 1.1 x 10⁻⁴). This indicates that the logistic estimates are not equal across all levels of the dependent variable therefore the combined estimate for the model is not accurate. This was confirmed by comparing the coefficients for binary regressions for each cut-off point in the scale (see Appendix E). The results were

similar when social cognition was excluded from the composite score and after adjustment for olanzapine equivalent dose, antipsychotic exposure in months and current negative symptoms (OR = 1.35, $p = 4.5 \times 10^{-5}$). The analysis was followed up with binary regressions between the diagnostic groups to compare the gradients from one diagnosis to the next on the scale. These results indicated that participants with a one standard deviation higher score in composite cognition were only 8% more likely to be diagnosed with schizoaffective disorder - depressive type type compared to schizophrenia suggesting that these diagnoses could be considered as a single category.

Table 3-16 Ordinal regression results and post hoc comparisons

	Logistic Coefficient	Standard Error	Odds Ratio	95% Confidence Intervals	p value
Composite score ¹	0.46	0.06	1.59	1.40 to 1.80	2.7×10^{-13}
Composite score without social cognition	0.44	0.06	1.56	1.37 to 1.75	2.4×10^{-12}
With clinical covariates	0.30	0.07	1.35	1.17 to 1.56	4.5×10^{-5}
<i>Post hoc tests</i>					
BD vs. SAB	0.50	0.16	1.65	1.20 to 2.26	0.002
BD vs. SAD	0.80	0.15	2.22	1.67 to 2.96	5.5×10^{-8}
BD vs. SZ	0.91	0.13	2.48	1.94 to 3.18	6.0×10^{-13}
SAB vs. SAD	0.42	0.13	1.52	1.17 to 1.97	0.002
SAB vs. SZ	0.47	0.11	1.60	1.29 to 1.99	1.9×10^{-5}
SAD vs. SZ	0.08	0.09	1.08	0.92 to 1.28	0.362

BD, Bipolar Disorder; SAB, Schizoaffective Disorder – Bipolar Type; SAD, Schizoaffective Disorder – Depressive Type; SZ, Schizophrenia. ¹Model fit: chi-square = 113.70 ($p = 1.8 \times 10^{-24}$). Goodness of fit: i) Pearson chi-square = 2434.90 ($p=0.653$); ii) Deviance chi-square = 1497.63 ($p=1.00$).

Schizoaffective disorder as one group

The final ordinal model included schizoaffective disorder as a single category (0 = schizophrenia, 1 = schizoaffective disorder and 2 = bipolar disorder). This was done to mirror the groups included in previous studies, which have combined the subtypes of schizoaffective disorder. Ordinal regression analysis indicated that higher cognitive scores were associated with higher scores on the diagnostic scale (see Table 3-17). Participants with a one standard deviation higher score in composite cognition were 57% more likely to be diagnosed with schizoaffective disorder or bipolar disorder compared to schizophrenia (OR = 1.57, $p = 2.1 \times 10^{-12}$). As previously, the test of parallel lines was significant ($\chi^2 = 20.03$, $df = 3$, $p = 1.7 \times 10^{-4}$) indicating the logistic estimates were not equal across all levels of the dependent variable. This was confirmed by comparing the coefficients for binary regressions for each cut-off point in the scale (see Appendix E). The results were similar when social cognition was excluded from the composite score. The results of the ordinal regression did not change after adjustment for olanzapine equivalent dose, antipsychotic exposure in months and current negative symptoms (OR = 1.33, $p = 1.5 \times 10^{-4}$). The analysis was followed up with binary regressions between the diagnostic groups to compare the gradients from one diagnosis to the next on the scale. These results indicated that participants with a one standard deviation higher score in composite cognition were twice as likely to be diagnosed with bipolar disorder compared to schizoaffective disorder but only 25% more likely to be diagnosed with schizoaffective disorder compared to schizophrenia. This suggests a steeper gradient between bipolar disorder and schizoaffective disorder than there is between schizoaffective disorder and schizophrenia.

Table 3-17 Ordinal regression results and post hoc comparisons

	Logistic Coefficient	Standard Error	Odds Ratio	95% Confidence Intervals	p value
Composite score ¹	0.45	0.06	1.57	1.38 to 1.78	2.1 x 10 ⁻¹²
Composite score without social cognition	0.42	0.06	1.54	1.35 to 1.72	2.4 x 10 ⁻¹¹
With clinical covariates	0.28	0.07	1.33	1.15 to 1.54	1.5 x 10 ⁻⁴
<i>Post hoc tests</i>					
BD vs. SA	0.68	0.13	1.98	1.53 to 2.55	1.9 x 10 ⁻⁷
SA vs. SZ	0.22	0.07	1.25	1.09 to 1.44	0.002
BD vs. SZ	0.91	0.13	2.48	1.94 to 3.18	6.0 x 10 ⁻¹³

BD, Bipolar Disorder; SA, Schizoaffective Disorder; SZ, Schizophrenia. ¹Model fit: chi-square = 111.16 (p = 6.2 x 10⁻²⁴). Goodness of fit: i) Pearson chi-square = 1596.08 (p=0.782); ii) Deviance chi-square = 1246.48 (p=1.00).

3.4.5 Cross disorder symptom dimensions and cognitive performance

Median symptom dimension scores for each diagnostic group are presented in Table 3-18. Figure 3-3 displays cognition scores plotted against each symptom dimension. Higher scores on the lifetime BADDs mania dimension predicted better cognitive performance (B=0.010, SE=0.001, p=3.6 x 10⁻¹⁴), whilst there was a trend association between BADDs depression scores and cognition (B=0.003, SE=0.001, p=0.056). Higher scores on the lifetime BADDs psychosis and incongruence dimensions predicted poorer cognitive performance (psychosis: B=-0.016, SE=0.002, p<2.2 x 10⁻¹⁶; incongruence: B=-0.017, SE=0.002, p<2.2 x 10⁻¹⁶). Higher scores on the lifetime SAPS and SANS scales also predicted poorer cognitive performance (SAPS: B=-0.051, SE=0.015, p=8.5 x 10⁻⁴; SANS: B=-0.088, SE=0.011, p=2.4 x 10⁻¹⁵).

Table 3-18 Median and interquartile ranges for symptom dimensions

	Bipolar Disorder	Schizoaffective Disorder – Bipolar Type	Schizoaffective Disorder – Depressed Type	Schizophrenia
BADDS Mania	82 (21.5)	82 (5)	0 (1)	0 (0)
BADDS Depression	69.5 (22.25)	81 (7.5)	85 (11)	60 (72)
BADDS Psychosis	22.5 (40)	75 (40)	80 (40)	100 (10)
BADDS Incongruence	18 (30)	70 (20)	70 (20)	97 (10.5)
SAPS	5 (5)	10 (4)	9 (3)	10 (4)
SANS	4 (4.75)	6 (5.5)	7 (5)	7 (6)

BADDS, Bipolar Affective Disorder Dimension Scale; SAPS, Scale for the Assessment of Positive Symptoms; SANS, Scale for the Assessment of Negative Symptoms.

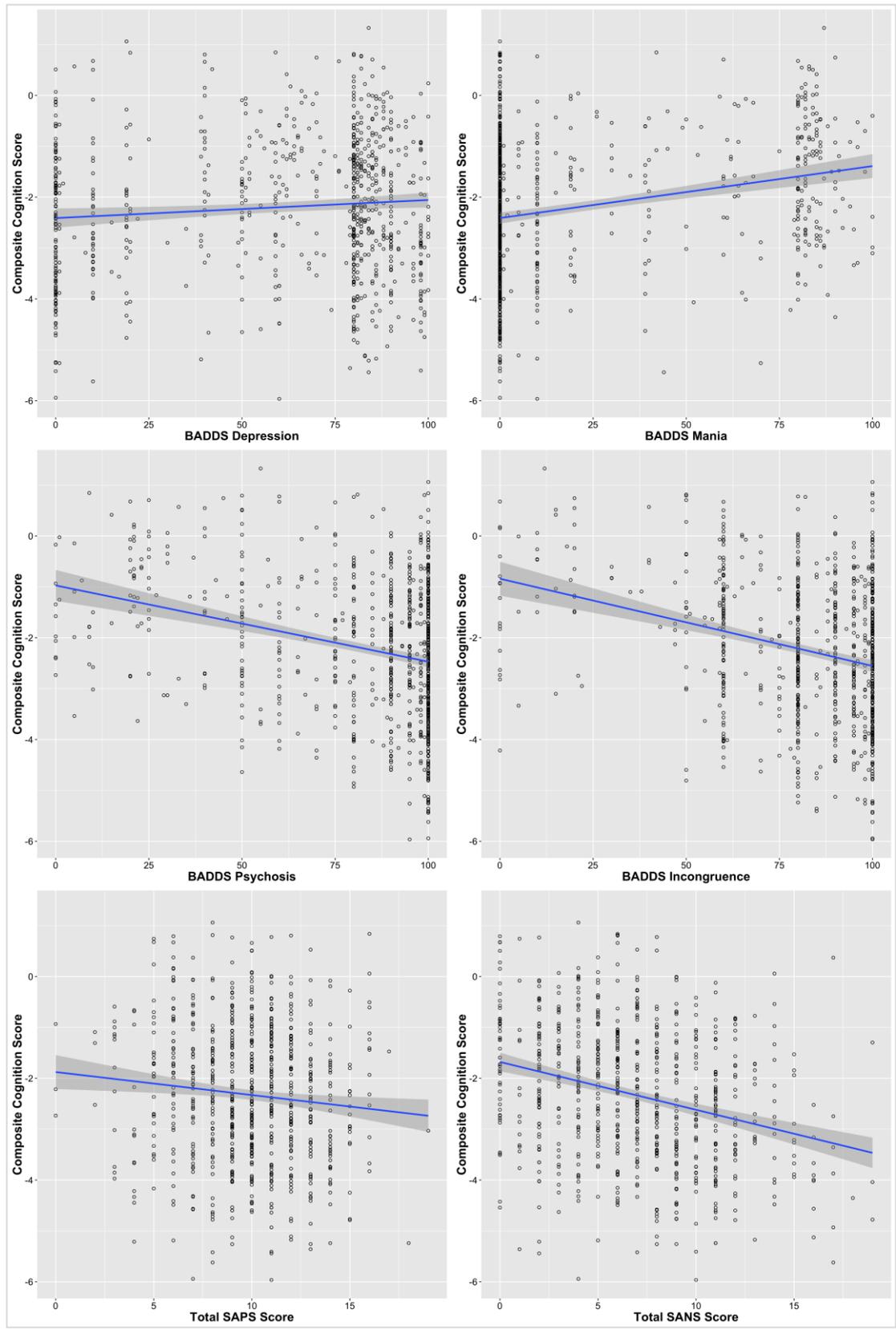


Figure 3-3 Symptom dimension scores and composite cognition scores

From top left to bottom right: BADDs depression, BADDs mania, BADDs psychosis, BADDs incongruence, total SAPS scores and total SANS scores. Line represents the regression line and the shaded region indicates 95% confidence intervals.

In the subgroup analyses (bipolar disorder and schizoaffective disorder - bipolar type only, schizophrenia and schizoaffective disorder - depressive type only), neither BADDs mania nor depression scores predicted performance but higher BADDs psychosis scores were associated with lower cognitive scores (*bipolar / schizoaffective disorder - bipolar type*: $B=-0.014$, $SE=0.003$, $p=7.9 \times 10^{-7}$; *schizophrenia / schizoaffective disorder - depressive type*: $B=-0.010$, $SE=0.003$, $p=0.0008$). Higher scores on the BADDs incongruence dimension were also associated with lower cognitive scores (*bipolar / schizoaffective disorder - bipolar type*: $B=-0.012$, $SE=0.003$, $p=0.0002$; *schizophrenia / schizoaffective disorder - depressive type*: $B=-0.012$, $SE=0.004$, $p=0.0008$). Higher lifetime SAPS total scores were associated with lower cognitive scores in the schizophrenia / schizoaffective disorder - depressive type ($B=-0.049$, $SE=0.017$, $p=0.004$) but not in the bipolar / schizoaffective disorder - bipolar type subgroup ($B=-0.023$, $SE=0.031$, $p=0.459$). Finally, lifetime SANS total scores were associated with lower cognitive scores in the schizophrenia and schizoaffective disorder - depressive type subgroup ($B=-0.088$, $SE=0.012$, $p=3.5 \times 10^{-13}$) but not in the bipolar disorder and schizoaffective disorder - bipolar type subgroup ($B=-0.052$, $SE=0.027$, $p=0.053$).

All analyses were repeated adjusting for age, sex, antipsychotic exposure in months, olanzapine equivalent dose and current negative symptoms (see Table 3-19). The associations between BADDs psychosis and cognition, as well as BADDs incongruence and cognition, remained significant. However, these associations did not survive correction for multiple testing in the subgroup analyses. Lifetime SAPS scores were not associated with cognitive scores after inclusion of the covariates ($B=-0.023$, $SE=0.02$, $p=0.14$). Higher lifetime SANS scores was associated with lower cognitive performance ($B=-0.081$, $SE=0.01$, $p=2.7 \times 10^{-12}$), except in the bipolar / schizoaffective disorder - bipolar type subgroup analysis.

Table 3-19 The associations between symptom dimensions and cognition after adjusting for age, sex, antipsychotic exposure in months, olanzapine equivalent dose and current negative symptoms*

	All Groups			BD and SAB			SAD and SZ		
	B	SE	p	B	SE	p	B	SE	p
BADDS Depression	0.002	0.001	0.07	-0.004	0.004	0.33	0.002	0.001	0.11
BADDS Mania	0.007	0.001	5.8 x 10 ⁻⁷	0.002	0.01	0.78	0.005	0.003	0.09
BADDS Psychosis	-0.011	0.002	9.2 x 10 ⁻⁸	-0.010	0.003	0.003	-0.006	0.003	0.04
BADDS Incongruence	-0.012	0.002	4.3 x 10 ⁻⁸	-0.007	0.003	0.03	-0.009	0.004	0.01
SAPS	-0.023	0.02	0.14	-0.001	0.03	0.97	-0.022	0.018	0.21
SANS*	-0.081	0.01	2.7 x 10 ⁻¹²	-0.024	0.03	0.41	-0.082	0.012	6.2 x 10 ⁻¹¹

*Current negative symptoms were not included as a covariate in the analysis of lifetime SANS scores and cognition due to collinearity. BADDS, Bipolar Affective Disorder Dimension Scale; SAPS, Scale for the Assessment of Positive Symptoms; SANS, Scale for the Assessment of Negative Symptoms; BD, Bipolar Disorder; SAB, Schizoaffective Disorder – Bipolar Type; SAD, Schizoaffective Disorder – Depressive Type; SZ, Schizophrenia.

3.5 Discussion

The main aim of this chapter was to test the hypothesis that there is a spectrum of increasing cognitive impairment from bipolar disorder to schizoaffective disorder - bipolar type to schizophrenia and schizoaffective disorder - depressive type. A second aim was to examine the relationship between lifetime measures of symptom domains and cognitive function. There were three key results of this study:

1. In accordance with the study hypothesis, cognitive profiles were similar across disorders but impairments increased in severity from bipolar disorder to schizoaffective disorder - bipolar type to schizophrenia and schizoaffective disorder - depressive type. There were no differences between schizophrenia and schizoaffective disorder - depressive type in severity of cognitive impairments. Ordinal regression modelling provided further support for a gradient of increasing cognitive impairment across disorders demonstrating a linear trend between cognitive scores and an ordered diagnostic scale.
2. Antipsychotic medication use, negative symptoms and premorbid IQ account for some of the variation between diagnoses but the overall effect of diagnosis persists after accounting for these variables.
3. Greater frequency and severity of psychosis and negative symptoms are associated with lower cognitive performance, whilst mania and depression are not.

Each of these findings is discussed in detail in the following sections.

3.5.1 Cognitive performance in the bipolar / schizophrenia spectrum

Cognitive profiles were similar across disorders but impairments increased in severity from bipolar disorder to schizophrenia and schizoaffective disorder - depressive type. Performance in the schizoaffective disorder - bipolar type group was intermediate between bipolar disorder and schizophrenia, although the differences between schizoaffective disorder – bipolar type and bipolar disorder were not significant. The ordinal regression model provided further support for a gradient of increasing impairment demonstrating an association between cognitive scores and an ordered diagnostic scale. The optimal ordinal model combined

schizoaffective disorder - depressive type and schizophrenia into a single category. These results are consistent with the results of previous studies showing that multiple domains of cognition are affected and these impairments increase in severity from bipolar disorder to schizophrenia [266, 303, 314, 319]. These results expand on existing literature by demonstrating that schizoaffective disorder - depressive type lies on the severe end of the cognitive spectrum with schizophrenia.

Performance across the cognitive domains was equivalent in the schizophrenia and schizoaffective disorder - depressive type groups. These results question the validity of distinguishing between schizophrenia and the depressive subtype of schizoaffective disorder. In addition, the two disorders did not differ on estimated premorbid IQ, years in education, antipsychotic medication use, current positive and negative symptoms and scores on the Global Assessment Scale.

Schizoaffective disorder – depressive type is distinguished from schizophrenia in DSM-IV on the basis that depressive episodes are present for a substantial proportion of the total illness duration (now defined as the majority of the illness duration in DSM-5). However, patients with schizophrenia are at increased risk of developing depression. It is estimated that approximately 40% of patients with schizophrenia meet criteria for depressive disorder at some point in their illness, although estimates range between 20-60% [16]. Taken together, this evidence suggests that schizoaffective disorder - depressive type and schizophrenia could be considered as a single diagnosis representing the severe end of a spectrum of cognitive impairment. This was supported by the findings of the ordinal regression analyses.

The schizoaffective disorder - bipolar type group was less cognitively impaired than the schizoaffective disorder - depressive type and schizophrenia groups, occupying an intermediate position between these disorders and bipolar disorder. This finding may at least partly explain why studies of cognition in schizoaffective disorder report conflicting findings. The subtypes of schizoaffective disorder were combined into a single category in a supplementary analysis (see Appendix F). Significant differences were found between schizoaffective disorder and schizophrenia in visual learning despite the similarities in performance between the depressive subtype and schizophrenia. These results suggest that amalgamation of the subtypes may obscure findings.

Differences in overall cognition between schizoaffective disorder - bipolar type and bipolar disorder were not significant after correction for multiple testing. However, the effect size between these groups ($g=0.44$) was larger than that observed between schizophrenia and schizoaffective disorder - depressive type ($g=0.07$). This may explain why a linear trend from bipolar disorder to schizoaffective disorder - bipolar type to schizophrenia and schizoaffective disorder - depressive type was still observed in the ordinal regression analysis. We used a conservative Bonferroni-corrected alpha value of 0.00625 to control the type-I error rate but at the cost of loss of power, which could explain the lack of significant difference. However, it should be noted that there were smaller differences between schizoaffective disorder - bipolar type and bipolar disorder on individual domains, which were not significant even at $\alpha=0.05$.

Diagnostic groups were differentiated based on severity of cognitive impairments but the overall pattern of impairment was similar between the groups (Fig. 3-1). This suggests cognitive impairment can be considered a dimensional phenotype that cuts across diagnostic boundaries. Similarities between the cognitive profiles of these disorders are consistent with a shared underlying neurobiology that differs quantitatively rather than qualitatively across the diagnostic groups [24, 26, 27]. Indeed, there is some evidence that regions of grey matter reductions overlap across these disorders, although results for bipolar disorder have been less consistent [347-350]. In addition, there is evidence of an overlap in genetic susceptibility across these disorders [30, 53, 73, 74]. Overall, these results question the validity of a Kraepelinian boundary between schizophrenia and bipolar disorder and provide support for a dimensional model of psychotic and affective disorders.

Whilst neurocognitive impairments were evident across all diagnoses, impairments in social cognition were not present in bipolar disorder but were observed in schizophrenia and both subtypes of schizoaffective disorder. This is consistent with previous studies that have measured cognitive impairment using the MCCB in bipolar disorder [335-337]. The largest difference between participants with schizoaffective disorder - bipolar type and bipolar disorder was observed in social cognition suggesting there may be some distinction in the cognitive processes underlying these disorders despite similar neurocognitive profiles. Social cognition was also the only domain associated with current positive symptoms. Previous

studies have demonstrated associations between domains of social cognition, particularly theory of mind deficits, and psychotic symptoms in schizophrenia [351-353]. These results suggest that certain social cognitive tasks may differentiate bipolar disorder from other disorders within the bipolar / schizophrenia spectrum. Whilst deficits in performance on the MSCEIT ME may not be present in bipolar disorder, there is evidence of impairments in facial emotion recognition and theory of mind in bipolar disorder [199, 243]. However, a meta-analysis identified more severe deficits in these domains in schizophrenia than bipolar disorder [265]. The association between social cognitive impairment and psychosis provides support to cognitive models of psychosis that posit a role for social interpretations in the development of psychotic thinking [354].

3.5.2 Demographic and clinical variables

Diagnostic groups differed on proportion of males, premorbid IQ, years in education, current dose of antipsychotic medication, lifetime duration of antipsychotic use, current symptoms and global functioning. Therefore, sex was included as a covariate in all analyses that compared the diagnoses and a series of secondary analyses were performed to determine whether differences in antipsychotic medication use, current symptoms or premorbid IQ could account for the differences found between diagnostic groups. The main effect of diagnosis remained significant in these secondary analyses. However, when these variables were included as covariates the differences between diagnostic groups were attenuated.

Higher doses of antipsychotic medication have been shown to be associated with poorer cognition [355] and this was observed in the sample. The current study expands on these findings by demonstrating that duration of antipsychotic exposure is also associated with cognitive performance. Both dose of and duration of exposure to antipsychotic medication partially accounted for the differences between diagnostic groups. It should be noted that duration of antipsychotic use in months is a simplistic measure of exposure and it does not consider the types or doses of antipsychotic medication taken by the participant. Antipsychotic exposure could also be measured as cumulative dose over time but this data was not available. Current positive symptoms were not associated with any of the cognitive

domains, except social cognition, suggesting that the effects of antipsychotic medication are not related to severity of current symptoms of psychosis. However, the findings from the linear regression analyses suggest that lifetime frequency and severity of psychotic symptoms are associated with cognitive deficits. Further work is needed to disentangle the effects of medication and severity of psychosis. The effect of diagnosis persisted after inclusion of antipsychotic medication despite the differences between groups being attenuated. This suggests that differences in antipsychotic medication use do not explain cognitive impairments. This is supported by studies showing that cognitive deficits are present prior to the onset of schizophrenia [159, 356]. The influence of other psychotropic medications, such as lithium, was not considered in these analyses. However, lithium use has been shown to have little impact on cognitive function and is unlikely to explain these results [261].

Whilst current positive symptoms were only associated with social cognition, current negative symptoms were associated with all domains of cognition. Current negative symptoms also explained a higher proportion of the variance in cognitive scores than diagnosis. Differences in social cognition, attention, speed of processing and working memory between groups were attenuated after accounting for current SANS scores. This is consistent with a meta-analysis that found differences in cognition between schizophrenia and affective psychosis were partly driven by differences in the severity of negative symptoms [263]. This result is not surprising given that negative symptoms include poverty of thinking and loss of motivation and interest, all of which are likely to influence performance on difficult cognitive tasks. These results were consistent with the linear regression analyses that demonstrated a relationship between lifetime history of negative symptoms and cognitive performance, which is discussed further in the section below.

Estimated premorbid IQ scores followed a similar pattern to the cognitive domains with the poorest scores evident in the schizophrenia and schizoaffective disorder – depressive type groups. When NART scores were included as a covariate, there were no significant differences between schizoaffective disorder - bipolar type and either schizophrenia or schizoaffective disorder - depressive type. This suggests that the cognitive decline associated with these disorders is similar but differences emerge because participants with schizophrenia and schizoaffective disorder -

depressive type have lower premorbid IQ. However, differences between schizoaffective disorder - bipolar type and bipolar disorder were larger after accounting for premorbid IQ. This suggests that schizoaffective disorder - bipolar type is associated with greater cognitive decline than bipolar disorder. However, this was not empirically tested in the present study. DeRosse et al. [299] used a regression model to estimate cognitive trajectories and identified greater cognitive decline in schizoaffective disorder compared to schizophrenia and bipolar disorder. However, both the current study and DeRosse et al. [299] used cross-sectional data and a retrospective estimate of premorbid IQ. Although the NART is one of the most widely used measures of premorbid IQ in the UK, it has been shown to differ from measures of IQ taken in childhood overestimating premorbid IQ by 15 points on average [357]. However, these analyses were concerned with the relative differences between participants in their NART score and therefore lack of accuracy in predicting exact IQ should not be an issue. A longitudinal study would provide more accurate estimations of cognitive decline across disorders.

3.5.3 Lifetime symptom dimensions and cognitive impairment

In the cross-diagnostic analysis, higher scores on the BADDS mania dimension were associated with better cognitive performance. However, this result was not replicated in the subgroup analyses and may be driven by the effect of diagnosis, as participants with schizoaffective disorder - bipolar type and bipolar disorder scored higher on the BADDS mania dimension and cognitive tasks. The BADDS depression dimension was also associated with better cognitive performance across the whole samples but the regression coefficient was small ($B=0.003$) and this association was not found in analyses of the subgroups. Again, this result is more likely to reflect diagnostic group differences than scores on the depression scale, as the largest group (schizophrenia) had lower scores on the depression scale.

Higher scores on the psychosis dimensions (BADDS psychosis and lifetime SAPS scores) were associated with poorer cognitive performance. Lifetime history of psychosis has been shown to be associated with poorer cognition in previous studies [284, 303, 316]. These studies have considered lifetime psychosis as a binary measure (present or absent) rather than a dimensional measure. Our results expand on these findings by demonstrating that lifetime frequency and severity of

psychosis predicts severity of cognitive impairments. However, only the BADDs psychosis dimension was associated with cognition after accounting for negative symptoms and antipsychotic medication. This discrepancy between the BADDs psychosis and SAPS results is likely to be caused by insufficient power in the SAPS analysis to detect an association due to missing data; 92 observations (11% of cases) were missing for the SAPS variable compared to 9 missing observations (1%) on the BADDs psychosis variable.

Higher scores on the lifetime SANS were associated with poorer cognitive performance. The association between the SANS scale and cognitive scores was consistent with previous meta-analyses of studies of schizophrenia [358, 359]. The relationship between negative symptoms and cognition remains unclear but there are similarities between these types of symptoms. Both negative symptoms and cognitive impairments present premorbid, current treatments are not effective for either set of symptoms and both are strong predictors of functional outcome. There is some evidence that negative symptoms partially mediate the relationship between cognition and functional outcome [359]. However, it has been argued that the associations between negative symptoms and cognition are weak and may indicate distinct neurobiological pathways [360, 361].

The final association was between the BADDs incongruence dimension and cognition. The incongruence dimension indicates the extent to which psychotic symptoms occur during or outside of mood episodes. It is based on diagnostic criteria for affective and psychotic disorders, as described in DSM-IV and ICD-10. Higher scores on this dimension indicate more frequent psychosis outside of mood and were associated with more severe cognitive impairment. Scores on this scale increase from bipolar disorder to schizoaffective disorder to schizophrenia, as the scale reflects diagnostic criteria for these disorders. Therefore the association in the cross-disorder analysis is not surprising and likely reflects the cognitive differences between diagnostic groups.

The BADDs was treated as a continuous measure in these analyses, although a previous study considered the BADDs as an ordinal measure [362]. The BADDs consists of “anchor points” whereby the participant’s worst episode defines the lowest rating they can be allocated and then points are added based on their

remaining episodes of illness. Therefore, the scale is not completely linear. Allardyce et al. [362] grouped participants on an ordinal scale based on their BADDS score. Whilst this makes interpretation of the scale easier, the disadvantage of this is that information is lost and it assumes that all participants within a certain range of the BADDS are the same. The BADDS was analysed as a continuous measure in this study to ensure that the complete range of scores could be included. The distribution of the residuals was normal and thus it did not violate the assumptions of linear regression. This does not impact the overall results, which would not have changed regardless of whether the BADDS were treated as continuous or ordinal variables.

3.5.4 Generalizability of the results

CoMPaSS is a UK-based study that recruits participants from outpatient clinics, clozapine clinics, depot clinics, early intervention psychosis services, and voluntary organisations. Despite the wide-ranging recruitment methods employed, there are number of potential sources of recruitment bias in the sample. The protocol for the study takes two to three hours to complete including a face-to-face interview, cognitive assessment and a blood sample. This may be a barrier to participation for some patients, particularly those who are most severely impaired or are functioning well and work full time. The predominant method of recruitment was through secondary services so the sample is over-represented by participants with a more chronic course of illness and under-represented by individuals who have been unwell in the past and subsequently recovered and were discharged from psychiatric services. A large proportion of the participants with schizophrenia were recruited through clozapine clinics so the schizophrenia group is predominantly those with treatment-resistant schizophrenia. The sample is comprised of stabilised participants rather than acutely unwell participants. Therefore, the results generalise to stable patients treated in the community but a different pattern of results may be observed in acutely unwell participants, such as inpatients. Finally, these findings are based on participants diagnosed according to DSM-IV criteria. This is important given differences in the criteria for schizoaffective disorder between diagnostic manuals. Diagnosis of schizoaffective disorder in DSM-IV relies on mood symptoms being present for a substantial proportion of the total illness duration, with a period of at least two weeks of psychosis in the absence of

mood. In contrast, ICD and RDC place more emphasis on the first rank symptoms of schizophrenia. Vollmer-Larsen et al. [329] demonstrated that using ICD-10 and DSM-IV to diagnose schizoaffective disorder results in a different set of patients. Therefore, the results presented here may not generalise to patients diagnosed according to ICD or RDC.

3.5.5 Concluding statements and future work

Several limitations of this study should be noted. There was a larger sample of participants with schizophrenia than bipolar disorder because the main aim of the CoMPaSS study was revised at a later stage of recruitment to focus solely on schizophrenia-spectrum disorders. However, all patient groups were recruited as part of a single study and all aspects of recruitment, response rates, phenotyping and determining diagnosis were equivalent across groups. In addition to this, all of the groups had a large number of participants and these analyses were able to detect differences between the groups. The inter-rater reliability for schizoaffective disorder – depressive type was low (Kappa=0.63), although this Kappa value is higher than those reported in a review of the diagnostic reliability of schizoaffective disorder [20]. As noted in section 3.5.1, depression is a common co-morbidity in patients with schizophrenia. Criterion C for schizoaffective disorder in DSM-IV states that the mood disturbance must be present for a “substantial proportion” of the illness but this proportion is poorly specified. Thus, schizoaffective disorder – depressive type is distinguished from schizophrenia and co-morbid depression based on a subjective judgement about the duration of depressive symptoms. The lack of evidence for clinical differences between these two disorders (except duration of depression) and poor reliability of the diagnosis of schizoaffective disorder further questions the validity of distinguishing between them. The bipolar disorder group consisted of a mixture of patients with and without a lifetime history of psychosis. Given the small number of participants without psychosis, it was not possible to separate the group into those with and without history of psychosis to examine differences between these groups and schizophrenia or schizoaffective disorder. However, analyses were conducted to determine whether there is a linear relationship between lifetime psychosis and cognitive function. Current depressive or manic symptoms were not considered as covariates in these analyses. Studies have shown that depressive and manic

symptoms are associated with poorer cognitive performance (particularly on measures of verbal fluency and executive function) in participants with bipolar disorder [257-259]. One study also demonstrated a negative correlation between depressive symptoms and cognitive performance in participants with schizophrenia [363]. However, cognitive impairments have been shown to persist during periods of remission in patients with bipolar disorder [238]. The MCCB was designed for use with participants with schizophrenia. Previous studies of bipolar disorder have failed to find deficits in executive functioning using the NAB Mazes task [242, 335, 337]. The authors of these studies note that more complex measures of executive function, such as the Wisconsin Card Sorting Task, may be more sensitive to detecting deficits in bipolar disorder. Although the bipolar group was impaired on the NAB Mazes relative to controls, this task may not have been sufficiently complex to differentiate bipolar disorder and schizoaffective disorder – bipolar type. Furthermore, the bipolar group was not impaired on the social cognition task (MSCEIT) but previous studies have identified deficits in theory of mind and emotion recognition suggesting that patients with bipolar disorder do have impairments in specific domains of social cognition [199, 243].

This study has several strengths. It is one of the largest samples to date and was sufficiently large enough to separate the subtypes of schizoaffective disorder. The sample is well characterised with consensus lifetime diagnoses based on semi-structured interview and medical records. The findings were robust to the inclusion of current symptoms and antipsychotic medication as covariates. A lifetime measure of antipsychotic medication (duration of exposure in months) was included in addition to controlling for current dose of antipsychotic medication.

In conclusion, it has been demonstrated that there is a gradient of increasing cognitive impairment from bipolar disorder to schizoaffective disorder - bipolar type to schizophrenia and schizoaffective disorder - depressive type. Differences in cognitive profiles between the diagnoses were quantitative rather than qualitative. Participants with the depressive subtype of schizoaffective disorder displayed comparable cognitive performance to participants with schizophrenia. This argues against separating schizophrenia and schizoaffective disorder - depressive type for such analyses. This study was the first to use a regression model to demonstrate a gradient of cognitive impairment. This study also showed that a dimensional

measure of lifetime psychosis is linearly associated with cognition. These results offer important insights for psychiatric nosology providing support for a dimensional model of psychotic and affective disorders rather than diagnostic categories. These findings also have implications for the development of therapies that restore cognitive function and the provision of social support for patients in the community. All patient groups exhibited cognitive impairments relative to the controls. Therapies developed to improve cognition should be targeted towards patients with schizoaffective disorder and bipolar disorder, as well as schizophrenia.

Chapter 4: Development of an Online Cognitive Battery for Use in Research of Psychiatric Disorders

4.1 Introduction

Emerging evidence in the fields of cognitive neuroscience, genetics and psychiatry has highlighted the need for large samples to be recruited [274]. There is increasing interest in examining genetic and environmental factors that contribute to the development of cognitive impairments in patients with psychiatric disorders both within and across diagnostic boundaries. However, few studies have collected sufficiently large cross-diagnostic datasets and collection of this data is logistically challenging and expensive.

Web-based data collection is an effective way to acquire large amounts of cognitive data using minimal resources. Advantages to web-based methods include: 1) relatively inexpensive costs per participant [272, 274]; 2) automatic data entry that limits errors [272]; 3) ability to recruit from locations that would normally be out of reach [268]; 4) promotion of research to the public [268]. Studies comparing web-based and traditional cognitive tasks have reported high correlations, few systematic differences between the assessments and good internal reliability of online tasks [273, 274, 276]. However, questions remain over whether unsupervised online tasks are a suitable alternative to traditional pen and paper tasks, particularly amongst individuals with psychiatric disorders who may have moderate to severe cognitive impairments. One issue is participation bias, as online studies may exclude individuals who are less computer literate or who do not have internet access.

An important consideration when developing a cognitive battery is which domains of cognition to include. There has been no consensus on which domains of cognition should be examined in psychiatric disorders with the exception of schizophrenia. The National Institute of Mental Health's (NIMH) Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative was formed to stimulate the development of new treatments for cognitive impairments in psychotic disorders. One of the objectives of the MATRICS was to

create a cognitive battery with good psychometric properties that could be used in research of cognition in schizophrenia [201]. Consultations with more than 130 scientists and an evaluation of factor analytic studies led to the selection of seven cognitive domains and a set of criteria for evaluating tasks for inclusion in the battery [202]. The seven cognitive domains were: speed of processing, working memory, verbal memory, visual memory, attention/vigilance, reasoning and problem solving, and social cognition. An expert committee then evaluated 90 nominated tasks and shortlisted 36 tasks for inclusion [203]. The psychometric properties, tolerability and relationship with functional outcome of each task were evaluated to select a final MATRICS Consensus Cognitive Battery (MCCB). Although the MCCB was developed to assess cognitive function in schizophrenia, the battery has also been used in studies of bipolar disorder [335, 336] and major depressive disorder [364]. Whilst the MCCB is considered a gold standard cognitive assessment, there are some disadvantages to administering the battery. The MCCB predominantly consists of pen and paper tasks and has to be administered by a specially trained researcher. The battery also takes up to one and a half hours to complete. The administration and duration of the battery means that collecting data on very large numbers of participants is labour intensive.

This chapter describes the development and validation of an online cognitive battery for use in research of psychiatric disorders. The conception and design of the online cognitive battery were completed in the first two years of the PhD, as well as the process of gaining ethical approval. The aim was to develop a cognitive battery that assessed the domains outlined by the MATRICS initiative. I developed the online cognitive battery in collaboration with The Many Brains Project, Inc. The Many Brains Project is a not-for-profit organisation that develops online cognitive testing tools for use in research studies. The tests are taken from published research. The Many Brains Project hosts a website, “testmybrain.org”, which collects cognitive data from around the world. The website includes cognitive tasks and questionnaires and provides individual feedback on the participant’s performance to encourage engagement in the research. They have collected data on hundreds of thousands of participants including those with cognitive impairments. Analysis of the data from the “testmybrain.org” website

showed few systematic differences between web-based and laboratory-based samples on mean performance, performance variance and internal reliability [273].

This chapter is separated into two parts. The first part details the development of the study website. I selected the tasks in consultation with researchers within the MRC Centre for Neuropsychiatric Genetics and Genomics at Cardiff University and The Many Brains Project. The second part of this chapter describes a pilot and validation study. I piloted the new cognitive battery with a group of participants with a range of psychiatric disorders and validated it against the MATRICS Consensus Cognitive Battery (MCCB).

4.2 Part 1. Development of the study website

4.2.1 Selection of the cognitive tasks

I selected the tasks to assess, as closely as possible, the domains outlined by the National Institute of Mental Health's (NIMH) Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative (see Section 1.7.1 for more details about the MATRICS domains). I chose The Many Brains Project as a collaborator (<http://www.manybrains.net/>), as the set-up of the website was simple, the tasks are taken from published studies and included computerised versions of some of the tasks included in the MATRICS Consensus Cognitive Battery (MCCB). The Many Brains Project provided trial versions of all of the tasks they have developed. Each task included a brief description of the task and the abilities that the task was designed to assess. I evaluated twenty tasks on administration times, similarities to the equivalent MCCB task and factors that would influence participants' engagement in the task, such as difficulty, enjoyment and ease of use. Based on these evaluations, I selected a preliminary battery in consultation with my supervisory team. We then consulted with The Many Brains Project before making the final selection. The tasks included in the battery and the equivalent MCCB tasks are shown in Table 4-1. Not all of the tasks are equivalent due to the lack of an available equivalent measure. In addition to tasks assessing the MATRICS domains, a measure of crystallised intelligence was included (Vocabulary). Vocabulary is thought to be preserved after onset of a psychiatric disorder and is used as an estimate of premorbid IQ [357, 365]. The National Adult Reading Test (NART, [339]) was included in the face-to-face assessment as a

comparison. The NART is a widely used measure of premorbid IQ [357, 366] and is included in the CoMPaSS study (see Chapter 3). There is increasing interest in measuring risk-taking propensity in participants with psychiatric disorders, particularly bipolar disorder, and so an additional domain (strategic risk taking) was included. A full description of each task and the reasons for their selection are given in the following sections.

Table 4-1 Online and MCCB tasks

Domain	Online Task	MCCB Task
Speed of Processing	Digit Symbol Coding	BACS: Digit Symbol Coding
Verbal Learning	Verbal Paired Associates	Hopkins Verbal Learning Test - Revised
Working Memory	Backward Digit Span	Letter-Number Sequencing
Visual Learning	Hartshorne Visual Working Memory	Brief Visuospatial Memory Test – Revised
Social Cognition	Morphed Emotion Identification	MSCEIT: Managing Emotions
Reasoning and Problem Solving	Matrix Reasoning Test	NAB: Mazes
Attention	Multiple Object Tracking	Continuous Performance Test – Identical Pairs
	Online Task	Offline Task
Premorbid IQ	Vocabulary	National Adult Reading Test

BACS: Brief Assessment of Cognition in Schizophrenia; MCCB: MATRICS Consensus Cognitive Battery; MSCEIT: Mayer-Salovey-Caruso Emotional Intelligence Test; NAB: Neuropsychological Assessment Battery

The order of the tests was initially selected to reflect the order of the tasks included in the MCCB. However, following consultation with The Many Brains Project, the Matrix Reasoning Test was moved closer to the end of the battery, as this task is one of the most challenging and the longest and may be most likely to discourage participants from completing the remaining tasks. As the Verbal Paired Associates (VPA) task is a delayed verbal memory task, it has two phases and so the order was also altered to accommodate another task between the learning and test phases of this task. The Morphed Emotion Identification was selected as the task to go

between the learning and test phases of the VPA, as there is no verbal component to this task and so it was less likely to interfere with performance on the VPA verbal task.

The tests were designed to run on desktop and laptop computers, touchscreen tablet computers and smart phones. It was important that tasks could be run on smart phones, as there is evidence that the increase in internet use amongst patients with psychiatric disorders between 2011 and 2016 was driven by the increase in daily use of internet-enabled mobile phones rather than an increase in computer use [270]. The Many Brains Project developed the cognitive tasks and hosted the cognitive tasks on their secure TestMyBrain server, which could be accessed using a study-specific website link. The assessments load in the participant's internet browser and the data is stored locally during each task. At the end of each task the data is encrypted and uploaded to a secure server. The websites were designed to comply with current UK data security best practice in consultation with Cardiff University's IT Systems Security Team and Research Governance Officers following ethical approval (SMREC reference number: 15/64). All aspects of the project are compliant with the principles of the United Kingdom's Data Protection Act 2018 and the General Data Protection Regulation (GDPR).

All tasks were trialled on a small sample of healthy volunteers (N=9) prior to the commencement of the validation study. This was to determine approximate administration times. Details of each task are described below and the tasks are shown in order of administration in Table 4-2. An example of the test website can be found in Appendix H and a test link is provided here:

<https://www.testmybrain.org/launch/cfgen/id-new.html?id=ThesisLink>.

Digit Symbol Coding (cognitive domain: speed of processing)

Digit Symbol Coding [367] is considered one of the most robust measures of cognitive impairment in schizophrenia and has been shown to better discriminate participants with schizophrenia from healthy controls compared with many widely studied cognitive tests [195]. It is included as a measure of processing speed in the MCCB. Scores on this task are associated with measures of functional outcome [368, 369]. Impairments in this task are also consistently found in participants with bipolar disorder [237, 238, 240]. During the task, a key of nine symbols and corresponding numbers is shown at the top of the screen (see Figure 4-1). Participants must select the number that corresponds to each target symbol (“1”, “2” or “3”). The outcome measure was the number of correct responses in 90 seconds.

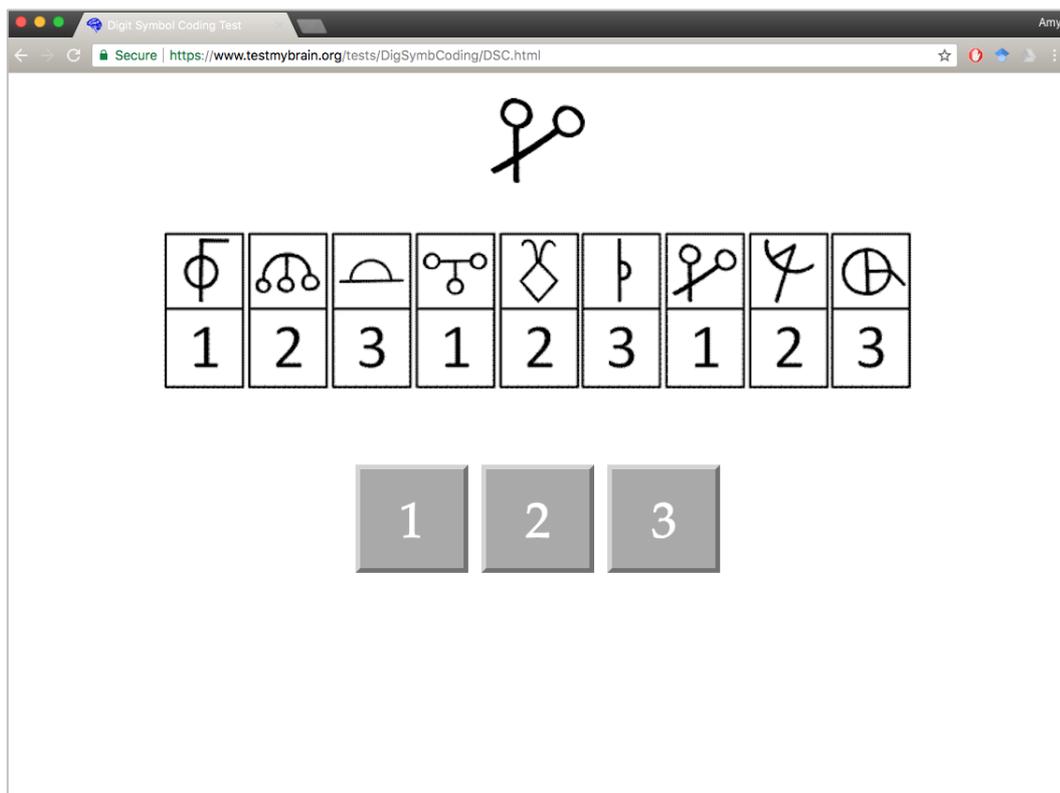


Figure 4-1 Example trial of Digit Symbol Coding

Morphed Emotion Identification (social cognition)

The MATRICS committee selected the Mayer-Salovey-Caruso Emotional Intelligence Test – Managing Emotions subtest (MSCEIT-ME) to be included in the MCCB as a measure of social cognition. Our experience in administering this task to over 1000 people is that participants frequently require guidance and explanations of the MSCEIT-ME task scenarios, which would not be possible in our online design of the tasks. Previous studies have not found impairments on the MSCEIT-ME in participants with bipolar disorder [335, 337], including the study described in Chapter 3. However, participants with bipolar disorder and schizophrenia have been shown to display impairments in their ability to recognise emotional facial expressions [243, 370]. Given that impairments are present across disorders, the Morphed Emotion Identification task was selected. This task uses the face datasets developed by Perrett and colleagues at the University of St. Andrews, United Kingdom [371, 372]. Participants are presented with a face and must decide whether the face looks angry, fearful, happy or disgusted (see Figure 4-2). Faces are morphed between a neutral face and each emotion at varying intensities. The outcome measure was the number of correct responses out of 60 faces. Each face is presented on the screen for one second and the participant has ten seconds to respond once the face has disappeared.

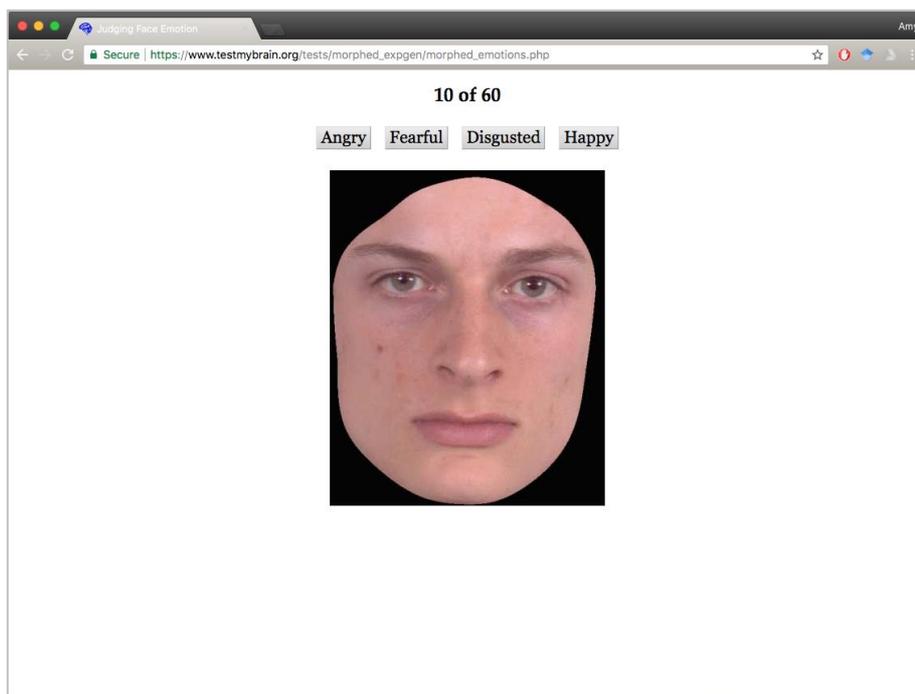


Figure 4-2 Example trial of Morphed Emotion Identification

Verbal Paired Associates (verbal learning)

There were specific challenges with selecting a suitable measure of verbal learning that would be practical in an unsupervised, online setting. If the words on the task were presented verbally then participants would be required to have a speaker on their computer or mobile device. This may have resulted in a greater number of participants requesting support given that some of the participants were likely to have substantial cognitive impairments. There were also issues with how the responses would be inputted. Participants would need access to a microphone if they were asked to recall the words aloud. Alternatively, the participants could have typed their responses but this could negatively impact the scores of participants who struggle with spelling or typing. In both cases, the responses would need to be scored by a researcher rather than automatically. This would be impractical for large samples of participants.

Measures of paired associate learning have been shown to load onto the same factor as list learning tasks in factor analytic studies [202]. Therefore, the Verbal Paired Associates task was included as an alternative to traditional verbal learning tasks [273, 373]. This task assesses word learning and episodic memory. A set of 25 unrelated word pairs are presented on the screen in the learning phase (see Figure 4-3). During the test phase, participants are presented with the first word from each previously presented word pair and must select the second word from four options. The outcome measure was the number of correct responses out of 25 word pairs.



Figure 4-3 Example of the learning phase of Verbal Paired Associates

Backward Digit Span (working memory)

Initially, an online version of the Letter-Number Sequencing task from the MCCB was selected as the measure of working memory. However, there were technical problems in developing a mobile version of the task and so the task was replaced with the Backward Digit Span. Scores on Backward Digit Span have been shown to load onto the same factor as Letter-Number Sequencing in factor analytic studies [202]. The Backward Digit Span task is a frequently used measure of working memory [367]. Participants are presented with a sequence of numbers and must recall them in the reverse order (see Figure 4-4). The lengths of the sequences increase every two trials until the participant is no longer able to correctly recall the sequence backwards. The outcome measure was the maximum length of number sequence the participant was able to recall backwards.

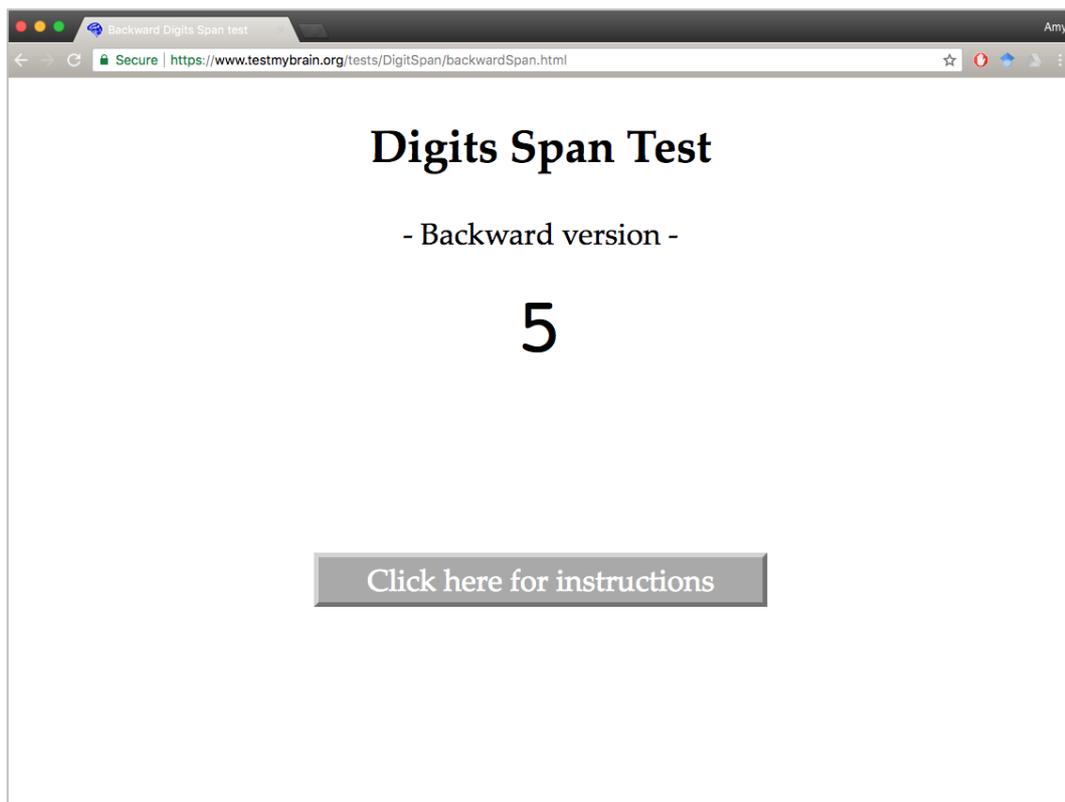


Figure 4-4 Screenshot of Backward Digit Span

Hartshorne Visual Working Memory (visual learning)

Like measures of verbal learning, there were challenges in selecting a measure of visual learning that would be suitable to administer online. It was not possible to include a free recall task such as the Brief Visuospatial Memory Test – Revised from the MCCB, as this would require participants to reproduce figures and could not be scored automatically. Therefore, a measure of recognition was included as an alternative.

The Hartshorne Visual Working Memory task was selected as a measure of visual learning [374]. In this task, four shapes are presented at four positions around a central cross (see Figure 4-5). These objects are then replaced with one object in the location of one of the previous objects. The participant must decide whether that object is the same or different than the object that was previously in that location. The outcome measure was the number of correct responses out of 42 trials.

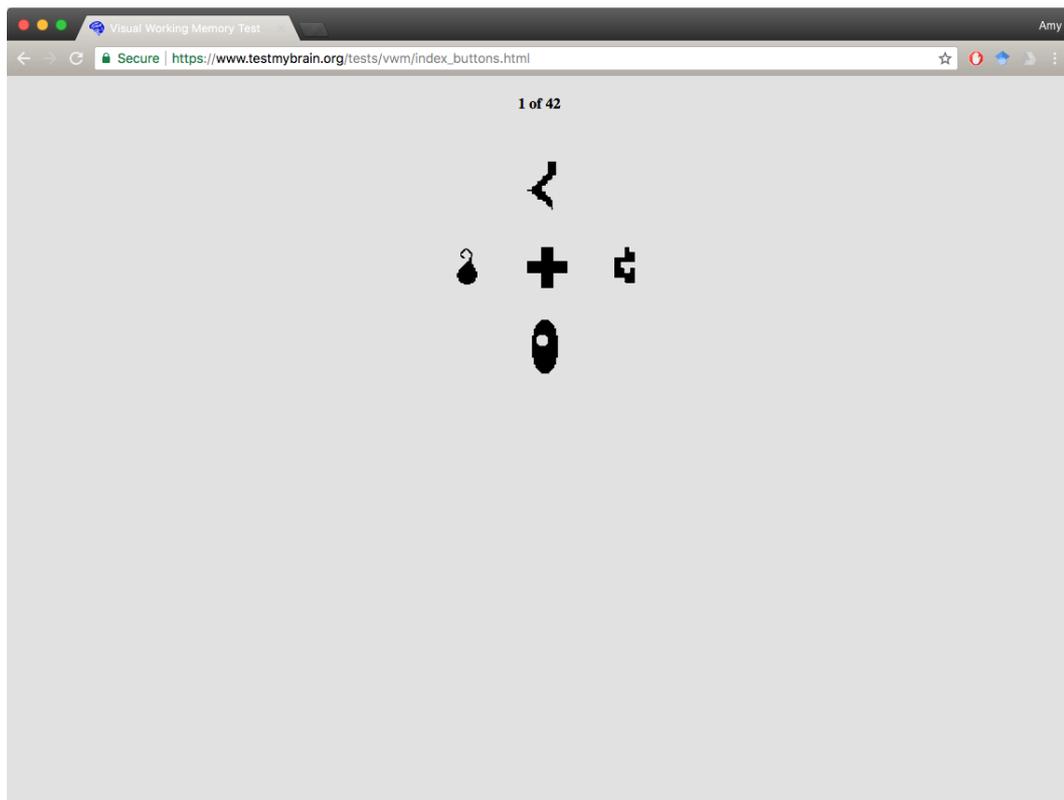


Figure 4-5 Example trial of Hartshorne Visual Working Memory Task

Matrix Reasoning Test (reasoning and problem solving)

The Matrix Reasoning Test is a nonverbal abstract problem-solving task [367]. Seven out of the 13 factor analytic studies evaluated by the MATRICS initiative identified a reasoning and problem solving or executive function dimension and the Matrix Reasoning Test was one of the tasks that loaded highly on this factor [202]. In this task, a set of images is shown on the screen that follows a logical rule (see Figure 4-6). The participant must determine the rule and select the image that best completes the set. The outcome measure was the number of correct responses out of 35 trials.

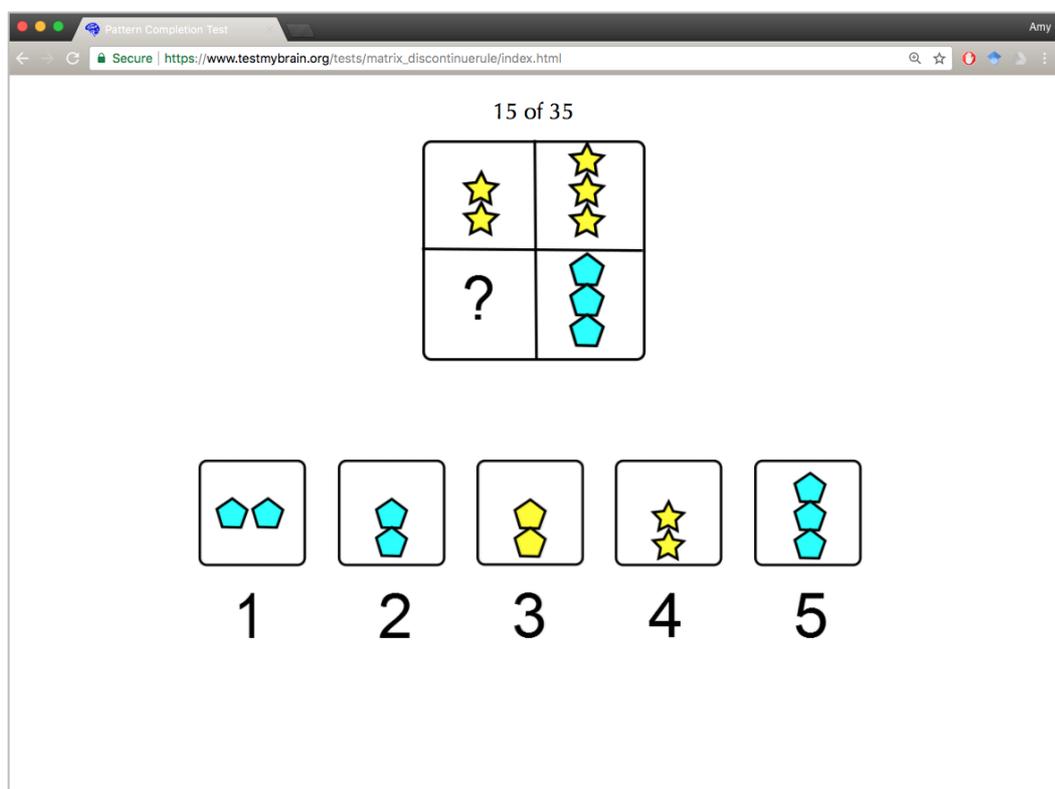


Figure 4-6 Example trial of the Matrix Reasoning Test

Balloon Analogue Risk Task (strategic risk taking)

The Balloon Analogue Risk Task (BART) [375] has been highlighted as a promising cognitive measure for use in bipolar disorder [242], although to date it has been used in a limited number of studies of psychiatric disorders. Performance on the BART has been associated with self-reported risk behaviours and impulsivity [375]. Over 30 trials, the participant is presented with a series of balloons that have different popping thresholds. For each trial, the participant must blow up the balloon by clicking on a button and decide when to stop and cash in their points (see Figure 4-7). The larger the balloon at the end of the trial, the more points a participant is rewarded but no points are given if the balloon pops. The primary outcome measure of the BART is the number of points awarded although the number of times the balloon pops is also recorded. The outcome measure was the number of points collected by inflating 30 balloons. Higher scores indicate more effective strategic risk-taking.

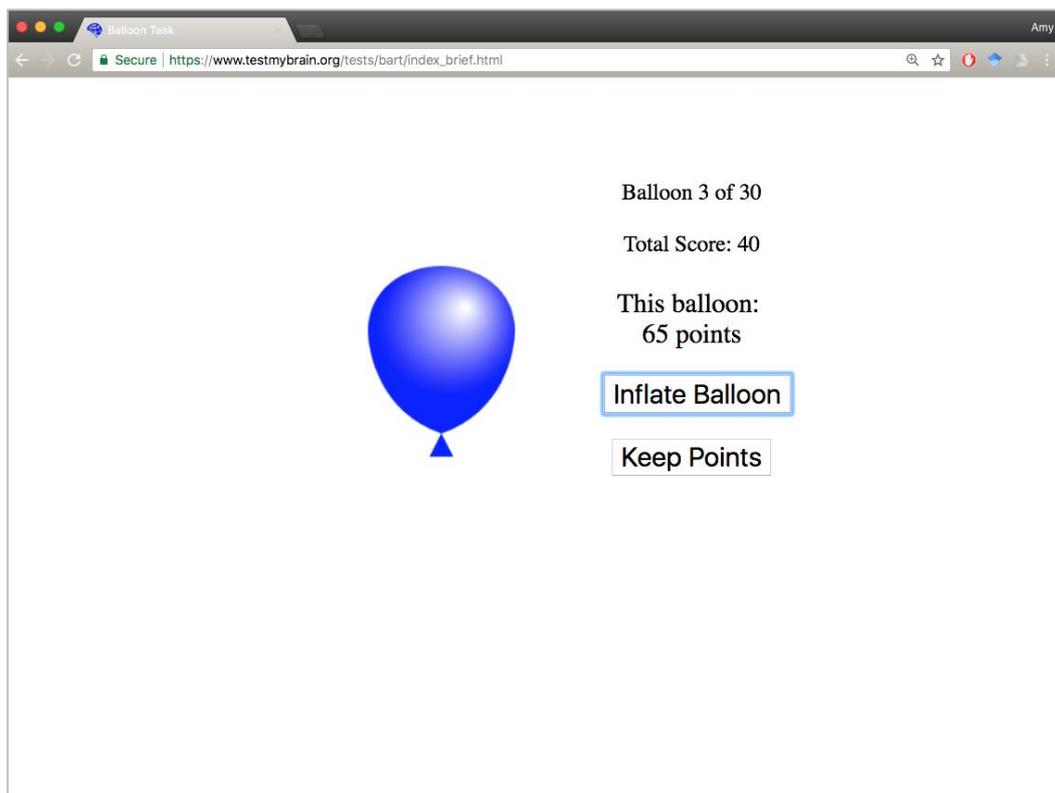


Figure 4-7 Example trial of Balloon Analogue Risk Task

Multiple Object Tracking (attention)

The Multiple Object Tracking paradigm was developed as a measure of visual cognition [376]. In this task, participants must follow multiple targets as they move across the screen amongst other identical objects (see Figure 4-8). This task has several advantages over other sustained attention tasks such as the Continuous Performance Test. The task involves attending to multiple moving objects rather than a single object and this is thought to be more characteristic of real-world attention. The task requires active attention to target objects rather than passive vigilance. This may be beneficial for keeping participants engaged in the task in an unsupervised setting. The outcome measure was the number of correct responses over 30 trials. Within a trial, each correctly identified target is one point.

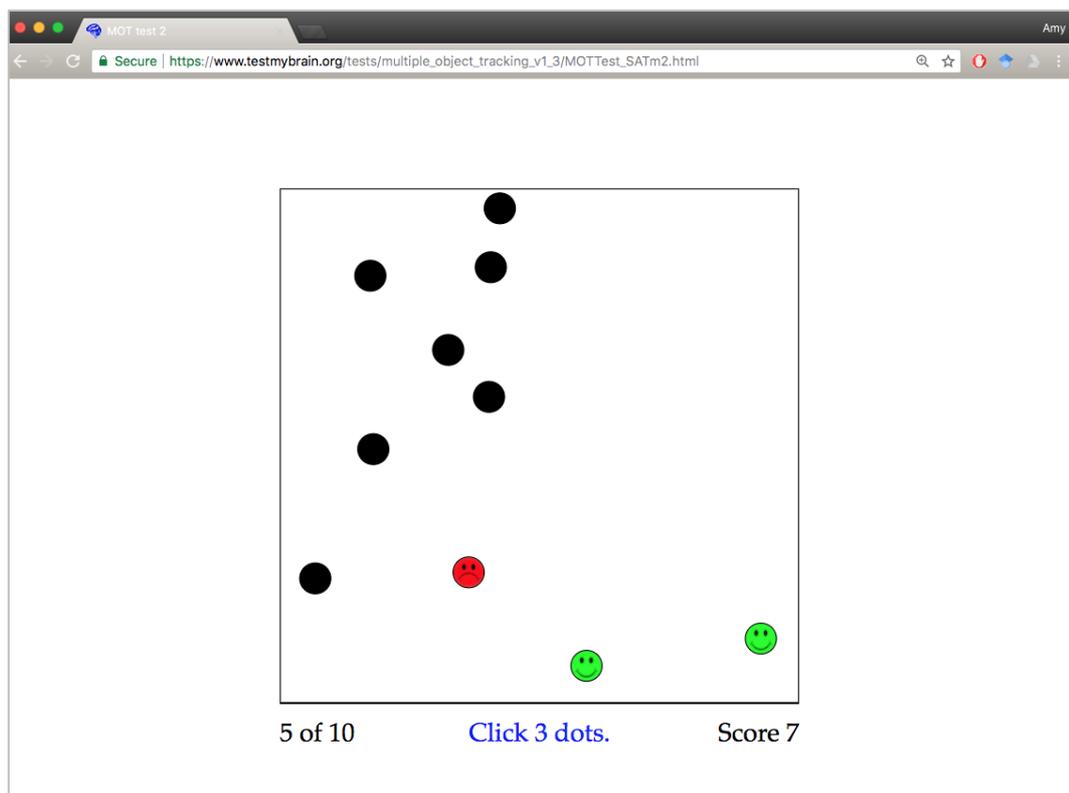


Figure 4-8 Example trial of Multiple Object Tracking

Vocabulary (premorbid IQ)

Vocabulary is thought to be preserved after onset of a psychiatric disorder and has been used in research as an estimate of premorbid IQ [357, 365]. In the Vocabulary test [377, 378], participants are shown a target word and asked to select which of four words is closest in meaning to the target word (see Figure 4-9). There are twenty words in total and the total score was used as the outcome measure for this task.

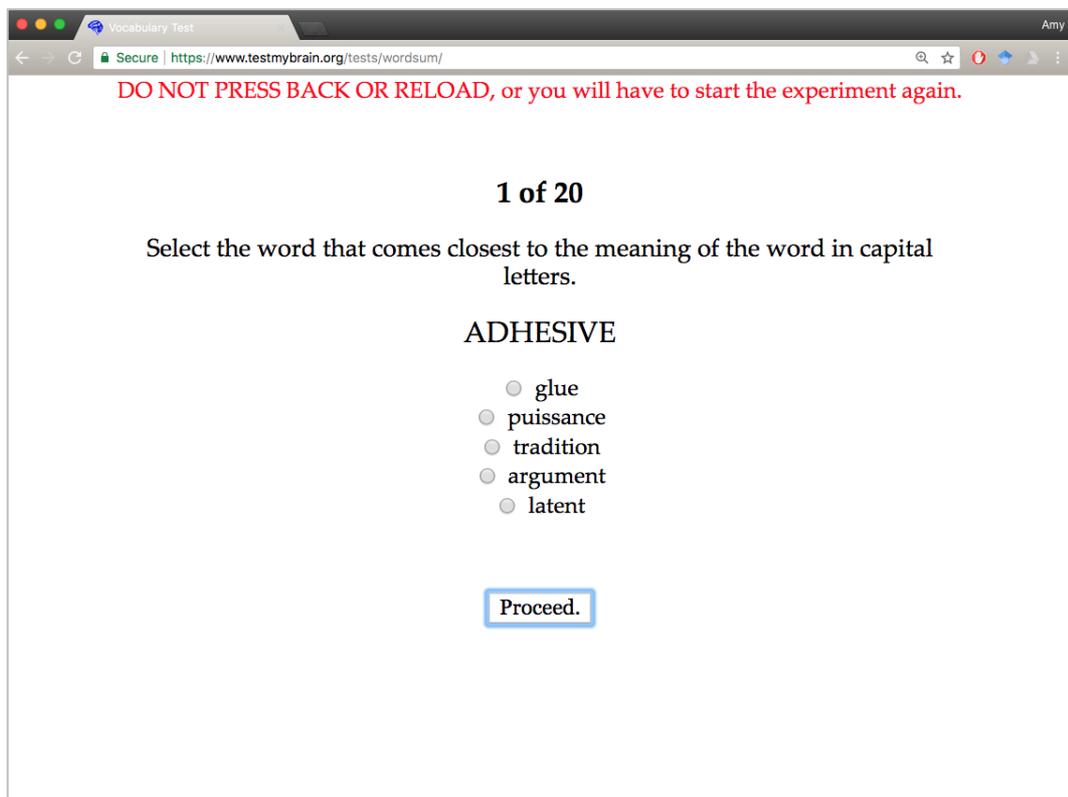


Figure 4-9 Example trial of the Vocabulary task

Table 4-2 Tasks included in the online cognitive battery

Domain	Task	Administration Time*	Outcome Scoring
Speed of Processing	Digit Symbol Coding	2 minutes 30 seconds	Number of correct responses in 90 seconds.
Social Cognition	Morphed Emotion Identification	3 minutes	Number of correct responses out of 60 faces.
Verbal Learning	Verbal Paired Associates	6 minutes	Number of correct responses out of 25 word pairs.
Working Memory	Backward Digit Span	3 minutes	Maximum length of number sequence the participant was able to recall backwards.
Visual Learning	Hartshorne Visual Working Memory	3 minutes 30 seconds	Number of correct responses out of 42 trials.
Reasoning and Problem Solving	Matrix Reasoning Test	15 minutes	Number of correct responses out of 35 patterns.
Strategic Risk Taking	Balloon Analogue Risk Task	4 minutes	Number of points collected by inflating 30 balloons. Higher scores indicate more effective strategic risk-taking.
Attention	Multiple Object Tracking	7 minutes 30 seconds	Number of correct responses over 30 trials. Within a trial, each correctly identified target is 1 point.
Premorbid IQ	Vocabulary	3 minutes	Number of correct responses out of 20 words.

*Administration times are based on the assessments of healthy volunteers recruited in a small pilot study (N=9)

4.2.2 Development of a brief online clinical questionnaire

In addition to the cognitive assessment, a brief online clinical questionnaire was designed to assess concurrent factors that may impact cognitive performance. The brief questionnaire was hosted online using the Bristol Online Survey (BOS, <https://www.onlinesurveys.ac.uk>). The assessment included questions about current diagnosis, medication, medical history, substance use and current mood. Current symptoms of depression and anxiety were assessed using Hospital Anxiety and Depression Scale (HADS)[379]. The reliability of administering the HADS online has been established, although scores may be inflated when the questionnaire is completed online compared to pen and paper administration [380-382]. Current symptoms of mania and hypomania were assessed using the Altman Self-Rating Mania Scale (AMS)[383]. The AMS has been administered on smartphones and via the internet in studies of self-monitoring [384] and interventions [385, 386] for bipolar disorder. Current psychotic and negative symptoms were not assessed due to the lack of reliable, valid self-report questionnaires.

4.2.3 Website design

Each stage of participation in the online study is shown in Figure 4-10. The study was designed as a closed system, such that only participants who had been invited to take part could access the website. Each participant was assigned a linked anonymous unique identification number (ID) and a unique website link was generated using BOS. When participants clicked on this link, their ID was completed automatically in the relevant field. This reduced the possibility of participants' incorrectly entering their ID.

The study was separated across two websites, BOS and TestMyBrain. Participants were sent a link to the BOS website, which contained an information page, consent form and the clinical questionnaire (the pages of the website can be found in Appendix G). Participants indicated their consent by ticking a box at the bottom of the information page. The final page on BOS contained a unique website link to the TestMyBrain cognitive assessments. The study was designed such that the participant's ID would be linked from the BOS website to the TestMyBrain website without input from the participant. The TestMyBrain website contained links to each task in the order shown in Table 4-2 (the main page of the website is

shown in Appendix H). Once each task had been completed, the link would be crossed out to prevent participants completing the same task twice and their score was saved on the server. Participants who did not complete all of the tasks in the battery were sent a follow-up email by a member of the study team that included their link to the TestMyBrain website to enable them to complete the remaining tasks. It was not possible to include a button on the TestMyBrain website that would send participants the link automatically, as this would have compromised their anonymity. The websites were designed to comply with current UK data security best practice in consultation with Cardiff University's IT Systems Security Team and Research Governance Officers following ethical approval (SMREC reference number: 15/64).

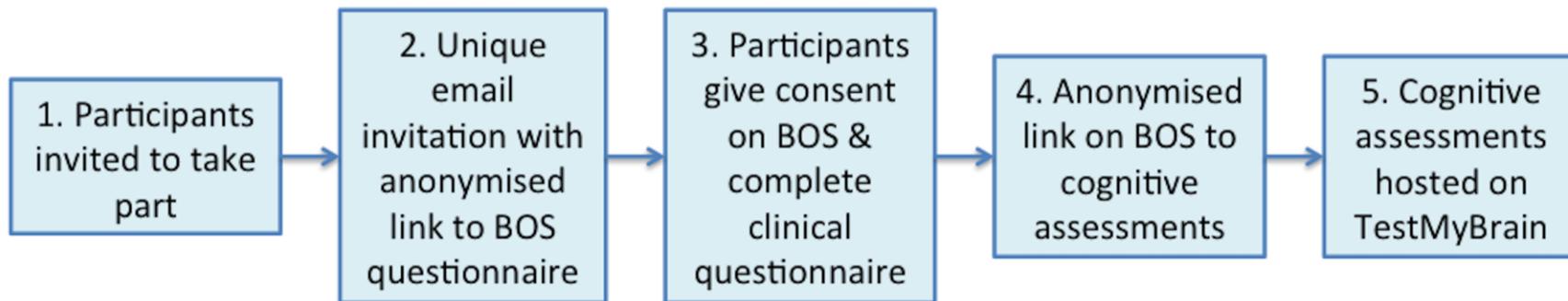


Figure 4-10 Stages of the online study BOS: Bristol Online Survey

4.3 Part 2. Pilot and validation of the online cognitive assessment

4.3.1 Method

Methodological considerations and power calculation

In the validation study, convergent validity was examined by conducting correlations between MCCB and online tasks that assess equivalent cognitive domains. There is no consensus on the minimum acceptable correlation between tasks for validation because the correlation partly depends on the extent to which the new task and gold standard task are purported to measure the same concept [387]. In addition, the correlation between a new task and the gold standard task cannot exceed the square root of the product of the test-retest reliabilities of both tasks so the limit of the correlation between the tasks is not ± 1 [272]. However, previous validation studies using the MCCB have reported correlations of 0.22-0.84 between tasks assessing equivalent domains [277, 278]. Some of the online tasks were more similar to the equivalent MCCB tasks than others. Therefore a minimum acceptable threshold of $r > 0.2$ was set, as large correlations would not be expected between tasks that did not use similar methodology to measure the domains (for example, social cognition was assessed using a facial recognition task in the online battery and emotion management task in the MCCB). An exception to this rule was applied for the speed of processing domain. I selected the same task online as was included in the MCCB (Digit Symbol Coding) to measure speed of processing. A higher correlation was expected between these tasks given that the methodology used is almost identical so the minimum acceptable threshold for correlation was set at $r > 0.4$.

A priori power calculations determined that a sample size of 65 would give 80% power to detect a correlation coefficient of 0.4 with a Bonferroni-corrected alpha value of 0.00625 (0.05/8 correlations). A sample of 65 would give 13% power to detect a correlation coefficient of 0.2 with a Bonferroni-corrected alpha value of 0.00625 and 37% power at an alpha value of 0.05. A sample size of 311 participants would have been required to achieve 80% power to detect a correlation coefficient of 0.2 at an alpha value of 0.00625. This would not have been feasible within the time period and thus the recruitment target was set at 65 participants.

This number included healthy controls and participants with major depressive disorder, bipolar disorder and schizophrenia.

Sample

Participants (N=67) were recruited from two previous studies conducted within the MRC Centre for Neuropsychiatric Genetics and Genomics: National Centre for Mental Health (NCMH) and Cognition in Mood, Psychosis and Schizophrenia Study (CoMPaSS). The aim of both studies is to investigate the genetic and environmental factors that contribute to susceptibility to mental health disorders and as such there are genotype and phenotype data available for all participants. Recruitment for these studies is ongoing and includes recruitment through outpatient clinics as well as non-systematic methods, such as leaflets, radio advertisements and through their websites. Both studies include confirmation of consent from participants to be approached for other research within the centre. Participants with one of three diagnoses, major depressive disorder, bipolar disorder or schizophrenia, were recruited for this PhD study. These three diagnostic groups were selected given extensive research establishing the characteristics of cognitive performance of those with each of these disorders using offline, traditional cognitive testing. In addition, there were large numbers of participants with these disorders in the samples that would be invited to take part in the main study (Chapter 5).

National Centre for Mental Health

Participants with bipolar disorder (N=17) and major depressive disorder (N=15) were recruited from the National Centre for Mental Health (NCMH). Participants were recruited both prospectively at the time of interview by NCMH and retrospectively through invitation letters or emails to past NCMH participants who had provided consent to be re-contacted for future research. The NCMH sample includes over 10000 individuals with a range of diagnoses including bipolar disorder, schizophrenia, autism, post-traumatic stress disorder and depression. One of the main aims of NCMH is to recruit a cohort of individuals who consent to be approached for other studies to develop psychiatric research in Wales. Participants are administered a brief interview and provide a blood sample. Participants are asked the question, “Has a doctor or health professional ever told you that you have

any of the following diagnoses?” Participants are given a list of diagnoses and asked to indicate all diagnoses that apply. They are then asked to indicate which of the diagnoses they have ticked would they consider to be their primary, secondary and tertiary diagnoses. Finally, they are asked the question, “If we were to speak to your clinical team or general practitioner, would they agree with that?” This is consistent with the approach taken by other large studies with self-report measures of diagnosis, such as the UK Biobank [388]. Their diagnosis is then confirmed with their clinical team where possible. Participants who responded that their primary diagnosis was major depressive disorder or bipolar disorder were included in this study.

For this study, a conservative definition of depression was chosen that required a reported diagnosis and previous treatment with at least one antidepressant medication. The 17 participants who self-reported a diagnosis of bipolar disorder included 11 participants with type I, five participants with type II and one participant with schizoaffective disorder – bipolar type. Of these 17 participants, 10 participants had also been interviewed with the Mini-International Neuropsychiatric Interview (MINI, [334]) as part of another study and their diagnosis of bipolar disorder was confirmed for all ten participants. A further participant had completed the Schedule for Clinical Assessment in Neuropsychiatry (SCAN, [331]) as part of an in depth NCMH assessment and their diagnosis was confirmed.

Cognition in Mood, Psychosis and Schizophrenia Study (CoMPaSS)

Participants with a DSM-IV diagnosis of schizophrenia (N=16) were recruited retrospectively from the Cognition in Mood, Psychosis and Schizophrenia Study (CoMPaSS). The recruitment methods and protocol of CoMPaSS have been previously described in Chapter 3. The study includes over 1200 individuals with schizophrenia and related psychotic disorders. The aim of this study is to examine the associations between genetic and environmental factors and cognitive impairment in psychosis. Participants are interviewed using the SCAN [331]. This interview is then reviewed along with available clinical records by trained raters to determine a consensus lifetime DSM-IV diagnosis.

Inclusion criteria for the validation study were aged 16 or above, able to understand written and spoken English and no uncorrected deficits in sight or hearing.

Exclusion criteria included any individuals who at the time of screening were current inpatients, under the care of a crisis resolution and home treatment team, had been admitted to hospital in the last three months or had changed their psychiatric medication in the last three months. Potential participants were discussed with a member of their clinical team to determine suitability for the study and assess risk prior to participation. There were no specific exclusion criteria for neurological conditions but information was collected on medical conditions that are related to cognitive impairments.

Controls (N=19) were recruited from the same communities as cases through the NCMH and advertisements in job centres, leisure centres and local shops.

Participants who reported a current or previous psychiatric diagnosis or had ever been prescribed psychiatric medication were excluded. Of the 19 participants, 13 completed the MINI [334] as part of another study and the remaining participants completed the NCMH assessment. None of the controls met criteria for any psychiatric disorder or reported taking psychiatric medication.

Study design

Participants were asked to complete two cognitive batteries on consecutive days:

1. MATRICS Consensus Cognitive Battery (MCCB) and the National Adult Reading Test. Full details of the MCCB are available in Chapter 3 and a summary of the tasks is shown in Table 4-3.
2. The online cognitive battery

Table 4-3 Summary of MCCB Tasks

Domain	Task	Task Description
Speed of Processing	Brief Assessment of Cognition in Schizophrenia: Symbol Coding	P uses the key to assign the correct numbers to a series of symbols
	Category Fluency: Animal Naming	P names as many animals as they can in 60 seconds
	Trail Making Test: Part A	P connects the numbered circles in ascending order
Working Memory	Wechsler Memory Scale III: Spatial Span	P must tap the blocks in the sequence they have just seen
	Letter-Number Span	P rearranges a string of numbers and letters into ascending numbers followed by letters alphabetically
Attention / Vigilance	Continuous Performance Test: Identical Pairs	P responds every time an identical pair of numbers flash on the screen consecutively
Verbal Learning	Hopkins Verbal Learning Test – Revised	P immediately recalls a list of 12 words
Visual Learning	Brief Visuospatial Memory Test – Revised	P immediately recalls the shape and location of 6 figures
Reasoning and Problem Solving	Neuropsychological Assessment Battery: Mazes	P draws a line through the maze from the start point to the finish point
Social Cognition	Mayer-Salovey-Caruso Emotional Intelligence Test: Managing Emotions	P presented with a social scenario and must judge a response on a scale of very ineffective to very effective.

The batteries were completed on separate days to combat potential fatigue effects. The total study time was three hours (one and a half hours each day). A trained researcher administered the MCCB in a supervised setting on the first day then participants completed the online cognitive battery and clinical questionnaire unsupervised on the second day. Most participants completed the online stage at home. However, individuals without personal internet access were given the opportunity to complete the online stage in a clinical testing room within the Division of Psychological Medicine and Clinical Neurosciences at Cardiff University. Two participants completed the online stage at the university and one participant completed the online stage at their local psychiatric clinic. Although this environment does differ from a home setting, every effort was made to ensure that participants completed the tasks without input from the researcher. The order of completion was not counterbalanced for practical reasons; firstly, participants from NCMH could be recruited prospectively by completing the MCCB with a researcher immediately after completing the NCMH assessment therefore the order of completion could not be randomly assigned, secondly, it would have been difficult to ensure that participants assigned to complete the online part first did so before their appointment, as they were not supervised. However, the order of completion was counterbalanced for participants in the healthy control group (N=19). Informed consent was obtained at both stages, in writing prior to administration of the MCCB and online prior to completing the online cognitive battery.

The stages of the study were:

1. Participants met with a researcher, gave informed consent and completed the MCCB. Participants also completed the mood questionnaires, HADS and AMS.
2. The researcher entered the participant's ID number onto the BOS study page and a personalised website link was generated and emailed to the participant.
3. The participant clicked on the link in the email and was taken to a study welcome page on BOS (see Appendix G). They read an information page, indicated their consent to participate by clicking on a tick-box and completed the questions (including HADS and AMS). At the end of the

questionnaire, they were asked to click on another link to the online cognitive battery.

4. Participants completed the online cognitive tasks on a study-specific website created by The Many Brains Project.
5. Participants were asked to return a feedback questionnaire on completion of the study (see Appendix I). They rated the overall online battery on enjoyment, duration and difficulty and rated the clarity of the instructions and information given. They named the tasks they liked the most and least. They also provided information on any technical difficulties they experienced.

Statistical analysis

All statistical analyses were conducted in R version 3.3.0. Completion rates for each task of the new battery were examined to assess the tolerability in an unsupervised setting. Data from the feedback questionnaires were studied to further assess tolerability. The demographic and clinical characteristics of the sample were examined. The distribution of scores for each task was examined to identify obvious floor or ceiling effects and determine if the data was normally distributed. Basic summary statistics were calculated for each task in each group, including mean, standard deviation, skew and kurtosis. Z scores on each MCCB task were calculated for each participant using the means and standard deviations of the control group recruited as part of CoMPaSS (N=103, see Chapter 3 for full details).

Validation analyses

Convergent validity was examined by conducting correlations between the MCCB and online tasks that assess equivalent cognitive domains (see Table 4-1 for comparisons). There is no equivalent to the Balloon Analogue Risk Task in the MCCB so this task was not included in these correlation analyses. Correlations were conducted across the whole sample and for cases only. Based on previous validation studies using the MCCB [277, 278], the minimum acceptable thresholds for the correlations was set at $r > 0.4$ for speed of processing and $r > 0.2$ for all other domains (see “Methodological considerations and power calculation” section for details). Pearson’s correlations were used when task performance was normally distributed, whilst Spearman’s correlations were used for tasks that were not

normally distributed. Bonferroni correction was used to adjust for multiple comparisons resulting in an alpha of 0.00625 (0.05/8, 8 domains). These correlations were followed up with correlations between each online task and all other individual tasks of the MCCB.

Exploratory analyses were conducted to determine whether each online task was correlated with a measure of general cognitive performance ('g'). To derive 'g' a principal components analysis was conducted including all tasks from the MCCB. The first principal component score for each participant was taken as a measure of 'g'. In the whole sample (all cases and controls), 'g' explained 48% of the total variance. Within the combined cases only group, 'g' explained 52% of the total variance. Pearson's and Spearman's correlations were used to test whether there was a significant association between each online task and 'g' measured offline at a Bonferroni corrected alpha of 0.00556 (0.05/9 online tasks).

4.3.2 Results

Demographic and clinical characteristics of the sample

The demographic and clinical characteristics of each group are shown in Table 4-4. The sample had a wide age range (22 to 78 years old, mean=47 years, SD=14.8) and had a higher percentage of females (58%) than males. Most participants with a psychiatric diagnosis were taking psychiatric medication at the time of the online assessment (80%) and all had taken psychiatric medication in the past. Rates of current depression and anxiety were calculated based on the cut-off points specified in the HADS questionnaire (score >10) [379]. Based on this threshold, 6% of the sample had current depression and 28% had current anxiety. Over two-thirds of the sample had at least A-level qualifications (72%).

Table 4-4 Demographic and clinical characteristics of sample

	Healthy Controls	Major Depressive Disorder	Bipolar Disorder	Schizophrenia
N	19	15	16	15
Age	49.8 (15)	52.4 (10.5)	51.1 (13.8)	49.8 (12.4)
Proportion Female (% Female)	12 / 19 (63%)	10 / 15 (67%)	11 / 16 (69%)	5 / 15 (33%)
Estimated IQ¹	105.4 (17.8)	100.2 (14.7)	96.2 (19.6)	86.9 (19.2)
Highest Qualification				
None	0	1	0	1
11+	0	0	0	1
CSE or equivalent	0	2	0	2
GCSE or equivalent	0	2	5	3
A-level or equivalent	5	5	5	6
Degree	8	3	5	1
Postgraduate degree	5	2	1	1
Lifetime Occupation				
Senior official	0	0	1	1
Professional	8	7	5	1
Technical	3	1	3	2
Administration	2	4	2	1
Service work	3	2	1	5
Trade work	0	0	0	3
Factory or plant work	0	1	0	0
Elementary occupation	1	0	2	0
Armed forces	0	0	0	1
Never worked	0	0	1	0
Full-time student	1	0	0	0
Voluntary work	0	0	0	1
Proportion Taking Psychiatric Medication (% taking)	0/19 (0%)	8 / 15 (53%)	14 / 16 (88%)	15/15 (100%)
HADS Depression Score²	2 (4)	3 (6)	4 (8)	6 (5)
Proportion Current Depression (%)	1/19 (5%)	0/15 (0%)	1/16 (6%)	2/14 (14%)
HADS Anxiety Score²	3 (6)	8 (7)	8 (5)	12 (12)
Proportion Current Anxiety (%)	1/19 (5%)	4/15 (27%)	5/16 (31%)	8/14 (57%)
AMS Score²	5 (5)	2 (5)	2.5 (3)	4 (4)

Numbers indicate mean and standard deviation for continuous data and proportions for categorical data. Mood scores shown are based on HADS and AMS responses on the day participants completed the MCCB. ¹IQ score estimated based on NART scores [339]. ²Median and interquartile range shown.

Completion rates

Sixty-seven participants were initially recruited into the study but two participants were excluded resulting in a total sample size of 65. The first of these participants failed to complete the online study and did not respond to further attempts to contact and was thus excluded from further analyses. The second participant did not wish to continue with the online study due to a relapse in their illness so was excluded from these analyses.

Although participants were encouraged to complete the online battery and MCCB on consecutive days, they completed the online battery unsupervised and therefore it was difficult to ensure that they did so (see Figure 4-11). Participants who did not complete the online battery within 24 hours of the face-to-face interview were followed up with a telephone call and again at 1 and 2 weeks. Twenty-two (out of 65) participants completed the tasks as requested over two consecutive days. Four participants completed the online tasks on the same day as the MCCB tasks. Of the remaining participants, the majority completed the second battery within 2-7 days (N=26), seven participants completed the second battery 8-14 days later, two participants completed the second 15-30 days later and four completed over 30 days later. The longest duration between batteries was 74 days.

These figures are based on the day participants began completing the online tasks. However, five participants completed the online battery over two days. Three of these participants had a diagnosis of schizophrenia and two had a diagnosis of bipolar disorder. One of the participants did not complete all the tasks, completing five out of the nine tasks. Two participants reported technical difficulties that were subsequently resolved and so they completed the remaining tasks on a different day. Notably, all five participants had lower composite cognition z scores than the mean for their diagnostic group.

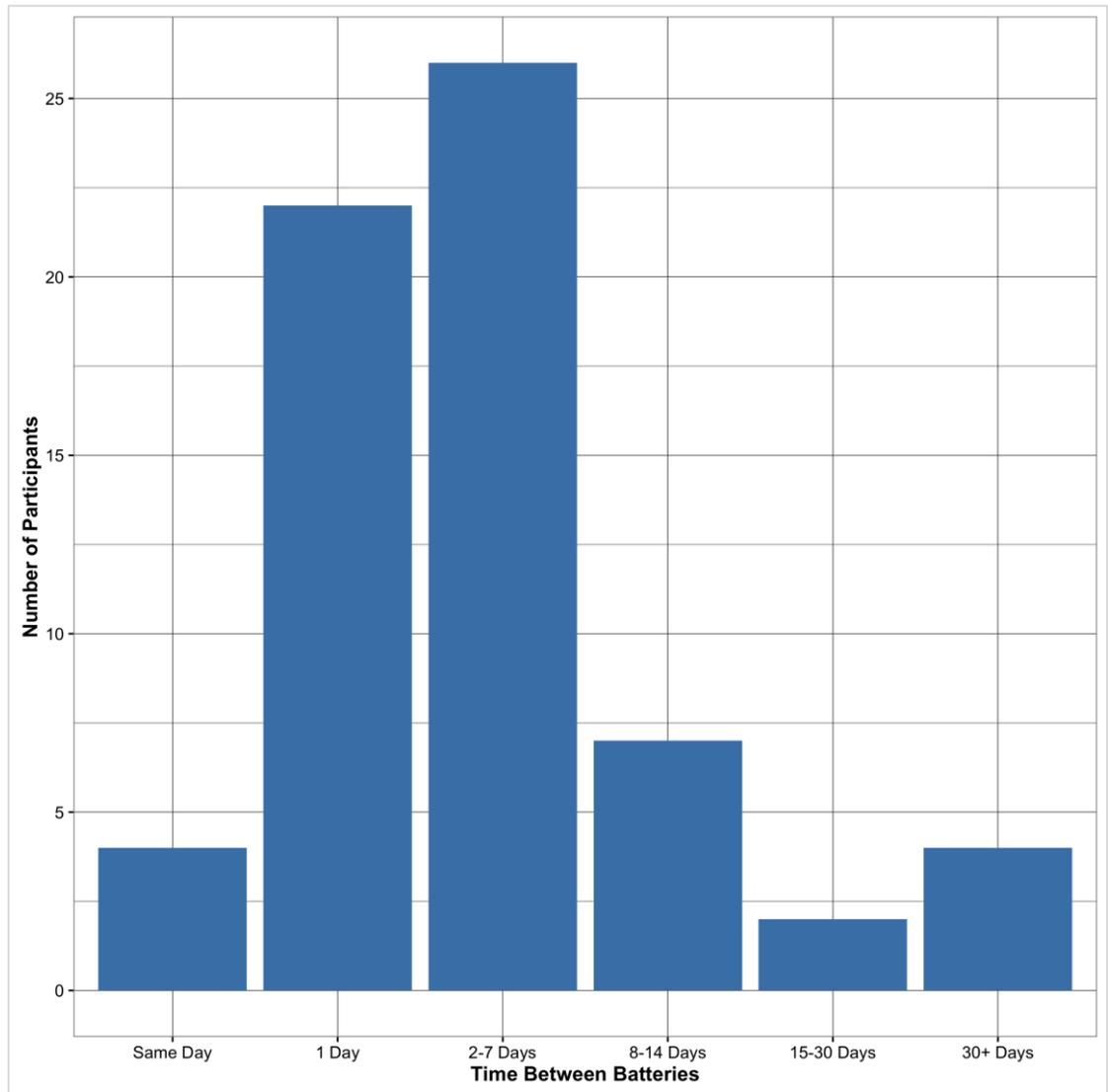


Figure 4-11 Time taken between completing the online and MCCB batteries

Online task completion

In total, 58 out of 65 participants (89%) completed all the online tasks. Complete data was available for Digit Symbol Coding, Backward Digit Span and Morphed Emotion Identification. The number of scores for each task is shown Table 4-5.

Table 4-5 Completion rates for online battery

Online Task	Healthy Controls	Major Depressive Disorder	Bipolar Disorder	Schizophrenia	Total
N	19	15	16	15	65
Digit Symbol Coding	19	15	16	15	65
Verbal Paired Associates	19	15	15	14	63
Backward Digit Span	19	15	16	15	65
Hartshorne Visual Working Memory Test	19	15	16	13	63
Morphed Emotion Identification	19	15	16	15	65
Matrix Reasoning Test	19	15	15	15	64
Balloon Analogue Risk Task	19	15	15	14	63
Multiple Object Tracking	19	15	14	15	63
Vocabulary	17	15	15	15	62

MCCB task completion

The majority of participants completed all the MCCB tasks (60 out of 65 participants (92%)). One participant with schizophrenia did not complete the Letter-Number Sequencing or Continuous Performance Test – Identical Pairs but was able to complete all the online tasks. Two participants with major depressive disorder were unable to tolerate the Continuous Performance Test – Identical Pairs of the MCCB. One participant with bipolar disorder was unable to complete the Hopkins Verbal Learning Test – Revised, Letter-Number Sequencing, Brief Visuospatial Memory Test – Revised and Animal Naming. This participant completed all the online tasks. Another participant with bipolar disorder was unable to tolerate the Continuous Performance Test – Identical Pairs of the MCCB.

Complete data was available for the control group for both the online and MCCB tasks. However, two participants were excluded from analyses of NART scores because English was their second language and the NART is not recommended in these cases, as the scores are likely to be underestimates of IQ [339].

Comparison of completion rates between batteries

Table 4-6 shows the completion rates for the online and MCCB batteries in this sample, as well as completion rates for the tasks in the CoMPaSS sample in Chapter 3. Completion rates did not differ between the batteries ($\chi^2(14)=2.11$, $p=1$).

Table 4-6 Available data for online battery, MCCB battery and MCCB data from CoMPaSS sample

Domain	Online Battery	MCCB	MCCB (CoMPaSS Sample, Chapter 3)
Speed of Processing¹	65 (100%)	65 (100%)	923 (99%)
Verbal Learning	63 (97%)	64 (98%)	927 (100%)
Social Cognition	65 (100%)	64 (98%)	907 (98%)
Working Memory²	65 (100%)	63 (97%)	921 (99%)
Visual Learning	63 (97%)	64 (98%)	923 (99%)
Reasoning & Problem Solving	64 (98%)	65 (100%)	927 (100%)
Attention	63 (97%)	61 (94%)	872 (94%)
	Vocabulary	NART	NART Chapter 3
Vocabulary	62 (95%)	62 (95%)	780 (84%)

¹Only Digit Symbol Coding included from the MCCB; ²Only Letter-Number Sequencing included from the MCCB.

Feedback questionnaire results / tolerability

Feedback was received from 41 participants, including 15 healthy controls, 7 participants with depression, 6 with bipolar disorder and 11 with schizophrenia (two questionnaires were returned without ID numbers and so their diagnoses were unknown). All participants agreed that the instructions given at the start of the study were clear and rated the clinical questionnaire on BOS positively.

Overall the cognitive tasks were rated as enjoyable and of reasonable duration and difficulty (see Figure 4-12). Two participants rated the duration of the battery as “poor”. One commented that they found the duration “very tiring”. Both participants had a diagnosis of schizophrenia. Two participants rated the difficulty as “poor”. One participant commented that the tasks were “too quick” and “much harder than I thought”. This participant had a diagnosis of depression. A quarter of participants who returned their feedback questionnaire reported Multiple Object Tracking as the best task (N=12) and Verbal Paired Associates as the worst task (N=11). Of the 40 that responded to the question, 34 participants (85%) reported that they would be “more likely” to take part in future online studies after taking part in this study, whilst 5 participants responded, “don’t know” and 1 participant responded that they were “less likely”.

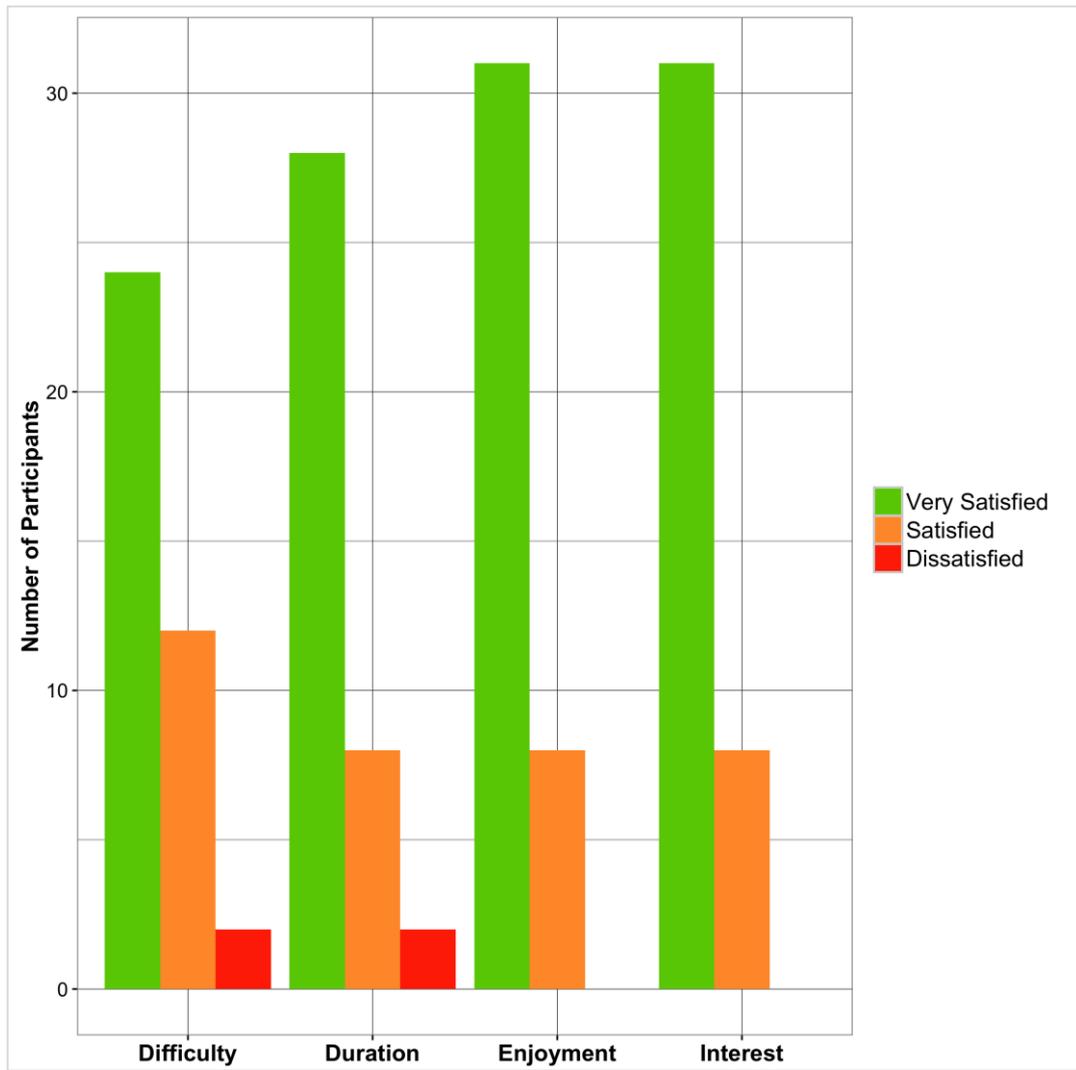


Figure 4-12 Feedback received from participants

Technical difficulties

Six participants (9%) reported technical difficulties. Four of these technical issues were resolved and it was not possible to identify the cause of the remaining two problems. Five participants were able to complete all the tasks so this did not impact on the availability of data for these participants. One participant did not complete the Hartshorne Visual Working Memory task, as the task kept freezing on their computer. It was unclear what caused this issue but as the tasks are downloaded onto the local computer, it is possible that this may have been a problem with the participant's computer. This participant completed the remaining tasks. As noted above, two participants who reported technical issues had to complete the tasks over two days.

Two participants reported problems related to their own computer or internet. One participant reported that the website kept redirecting to "testmybrain.org". This was identified as a problem with the participant's browser settings and the participant resolved this with instructions from the researcher. One participant reported that their signal was lost halfway through but was able to complete the study when they reloaded their browser.

The remaining four participants reported problems with the tasks. As noted above, one participant reported that the Hartshorne Visual Working Memory task kept freezing. Three participants reported a task repeating. On further inspection, two of these participants had completed a task twice. In both cases, the tasks had been completed hours apart suggesting that the participant had accidentally clicked on the same link twice. To combat this, we implemented a feature that crossed out a task upon completion. The first score recorded was taken for each participant. The third participant reported that the Vocabulary task repeated twice within a three-minute period. It was unclear what caused this.

For the latter four participants, the impact of technical difficulties on task performance was evaluated by calculating their ranks on tasks completed before and after the problem occurred (see Table 4-7). Participants were ranked within their diagnostic group. For two of the participants, the technical problem occurred on either the first or last task so it was not possible to compare performance before and after the problem occurred. One of the participants (A) exhibited their worst

performance on all of the tasks they completed after the technical issue. The remaining participant (C) exhibited their worst performance on three of the four tasks completed after the technical issue.

Table 4-7 Ranks for participants who experienced technical difficulties

	DGS	MEIT	VPA	BDS	HVMT	MRT	BART	MOT	Vocab
A	5	4	4	2.5	4.5	9	6.5	14	9.5
B	15	12	1	13.5	15	13.5	14	14	4
C	7	1	6	1		11	13	5	7
D	6	10.5	5.5	11	9	1.5	7	3	8.5

Tasks completed after the technical issue occurred are shown in bold. DGS, Digit Symbol Coding; MEIT, Morphed Emotion Identification Task; VPA, Verbal Paired Associates Task; BDS, Backward Digit Span; HVMT, Hartshorne Visual Memory Task; MRT, Matrix Reasoning Test; BART, Balloon Analogue Risk Task; MOT, Multiple Object Tracking; Vocab, Vocabulary

Descriptive statistics

MCCB tasks

Z scores on each MCCB task were calculated for each participant to quantify the levels of impairment exhibited by participants relative to a control group (see Table 4-8). Z scores were derived using the means and standard deviations of the 103 control participants recruited as part of CoMPaSS. These scores were not adjusted for age or gender. The healthy control group performed on average half a standard deviation below the controls from the CoMPaSS study (mean Z score = -0.51). The major depressive disorder group performed over half a standard deviations below the CoMPaSS controls (mean Z score = -0.62). Performance in the bipolar disorder group was between a half and one standard deviation below the CoMPaSS controls (mean Z score = -0.85). The schizophrenia group performed between one and two standard deviations below the CoMPaSS controls (mean Z score = -1.76).

Table 4-8 Mean z scores for each group

MCCB Domain Task	Healthy Controls	Major Depressive Disorder	Bipolar Disorder	Schizophrenia
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Speed of Processing	-0.40 (0.83)	-0.92 (0.76)	-1.00 (1.01)	-1.77 (1.26)
Trail Making Test – Part A	-0.43 (0.83)	-0.92 (0.83)	-1.07 (1.43)	-1.90 (1.27)
BACS Digit Symbol Coding	-0.33 (1.06)	-0.85 (1.02)	-1.13 (1.09)	-1.44 (1.19)
Fluency: Animal Naming	-0.20 (0.74)	-0.43 (0.59)	-0.39 (0.55)	-0.89 (0.79)
Verbal Learning				
Hopkins Verbal Learning Test - Revised	-0.45 (1.23)	-0.89 (1.21)	-1.05 (1.69)	-2.11 (1.90)
Working Memory				
WMS-III Spatial Span	-0.44 (0.78)	-0.62 (0.88)	-0.66 (0.97)	-1.20 (1.21)
Letter-Number Span	-0.51 (0.77)	-0.81 (0.90)	-0.85 (1.19)	-1.07 (1.30)
	-0.30 (1.03)	-0.32 (1.10)	-0.47 (0.91)	-1.21 (1.07)
Reasoning & Problem Solving				
NAB Mazes	-0.35 (1.15)	-0.50 (1.46)	-0.62 (1.37)	-1.32 (1.16)
Visual Learning				
Brief Visuospatial Memory Test - Revised	-0.71 (1.15)	-0.66 (1.45)	-0.81 (1.23)	-1.27 (1.33)
Social Cognition				
MSCEIT: Managing Emotions	0.45 (0.78)	0.35 (0.96)	-0.27 (0.53)	-1.07 (0.82)
Attention				
Continuous Performance Test – Identical Pairs	-0.63 (0.85)	-0.31 (1.02)	-0.84 (1.12)	-0.69 (0.82)
Composite Cognition	-0.51 (0.81)	-0.62 (1.19)	-0.85 (0.96)	-1.76 (1.17)

Means and standard deviations are shown. BACS: Brief Assessment of Cognition in Schizophrenia; WMS-III: Wechsler Memory Scale – Third Edition; NAB: Neuropsychological Assessment Battery; MSCEIT: Mayer-Salovey-Caruso Emotional Intelligence Test.

Online tasks

Table 4-9 shows means and standard deviations for each task grouped by diagnosis, along with maximum possible scores, skew and kurtosis. The proportion of participants who achieved the lowest and highest possible score were calculated for each task to determine whether floor or ceiling effects were present. Except for Vocabulary where five participants achieved the maximum score, none of the participants achieved the maximum or minimum scores on any of the tasks. This suggests that there were no ceiling or floor effects present. The distributions of scores for each task are shown in Figure 4-13. The distribution of scores on the Verbal Paired Associates task was highly positively skewed (skew=1.31), whilst the distribution of the Backward Digit Span was moderately positively skewed (skew=0.42). Scores on three tasks were negatively skewed: Balloon Analogue Risk Task (skew=-1.65), Matrix Reasoning Test (skew=-0.97) and Vocabulary (skew=-0.57).

Table 4-9 Group performance on the online tasks

Online Task	Max. Score	Healthy Controls	Major Depressive Disorder	Bipolar Disorder	Schizophrenia	Skew	Kurtosis
Digit Symbol Coding	N/A	38.00 (7.79)	34.60 (6.03)	33.81 (8.73)	30.07 (8.80)	-0.17	-0.23
Morphed Emotion Identification	60	36.32 (8.91)	34.20 (5.97)	33.88 (6.60)	27.53 (5.17)	0.04	-0.54
Verbal Paired Associates	25	8.42 (3.72)	7.27 (5.44)	9.27 (5.04)	7.57 (4.77)	1.31	1.60
Backward Digit Span	N/A	4.58 (1.50)	5.47 (1.85)	3.50 (1.03)	3.87 (1.77)	0.42	-0.74
Hartshorne Visual Working Memory Test	42	32.58 (4.13)	31.33 (3.48)	30.38 (3.86)	29.85 (4.10)	-1.21	-0.10
Matrix Reasoning Test	35	24.11 (6.71)	25.00 (7.81)	21.13 (8.19)	18.8 (7.45)	-0.97	-0.03
Balloon Analogue Risk Task	N/A	836.84 (206.67)	938.67 (101.57)	828.33 (217.17)	800.71 (221.86)	-1.65	3.16
Multiple Object Tracking	120	83.16 (12.95)	79.73 (15.15)	76.07 (17.54)	72.13 (13.30)	0.01	-0.90
Vocabulary	20	14.78 (3.62)	16.80 (2.40)	14.13 (3.64)	11.47 (4.14)	-0.57	-0.52

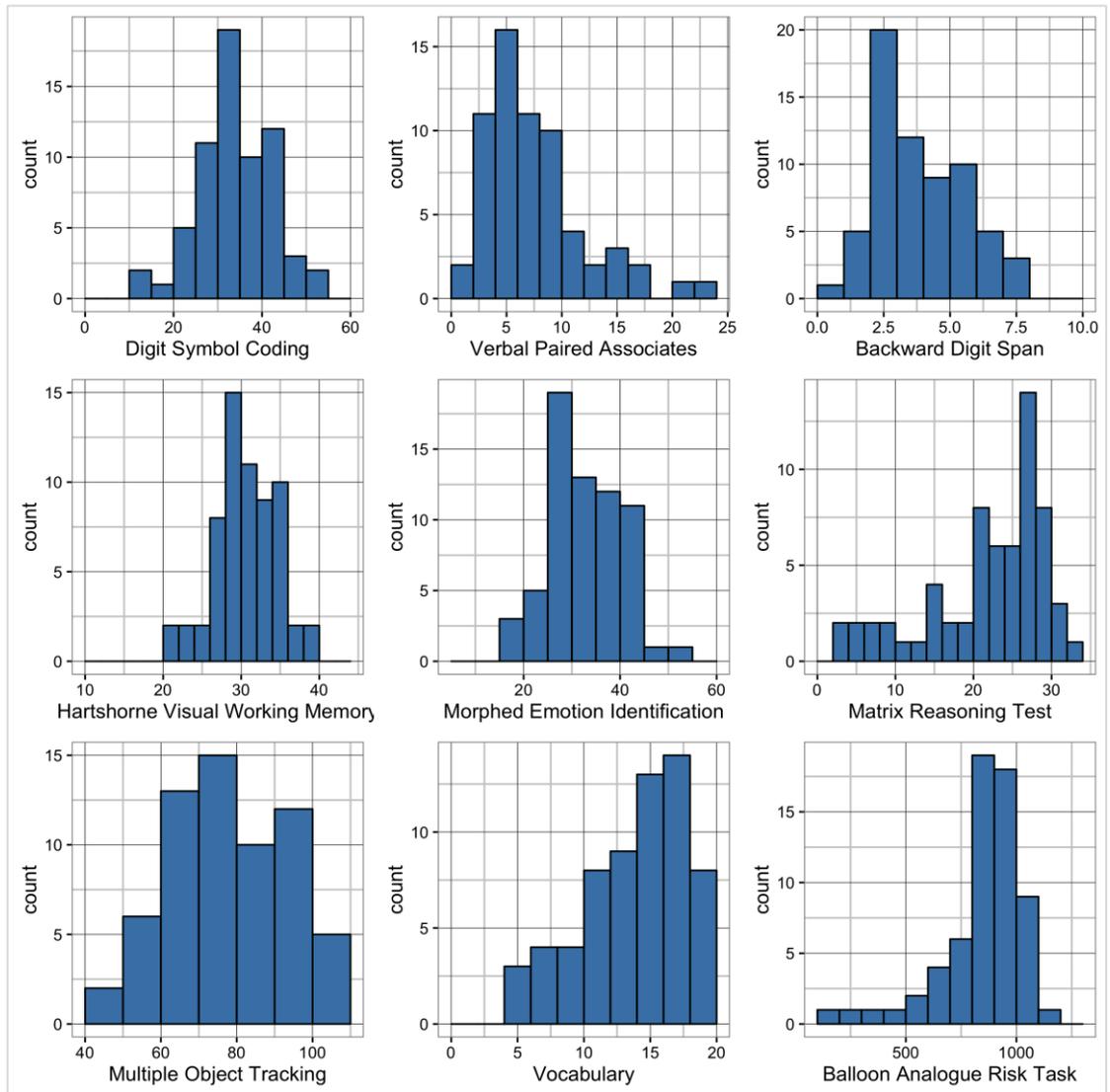


Figure 4-13 Histograms showing the distribution of scores for each online task

Convergent validity: Comparison of the MCCB and online battery

The results of correlations between tasks measuring equivalent domains are shown in Table 4-10. In the entire group, scores from seven out of the eight online tasks were correlated with scores from the MCCB equivalents (r ranged from 0.26 to 0.73). Correlations between tasks assessing speed of processing (r=0.73, 95% CIs: 0.59-0.83), verbal learning (r=0.41, 95% CIs: 0.18-0.57), reasoning and problem solving (r=0.53, 95% CIs: 0.33-0.70) and premorbid IQ (r=0.64, 95% CIs: 0.44-0.78) were significant at the Bonferroni-corrected alpha level of 0.00625. In the cases only group, scores from six out of the eight online tasks were correlated with scores from the MCCB equivalents (r ranged from 0.33 to 0.69). Correlations between tasks assessing speed of processing (r=0.69, 95% CIs: 0.50-0.82), reasoning and problem solving (r=0.55, 95% CIs: 0.29-0.75) and premorbid IQ (r=0.60, 95% CIs: 0.38-0.76) were significant at the Bonferroni-corrected alpha level of 0.00625.

Table 4-10 Results of correlation analyses between online and offline tasks that assess equivalent domains

Domain	Cases and Controls			Cases Only		
	r	95% CIs	p	r	95% CIs	p
Speed of Processing	0.73	0.59-0.83	4.4 x 10 ⁻¹²	0.69	0.50-0.82	1.1 x 10 ⁻⁷
Verbal Learning*	0.41	0.18-0.57	0.001	0.40	0.11-0.64	0.008
Working Memory	0.34	0.10-0.54	0.007	0.36	0.07-0.59	0.02
Visual Learning	0.12	-0.13-0.36	0.35	0.15	-0.15-0.43	0.33
Social Cognition	0.26	0.01-0.47	0.04	0.33	0.04-0.56	0.03
Reasoning and Problem Solving*	0.53	0.33-0.70	7.1 x 10 ⁻⁶	0.55	0.29-0.75	9.7 x 10 ⁻⁵
Attention	0.34	0.09-0.55	0.008	0.31	-0.01-0.56	0.06
Premorbid IQ*	0.64	0.44-0.78	2.1 x 10 ⁻⁸	0.60	0.38-0.76	4.4 x 10 ⁻⁶

*Spearman's rank correlation rho shown instead due to non-normal distribution for these tests.

The cases completed the MCCB prior to the online battery for practical reasons; firstly, participants from NCMH could be recruited prospectively by completing the MCCB with a researcher immediately after completing the NCMH assessment therefore the order of completion could not be randomly assigned, secondly, it would have been difficult to ensure that participants assigned to complete the online part first did so before their appointment, as they were not supervised. However, the controls were counterbalanced. Although the groups were small, the controls were grouped according to whether they completed the MCCB (N=10) or online battery first (N=9) and scores on tasks were compared between the two groups, adjusting for age and gender. If one group scored consistently higher on one battery than the other then this may indicate the presence of greater practice effects when completing the batteries in a specific order. This would indicate a methodological issue with administering the MCCB first to all the cases. There were no differences in performance between the groups, except that the group who completed the MCCB had better scores on the MSCEIT (see Appendix J).

Correlations between all tasks

Figure 4-14 displays correlations between the online and MCCB tasks. Scores for the online Digit Symbol Coding, Verbal Paired Associates, Matrix Reasoning Test and Vocabulary were most highly correlated with their equivalent MCCB tasks. The remaining tasks were more highly correlated with tasks other than their equivalent MCCB task. The Morphed Emotion Identification Task was most highly correlated with the Mazes task ($r=0.56$, 95% CIs: 0.36-0.71). The Backward Digit Span was most highly correlated with the Continuous Performance Test ($r=0.41$, 95% CIs: 0.18-0.60). The Multiple Object Tracking Test was most highly correlated with the Digit Symbol Coding ($r=0.54$, 95% CIs: 0.34-0.69). Whilst the Hartshorne Visual Working Memory task was not correlated with the Brief Visuospatial Memory Test – Revised, scores from this task were correlated with Digit Symbol Coding ($r=0.28$, 95% CIs: 0.04-0.50). The Balloon Analogue Risk Task did not have an equivalent task in the MCCB and scores from this task showed low correlations with the MCCB tasks; the highest correlation observed was with the Hopkins Verbal Learning Test - Revised ($r=0.25$, 95% CIs: 0.00-0.47).

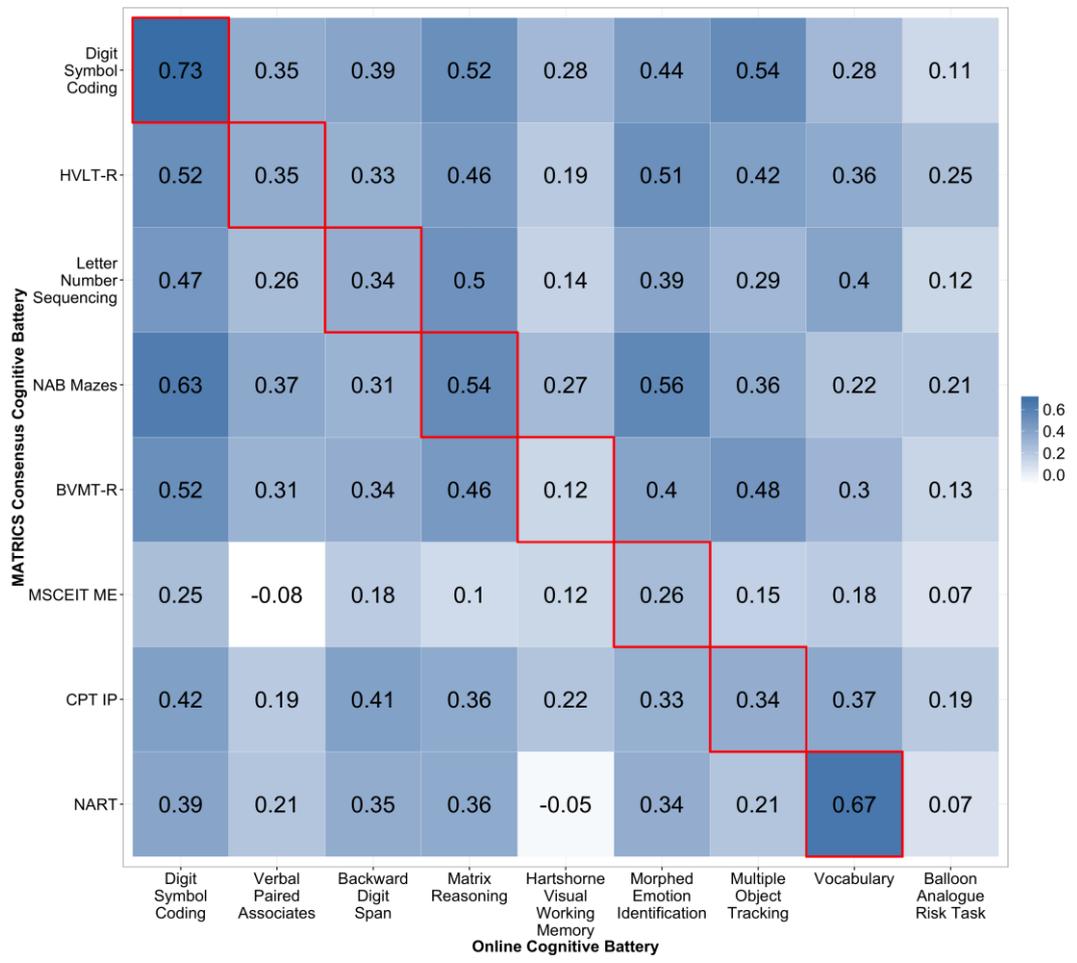


Figure 4-14 Pearson correlations between all online and MCCB tasks

Red squares indicate tasks assessing the same domain. Only tasks from the MCCB with an equivalent online task are shown (Trail Making Test – A, Animal Naming and Wechsler Memory Scale III: Spatial Span have been excluded). BVMT-R, Brief Visuospatial Memory Test – Revised; CPT IP, Continuous Performance Test: Identical Pairs; HVLT-R, Hopkins Verbal Learning Test – Revised; MSCEIT ME, Mayer-Salovey-Caruso Emotional Intelligence Test: Managing Emotions; NAB, Neuropsychological Assessment Battery; NART, National Adult Reading Test.

Comparison of the online tasks and g

Each online task was correlated with a measure of general intelligence (g) derived from the MCCB tasks (see Table 4-11). In the entire group, scores from eight out of the nine online tasks were correlated with g (r ranged from 0.30 to 0.74). Correlations between g and Digit Symbol Coding ($r=0.74$, 95% CIs: 0.60-0.84), Verbal Paired Associates ($r=0.44$, 95% CIs: 0.19-0.62), Morphed Emotion Identification ($r=0.58$, 95% CIs: 0.39-0.73), Backward Digit Span ($r=0.42$, 95% CIs: 0.18-0.61), Matrix Reasoning Test ($r=0.59$, 95% CIs: 0.38-0.73), Multiple Object Tracking ($r=0.53$, 95% CIs: 0.31-0.69) and Vocabulary ($r=0.36$, 95% CIs: 0.08-0.61) were significant at the Bonferroni-corrected alpha level of 0.00556. In the cases only group, scores from seven out of the nine online tasks were correlated with g (r ranged from 0.36 to 0.73). Correlations between g and Digit Symbol Coding ($r=0.73$, 95% CIs: 0.54-0.85), Morphed Emotion Identification ($r=0.54$, 95% CIs: 0.27-0.72), Backward Digit Span ($r=0.43$, 95% CIs: 0.14-0.65), Matrix Reasoning Test ($r=0.61$, 95% CIs: 0.35-0.78) and Multiple Object Tracking ($r=0.50$, 95% CIs: 0.22-0.71) were significant at the Bonferroni-corrected alpha level of 0.00556.

Table 4-11 Correlations between online tasks and g

Online Task	Cases and Controls			Cases Only		
	r	95% CIs	p	r	95% CIs	p
Digit Symbol Coding	0.74	0.60 – 0.84	1.1 x 10 ⁻¹¹	0.73	0.54 – 0.85	7.0 x 10 ⁻⁸
Verbal Paired Associates*	0.44	0.19 – 0.62	0.001	0.35	0.01-0.62	0.03
Morphed Emotion Identification	0.58	0.39 – 0.73	1.0 x 10 ⁻⁶	0.54	0.27 – 0.72	0.0003
Backward Digit Span	0.42	0.18 – 0.61	0.001	0.43	0.14 – 0.65	0.005
Hartshorne Visual Working Memory	0.30	0.04 – 0.52	0.023	0.25	-0.07 – 0.53	0.12
Matrix Reasoning Test*	0.59	0.38-0.73	9.7 x 10 ⁻⁷	0.61	0.35-0.78	3.4 x 10 ⁻⁵
Balloon Analogue Risk Task*	0.11	-0.17-0.35	0.43	0.15	-0.17-0.46	0.37
Multiple Object Tracking	0.53	0.31 – 0.69	2.2 x 10 ⁻⁵	0.50	0.22 – 0.71	0.001
Vocabulary*	0.36	0.08-0.61	0.006	0.38	0.06-0.65	0.02

*Spearman’s rank correlation rho shown instead due to non-normal distribution for these tests.

4.4 Discussion

This chapter describes the development of an online cognitive battery for use in research of psychiatric disorders. The battery was designed to test the domains specified by the NIMH’s MATRICS initiative. Participants with either one of three psychiatric diagnoses or no history of mental health problems were recruited as part of a pilot and validation study. Feedback received from participants was largely positive with only three participants rating any aspect of the battery as “poor”. The results of the validation study indicated that the online battery is a suitable tool for mental health research, providing valid measurements of the majority of MATRICS domains.

The tasks were well tolerated with 58 out of 65 participants completing all the online tasks. This was comparable to the MCCB, which was completed by 60 of the 65 participants. Five participants completed the online battery over at least two separate visits to the website. These participants had a diagnosis of either schizophrenia or bipolar disorder. Notably, all five participants had lower MCCB composite cognition z scores than the mean for their diagnostic group. This suggests that participants with greater cognitive impairment may poorly tolerate the online battery over a single session. A solution to this problem would be to include a feature that allows participants to quit the study, save their website link and continue later. The issue with completing the task over two or more days is that questionnaires containing measures of current mood or current substance use could only be analysed with cognitive data collected on the same day. Another solution would be to reduce the number of tasks included in the battery.

4.4.1 Validation of the online battery

Convergent validity was assessed by conducting correlations between tasks that measure equivalent domains. Seven out of eight online tasks were correlated with the MCCB equivalent ($r=0.26-0.73$). The validation study sought to determine whether the online tasks provide suitable measures of the MATRICS domains. However, there are two considerations. Firstly, this study compared unsupervised online tasks to primarily pen and paper tasks administered by a researcher. Secondly, the online tasks were different to those included in the MCCB. Both of these differences are likely to affect the magnitude of the correlations between the tasks. Examining the correlation for speed of processing provides some insight into the extent to which the correlations are affected by online/offline testing or differences in the methodology of the tasks since the speed of processing domain was measured using offline and online versions of the same task, Digit Symbol Coding. These tasks were the most highly correlated in the whole sample ($r=0.73$, 95% CIs: 0.59-0.83) and amongst the cases only ($r=0.69$, 95% CIs: 0.50-0.82). When considering the validity of a new cognitive task, the correlation between a new task and the gold standard task cannot exceed the square root of the product of the test-retest reliabilities of both tasks [272]. The test-retest reliability of the Digit Symbol Coding subtest of the BACS has been estimated to be between 0.83 and 0.90 [389]. Taking this into account, the online and offline versions of Digit

Symbol Coding were highly correlated. This suggests that differences in online and offline administration do not have a large impact on the magnitude of the correlations. Therefore, differences in the methodology of the online tasks and the MCCB tasks may explain the smaller correlations observed for some domains. A further consideration is the delay between administering the first and second battery, which may have affected the results. This difference was minimised by requiring participants to complete the online battery 24 hours after the MCCB, although it was difficult to ensure they did so and concomitant factors, such as mood scores, could change even across short time periods. However, the majority of participants exhibited minimal changes in mood scores across the two assessments. For example, 69% of participants exhibited a change of two points or less between the first and second administration of the HADS depression subscales, whilst 72% of the sample exhibited a change of two points or less in the HADS anxiety subscale. The association between mood scores and performance on the online battery is examined further in Chapter 6.

The remaining online tasks were selected to measure the same domains of the MCCB but did not use similar methodology. Three online tasks were most highly correlated with MCCB tasks assessing the same domain: Verbal Paired Associates (VPA), Matrix Reasoning and Vocabulary. The VPA task was selected as an alternative measure of verbal learning due to the practical difficulties of creating internet-based list learning, free recall tasks (such as the Hopkins Verbal Learning Test – Revised (HVLTR) from the MCCB). The VPA task assesses delayed recognition of word pairs. Measures of paired associate learning have been shown to load onto the same factor as list learning tasks in factor analytic studies [202]. Despite the differences in methodology between the tasks, the correlation between scores on the VPA and HVLTR was moderate ($r=0.41$, 95% CIs: 0.18-0.57) and the VPA was more highly correlated with HVLTR than any other MCCB task. The MATRICS initiative selected the NAB: Mazes subtest as their measure of reasoning and problem solving. This task was not available using the TestMyBrain platform so Matrix Reasoning was selected as an alternative. Both the NAB: Mazes subtest and Matrix Reasoning are measures of non-verbal problem solving but their methodology differs. The NAB: Mazes subtest requires the participant to find the correct route through a maze and each trial includes an increasingly complex maze.

Performance on Matrix Reasoning depends on the participant identifying the correct pattern and selecting the image that completes this pattern. Performances on these two tasks were moderately correlated ($r=0.53$, 95% CIs: 0.33-0.70) suggesting that Matrix Reasoning is a suitable alternative to the NAB: Mazes. Finally, performance on the Vocabulary test was correlated with the NART ($r=0.64$, 95% CIs: 0.44-0.78). The NART is a widely used measure of premorbid IQ [357, 366]. Vocabulary was included as a measure of crystallised intelligence. However, a longitudinal study is required to examine whether performance on the Vocabulary task is stable before and after illness onset.

Three online tasks had correlations that met the minimum acceptable threshold of $r>0.2$: Backward Digit Span, Morphed Emotion Identification and Multiple Object Tracking. These tasks had higher correlations with MCCB tasks other than their equivalent. This suggests that there was significant overlap in the processes being assessed by the online tasks and these tasks may lack specificity in measuring the MATRICS domains. This is consistent with research showing that cognitive domains are at least moderately correlated and different cognitive abilities are related to a higher order factor (g) [204, 205]. The majority of the online tasks were correlated with a measure of g derived from scores on the MCCB. Studies have examined whether the cognitive domains measured by the MCCB are separable. Factor analytic studies of the MCCB are conflicting, with studies indicating that this battery can be reduced into fewer domains [390, 391] but another showing that the seven domain model is the best fit for the data [392]. A factor analysis of the online battery with a larger dataset would assess whether the online battery assesses separable domains.

The Hartshorne Visual Working Memory task was not correlated with the BVMT-R ($r=0.12$, 95% CIs: -0.13-0.36). This task had low correlations with g ($r=0.30$, 95% CIs: 0.04-0.52), Digit Symbol Coding ($r=0.28$, 95% CIs: 0.04-0.50) and NAB Mazes ($r=0.27$, 95% CIs: 0.03-0.49). This suggests the task may be an adequate measure of general cognitive function but should not be considered a measure of visual learning. It should be noted that 8% of the sample reported that Hartshorne Visual Working Memory was their least favourite task. Therefore, the low correlations may reflect participants disengaging with this task.

The Balloon Analogue Risk Task (BART) was not correlated with g ($R=0.18$, 95% CIs: $-0.09-0.42$) or any of the MCCB tasks. This was not surprising given the BART is a behavioural measure rather than a neurocognitive task and the MCCB is primarily made up of neurocognitive measures. Nevertheless, the BART is a useful measure of risk taking behaviour that does not rely on self-report. Lejuez et al. [375] examined correlations between the adjusted number of balloon pumps (average number of pumps excluding exploded balloon trials) and measures of risk taking. Performance on the BART was correlated with questionnaires assessing sensation seeking, impulsivity and behaviour constraint (control, harm avoidance and traditionalism). The BART was also correlated with actual risk taking behaviours over the past twelve months, including smoking, excessive alcohol use, number of classes of drugs taken, gambling, unsafe sexual practices, stealing and infrequent seatbelt use. Therefore, inclusion of this task in the battery will allow us to assess strategic risk taking across a range of psychiatric disorders and determine whether this is associated with functional outcome.

In conclusion, the majority of the online tasks were correlated with their MCCB equivalents but this may reflect the tendency for all cognitive tasks to be at least moderately correlated. Digit Symbol Coding, Matrix Reasoning, Vocabulary and Verbal Paired Associates were most highly correlated with their equivalent tasks suggesting that these tasks were the most valid measures of processing speed, reasoning and problem solving, premorbid IQ and verbal learning respectively.

4.4.2 Methodological considerations of validating cognitive assessments

The psychometric properties of a cognitive assessment should be evaluated under the same conditions as future studies. Whilst the online tasks were well tolerated in the current study, the participants may have been motivated by factors such as the interaction with a researcher. The motivations of participants in a completely unsupervised study are relatively unknown and therefore it is not possible to predict how many of these participants are likely to complete all the tasks based on the current study. Participants also needed to be available during the weekdays to complete the MCCB with a researcher, although appointments were flexible and included evenings to limit recruitment bias. This would not be a constraint in an unsupervised online study. Most participants completed the online battery at home

but a small number attended the clinical testing facility in MRC CNGG, as they did not have internet at home. These participants were left to complete the tasks uninterrupted. This option will also be made available to participants without internet during the main study.

The psychometric properties of a cognitive assessment should also be evaluated in a sample that is representative of the population that it is intended to be used to assess. Participants with depression, bipolar disorder and schizophrenia were recruited for this study, as these diagnoses are associated with varying levels of cognitive impairment (from mild to severe). However, the schizophrenia and bipolar disorder groups (mean z scores: -1.76 and -0.85 respectively) were not as cognitively impaired as the schizophrenia and bipolar groups in CoMPaSS (mean z scores: -2.40 and -1.21 respectively, see Chapter 3). The explanations for this are unclear but participants with more severe impairments may be less likely to 1) have internet access; 2) have sufficient computer skills or 3) want to take part in an unsupervised study. There were also some differences in the recruitment methods between the validation study and CoMPaSS, which may explain the differing levels of impairment. Recruitment for the validation study was predominantly through letters, whilst the recruitment methods of CoMPaSS are varied and include face-to-face recruitment from mental health clinics. The latter method may be more effective in recruiting patients with more severe impairments, which is an important consideration for an online cognitive study.

There was some evidence of recruitment bias in this study. Examination of the demographic and clinical characteristics of the sample indicated that participants had a wide age range (22 to 78 years old) and consisted of slightly more females than males (58%). Most of the sample had at least A-level qualifications and 32% of the participants were professionals. The protocol for the validation study was demanding, requiring a time commitment of three hours over two days and this is likely to affect recruitment in this study. Participants were also reimbursed for their time. Therefore, the characteristics of this sample may differ from those who complete the online study alone, which is an unpaid study with a time commitment of one hour. The participants were not compared to participants from the parent studies, as most participants from these studies were not invited to take part in the validation study. Comparisons between participants from the online study and

those who did not take part were conducted in a larger sample and can be found in the next chapter (Chapter 5).

4.4.3 Concluding statements and future work

The online cognitive battery has several strengths. Selection of the tasks was evidence-based and driven by the work of the NIMH-MATRICES initiative. All tasks were taken from published research and have been used extensively in online research through the work of The Many Brains Project and their website “testmybrain.org”. The tasks work on a range of devices including touchscreen devices such as tablet computers and smartphones. The strengths of the validation study include the recruitment of individuals with a range of psychotic and affective disorders. Participants completed the online battery unsupervised at home, as would be expected in an online study.

Several limitations of the validation study should be noted. The test-retest reliability of the online battery was not assessed in this study. In assessing validity, the correlation between a new task and the gold standard task cannot exceed the square root of the product of the test-retest reliabilities of both tasks [272].

Therefore, the upper limits of the correlations between tasks were unknown. However, whilst knowing the upper limits of the correlations would be helpful for interpretation of the results, these would not change the magnitude or significance of the correlations that were found between the tasks. Participants were asked to return feedback questionnaires after they had completed the online battery. Two-thirds of participants returned these questionnaires. Therefore, the experiences of the remaining third of participants are unknown. The order of completion of the batteries was not counterbalanced for practical reasons. However, the order of completion was counterbalanced in the healthy control group and there was no evidence that completing the MCCB first had a negative impact on the results. This study did not address whether the online tasks are associated functional outcome, although this is addressed in Chapter 6.

In conclusion, a new online cognitive battery was designed to assess the domains of cognition outlined by the NIMH-MATRICES initiative. Sixty-five participants with no history of mental disorder, major depressive disorder, bipolar disorder or schizophrenia were administered the MCCB and new online battery as part of a

pilot and validation study. Findings from the validation study indicated that the online cognitive battery is a suitable tool for mental health research, providing valid measurements of the majority of NIMH-MATRICES domains. The battery was well tolerated by the participants and feedback was largely positive. This online battery will be used to gather cognitive data from participants of large psychiatric genetics studies within the MRC Centre for Neuropsychiatric Genetics and Genomics. Data from this study will be combined with data from the parent studies to investigate the genetic and environmental factors that contribute to the development of cognitive impairments across psychiatric disorders.

Chapter 5: Internet-based Cognitive Testing in Research of Psychiatric Disorders

5.1 Introduction

Online cognitive testing is being increasingly utilised in studies of healthy populations to collect large datasets or for longitudinal studies with repeated testing [273, 274, 276, 279]. At the time of writing, there have been no published studies using online cognitive testing in populations with psychiatric disorders. In Chapter 4, the validity and tolerability of a new online cognitive battery for use in mental health research were examined. The next stage in development of the online cognitive battery is to determine whether this is an effective method for collecting cognitive data at large scale.

5.1.1 Internet-based research in mental health

A key consideration of internet-based research is the representativeness of the recruited sample, particularly given the possibility of recruitment bias. The most obvious problem is that participants need access to the internet and a computer to take part. A study of internet usage amongst individuals with psychiatric disorders identified barriers to accessing the internet include concerns about security, lack of financial resource to purchase internet enabled devices, impaired access to social environments with internet facilities and lack of confidence in using the internet [270]. Individuals with psychosis have been shown to be less likely to have internet access [270, 271]. One study identified a negative correlation between age and frequency of internet use in a cross-disorder sample of participants [271].

Most online studies of psychiatric populations have been clinical trials for internet-based therapies. The first trials for internet-based therapies began in the late 1990's and the most common form of internet-based therapy that has been studied is cognitive behavioural therapy (CBT) [393, 394]. Studies have examined the efficacy of online therapies and psychoeducation programmes in treating a wide-range of diagnoses, including depressive disorders [395, 396], anxiety disorders [397-402], post-traumatic stress disorder [403], obsessive-compulsive disorder [404, 405], bipolar disorder [385, 406-408] and psychotic disorders [409].

Participants are recruited into these studies through a range of methods including advertisements (both online and traditional media), epidemiological studies or referrals from health professionals [394]. Few studies have examined the characteristics of internet-based samples in mental health research but there is evidence that these participants have higher levels of education than the general population [394]. To my knowledge, there have been no studies examining the response rates and characteristics of participants with psychiatric disorders who have completed an online cognitive assessment.

5.1.2 Online cognitive testing

Several studies have utilised online cognitive assessments to recruit participants for research [273, 274, 276, 279](for a comprehensive overview of these studies see Chapter 1). Overall these studies have demonstrated that cognitive data collected using the internet is comparable to data gathered using face-to-face cognitive testing methods (pen and paper or supervised computerised tasks). These studies have included self-selected samples (participants who have found the study online themselves) [273] or invited participants from existing studies [274, 276, 279]. However, few studies have provided information on participation rates or formally compared the characteristics of the internet-based sample to the original cohort from which participants were recruited. This is an important consideration as internet-based samples may not be as representative as samples recruited for face-to-face studies. One study that reported response rates and completion rates for their online cognitive battery was the Twins Early Development Study (TEDS) [274]. This study recruited a sample of more than 4000 twins born in the United Kingdom between 1994 and 1996. The study developed online tasks to assess reading, language, mathematics, and general cognitive ability in children. Participants were assessed using the online battery at two follow-up periods at ten and twelve years old. At both follow-up periods, 71% of the TEDS sample agreed to participate in the study (80% of the sample had internet access). At 10 years old, the cognitive battery consisted of eight tasks and 65% of participants completed the entire battery. At 12 years old, the cognitive battery consisted of 15 tests separated into two parts. Completion rates for this follow-up period were lower with 62% completing all the tasks included in part A, 48% completing all the tasks in part B and 37% completing both parts of the cognitive battery (15 tasks). Another study

examined participant attrition using three online variants of a Stop Signal Task [410]. Participants were asked to complete a minimum of four sessions of cognitive testing over four days. Of the 482 participants who signed up to take part in the study, 419 (87%) participants completed at least one test and 265 (55%) participants completed the required four testing sessions.

To date, there have been no published studies that have examined completion rates for an online cognitive battery in an internet-based sample of participants with psychiatric disorders. Studies using face-to-face cognitive batteries, such as the MATRICS Consensus Cognitive Battery (MCCB) or the Brief Assessment of Cognition in Schizophrenia (BACS), in psychiatric populations have reported high completion rates [389, 411]. A large multi-site study of participants with schizophrenia reported that 98.5% of their sample had complete data on the MATRICS Consensus Cognitive Battery (MCCB) [411]. In Chapter 3, 89% of participants in the study had full data on the MCCB. Similar completion rates were reported by a study evaluating the reliability of the BACS to assess participants with schizophrenia (100% of the sample completed at least five out of six tasks [389]). However, completion rates may be lower for an online unsupervised study.

5.1.3 Factor analysis of cognitive batteries

Scores on pairs of cognitive tasks are moderately correlated and studies have shown that a single factor ‘g’ can account for a high percentage of the variance in cognitive batteries, such as the MCCB and BACS [206, 412]. Whilst the MCCB was designed to assess seven specific domains affected in schizophrenia, factor analytic studies of the MCCB have supported 7 factors [392] and 3 factor models [390, 391]. Hochberger et al. [412] examined the factor structure of the BACS battery in a large sample of participants with bipolar disorder, schizoaffective disorder and schizophrenia. A single factor solution was the best model for the BACS data across all diagnostic groups and accounted for 47-53% of the variance. The implication of this is that much of the pattern of cognitive deficits observed across disorders can be explained by a global deficit. The results of the validation study in Chapter 4 indicated that each online task assessed multiple domains of cognition rather than specific abilities. However, the factor structure of the battery was not assessed due to an insufficient sample size. The recommended sample size

for factor analysis is at least 300 participants with a minimum of ten respondents per variable [413, 414]. Therefore, a further aim of this chapter was to conduct an exploratory analysis to evaluate the structure of the online cognitive battery.

5.2 Chapter aims

This chapter describes the main recruitment phase of the online study. Participants from two studies within the MRC Centre for Neuropsychiatric Genetics and Genomics were invited to complete the study: National Centre for Mental Health (NCMH) and Cognition in Mood, Psychosis and Schizophrenia Study (CoMPaSS). Individuals with a range of mental health disorders were invited to participate. The first aim of this study was to determine whether online cognitive testing is a suitable method for mental health research. Three sets of analyses were conducted to evaluate the online sample:

- Analysis 1. Response rates were calculated across the two studies and within specific diagnostic groups.
- Analysis 2. The clinical and demographic characteristics of the sample were examined to evaluate whether there is recruitment bias in this online sample. These characteristics were compared with those of individuals who were invited to take part in the study but did not participate in order to determine whether the study sample was representative of the original cohort.
- Analysis 3. Completion rates were calculated for each task. The demographic and clinical characteristics of participants who completed all of the study were compared with those who did not complete the full battery.

The results of the validation study suggested that each online task assessed multiple domains of cognition rather than specific abilities. However, there were an insufficient number of participants to conduct a factor analysis. Therefore, a further aim of this chapter was to evaluate the structure of the cognitive battery (Analysis 4). The purpose of this exploratory analysis was to determine whether the new battery could be reduced into separable cognitive domains. The relationships between each task and a measure of general cognitive function (g) were examined.

5.3 Method

5.3.1 Sample

Participants were recruited from the databases of two studies: Cognition in Mood, Psychosis and Schizophrenia Study (CoMPaSS) and the National Centre for Mental Health (NCMH). These studies have been described in detail elsewhere (see Chapters 3 and 4) but brief details of recruitment and diagnoses are provided below. Both studies include confirmation of consent from participants to be approached for other research within the centre.

Recruitment to the online study is ongoing but this chapter includes data from participants who were recruited before October 2017. The total number of invitations sent between June and September 2017 was 3590. Inclusion criteria were aged 16 or above, able to understand written and spoken English and no uncorrected deficits in sight or hearing. There were no specific exclusion criteria given the practical difficulties involved in pre-screening participants for an online study but the online questionnaire included questions about current substance use, history of neurological conditions and whether participants had been admitted to hospital or had a change in their medication in the last three months.

CoMPaSS recruitment

CoMPaSS is a study of over 1200 individuals with schizophrenia and related psychotic disorders recruited primarily from outpatient clinics. Participants were interviewed using the Schedule for Clinical Assessment in Neuropsychiatry [331]. This interview is then reviewed along with available clinical records by trained raters to determine a consensus lifetime diagnosis.

At the time of writing, letters had been sent to 127 participants from CoMPaSS (see Appendix K for full letter). The letters included a website address for the study and a unique ID number and password for each participant. Participants who were interested in the study could type the website address into their internet browser and use their ID number and password to log in and access the information webpage, consent form and the study. Participants were also given the option to contact the study team by telephone, email or by returning a reply slip.

The reply slip had three options:

1. Would like to take part in the study and has provided an email address.
2. Does not have access to the internet but would like to hear about other ways to take part in the study.
3. Does not want to receive further contact about this study.

Participants who selected option 1 were contacted via email and given further information and instructions on how to access the website. Participants who selected option 2 (would like to participate but no internet) were contacted to discuss other ways that they could participate in the study. These participants were given the option to attend the clinical assessment suite at Cardiff University and provided with information about other potential locations, such as local libraries or charity centres.

NCMH recruitment

The NCMH sample includes over 10,000 individuals with a range of diagnoses including bipolar disorder (N=1083), schizophrenia (N=557), autism spectrum disorders (N=465), post-traumatic stress disorder (N=1050) and major depressive disorders (N=5050). One of the main aims of NCMH is to recruit a cohort of individuals prepared to be approached for other studies in order to develop psychiatric research in Wales. Participants are asked the question, “Has a doctor or health professional ever told you that you have any of the following diagnoses?” Participants are given a list of diagnoses and asked to indicate all diagnoses that apply. They are then asked to indicate which of the diagnoses they have ticked would they consider to be their primary, secondary and tertiary diagnoses. Finally, they are asked the question, “If we were to speak to your clinical team or general practitioner, would they agree with that?” Their diagnosis is then confirmed with their clinical team where possible.

The total number of invitations sent between June and September 2017 was 3463. Participants from NCMH were recruited in three stages:

- 1) An advertisement was put in the NCMH bi-annual newsletter calling for participants to contact the study team if they were interested in participating.
- 2) Invitations were sent in batches of between 200 and 400 to consecutive NCMH participants who had provided an email address and consented to be re-contacted (N=2772). These participants were sent an invitation email that contained their unique study link (see Appendix K for emails to cases and controls). Participants who were interested in the study could click on this link to access the information page, consent form and the study.
- 3) The remaining participants who had not provided an email address when they participated in the NCMH study were sent invitation letters (see Appendix K for full letter). These invitations were sent in batches of 200 to consecutive NCMH participants. Recruitment of these participants is ongoing but at the time of writing, letters had been sent to 691 participants. Letters were sent in groups according to the participant's reported diagnosis.

The first round of letters were sent to participants with schizophrenia and bipolar disorder, as these diagnoses were the focus of the final study described in Chapter 6. As has been previously described in the CoMPaSS recruitment section, participants were sent letters that contained a link to the study website and their unique username and password. They were given the option to go online and complete the study in their own time or contact the study team by telephone, email or by returning a reply slip. The reply slip had the same three options as those sent to the CoMPaSS sample: 1) would like to take part and has provided an email address, 2) does not have access to the internet but would like to hear about other ways to take part in the study, or 3) does not want to receive further contact about this study. Participants who selected option 1 were contacted via email and given further information and instructions on how to access the website. Participants who selected option 2 (would like to participate but no internet) were contacted to discuss other ways that they could participate in the study. These participants were given the option to attend the clinical assessment suite at Cardiff University and

provided with information about other potential locations, such as local libraries or charity centres.

Diagnostic categories

The NCMH cohort includes over 90 categories of mental health diagnoses. Therefore, participants were grouped into diagnostic categories for the purposes of reporting response rates. These groups were driven by current diagnostic criteria (DSM-V and ICD-10) but also depended on the number of participants in the cohort with that particular diagnosis. For example, NCMH has a special interest in recruiting participants with bipolar disorders, schizophrenia spectrum disorders and post-traumatic stress disorder, due to the research interests of the Division of Psychological Medicine and Clinical Neurosciences. Therefore, mood disorders were separated into unipolar and bipolar depression. Psychotic disorders were separated into schizophrenia-spectrum disorders (schizophrenia and schizoaffective disorder) and other psychotic disorders (delusional disorder, psychosis not otherwise specified). Participants with post-traumatic stress disorder were separated from participants with other anxiety disorders. A breakdown of the diagnostic categories and disorders can be found in Table 5-1.

An “other disorder” category was included for participants who could not be grouped into any of the other diagnostic categories or had been recorded as “other” for the diagnosis variable. This category included:

- 1) Diagnoses for which there were an insufficient number of participants to include a specific diagnostic category (total number of invited participants was less than 20), such as adult participants who had been diagnosed with behavioural or developmental disorders in childhood or adolescence, participants diagnosed with Alzheimer’s or other types of dementia, other neurological disorders with psychiatric symptoms, intellectual disability, alcohol misuse or dependence, mood disorder during pregnancy, tic disorder, or a psychotic episode with a specified organic cause.
- 2) Participants who had been rated as having an “other psychiatric disorder”, “other mood disorder” or “other psychological illness” in the NCMH sample. These categories included participants who reported:

- a. Subclinical symptoms of psychosis or mood disorder but had not been given a diagnosis by a health professional.
- b. A history of self-harm without a diagnosis.
- c. Bereavement or work stress requiring a period of leave from their occupation or referral to occupational health or counselling services.

Table 5-1 Diagnostic categories

Diagnostic Categories	Diagnoses Included
Unipolar mood disorders	Single episode or recurrent major depressive disorder and depressive disorder not otherwise specified (NOS)
Bipolar spectrum disorders	Bipolar disorder type I, type II, manic or hypomanic episode, cyclothymia and bipolar NOS
Schizophrenia spectrum disorders	Schizophrenia and schizoaffective disorder
Post traumatic stress disorder	
Anxiety disorders	Panic disorder, agoraphobia, specific phobias, social phobias, generalised anxiety disorder, anxiety NOS
Autism spectrum disorders	Autism, Asperger's syndrome
Attention deficit hyperactivity disorder	
Personality disorders	Borderline personality disorder and other personality disorders*
Other psychotic disorders	Delusional disorder, psychosis NOS, substance induced psychotic disorder
Eating disorders	Anorexia, bulimia, binge eating disorder and eating disorder NOS
Obsessive compulsive disorder	
Other psychiatric disorders	Behavioural or developmental disorders with onset in childhood or adolescence, Alzheimer's or other types of dementia, Parkinson's disease, intellectual disability, organic psychosis, alcohol misuse or dependence, mood disorder in pregnancy, tic disorder, other psychiatric disorder, other mood disorder, or other psychological illness.

*Participants with personality disorders other than borderline personality disorder are included in a single category ("other personality disorder") in NCMH and the type of personality disorder is not specified.

5.3.2 Measures

Cognitive assessment

All tasks from the validation study were included in the main study given that the battery as a whole was well tolerated by participants (see Chapter 4). This would also allow me to combine data from the validation and main studies in future analyses. However, it should be noted that Hartshorne Visual Working Memory was not correlated with the measure of visual learning from the MATRICS Consensus Cognitive Battery. Full details of the online cognitive battery can be found in Chapter 4. The battery comprises of 9 tasks that each assess a separate domain of cognition. The domains are speed of processing, verbal learning, working memory, visual learning, reasoning and problem solving, attention, social cognition, strategic risk taking and premorbid IQ. The tasks are shown in order of administration in Table 5-2. Participants clicked on a study-specific website link to access the tasks. Each task loads in the participant's internet browser and the data is stored locally until the task ends then the data is encrypted and uploaded to a secure server. The battery takes 45-50 minutes to complete.

Table 5-2 Descriptions of the tasks included in the online battery

Domain	Task	Description	Outcome Scoring
Speed of Processing	Digit Symbol Coding	P uses the key to assign the correct numbers to a series of symbols.	Number of correct responses in 90 seconds.
Social Cognition	Morphed Emotion Identification	P decides whether a face looks angry, fearful, happy or disgusted.	Number of correct responses out of 60 faces.
Verbal Learning	Verbal Paired Associates	P must memorise word pairs and select the word that was shown with each target word.	Number of correct responses out of 25 word pairs.
Working Memory	Backward Digit Span	P recalls a sequence of numbers in reverse order.	Maximum length of number sequence the participant was able to recall backwards.
Visual Learning	Hartshorne Visual Working Memory	P decides whether an object is the same or different from the previous object in that location.	Number of correct responses out of 42 trials.
Reasoning and Problem Solving	Matrix Reasoning Test	P selects the image that best completes a pattern.	Number of correct responses out of 35 patterns.
Strategic Risk Taking	Balloon Analogue Risk Task	P collects as many points as possible by blowing up balloons but no points are given if the balloon pops.	Number of points collected by inflating 30 balloons. Higher scores indicate more effective strategic risk-taking.
Attention	Multiple Object Tracking	P follows multiple targets as they move amongst identical objects.	Number of correct responses over 30 trials. Within a trial, each correctly identified target is 1 point.
Premorbid IQ	Vocabulary	P selects which word is closest in meaning to the target word.	Number of correct responses out of 20 words.

Scoring and imputation

The outcome measure for each task can be found in Table 5-2. For each task, z scores were derived using the mean and standard deviation of the healthy controls. This included the controls recruited during the pilot and validation study (total N = 67). Missing data was imputed using the method described in the manual of the MATRICS Consensus Cognitive Battery (MCCB) [338]. Full details of the imputation methods including formulas can be found in Appendix C. Imputed data was used solely to derive general cognitive performance scores (g). Imputed scores were not included in analyses of individual tasks given that the imputation algorithms rely on information from other tasks for that participant and so are not suitable for domain or task specific analyses. Data was imputed for participants that had completed at least 5 tasks of the battery, which is consistent with the approach used for MCCB data in Chapter 3, meaning that those with data for less than five tests were not included in the analysis calculating 'g'.

Demographic and clinical variables

Participants completed an online questionnaire prior to completing the cognitive battery (see Appendix G for full questionnaire). This questionnaire included questions about current diagnosis, medication, medical history, substance use and current mood. Current symptoms of depression and anxiety were assessed using the Hospital Anxiety and Depression Scale (HADS) [379]. Current symptoms of mania and hypomania were assessed using the Altman Mania Scale (AMS) [383]. Current psychotic and negative symptoms were not assessed due to the lack of reliable, valid self-report questionnaires. Following the pilot and validation study, two further questionnaires were added to assess level of disability, education and occupation. These two questionnaires are described in detail in the following sections. Data collected as part of the original parent studies were combined with the online data from the current study to evaluate further clinical variables, including lifetime diagnosis, age of onset and history of hospital admissions.

WHODAS 2.0

The 12-item self-report version of the World Health Organisation Disability Assessment Schedule Version 2 (WHODAS 2.0) was included as a measure of functional outcome [415]. The WHODAS 2.0 asks participants to rate how much

difficulty they have had in the last 30 days completing everyday tasks. It covers six domains of functioning: cognition (understanding and communicating), mobility, self-care, social interactions, life activities (domestic responsibilities, leisure and work) and participation in the community. Items were rated on a difficulty scale from none, mild, moderate, severe to extreme / cannot do and each item is allocated a score of 0-4 based on these respective ratings. The maximum score on the 12-item questionnaire is 48 and higher scores indicate more severe disability.

Participants were asked to record the number of days the difficulties were present in the last 30 days. They were also asked how many days they were either “totally unable” to carry out their activities or had to “cut back or reduce” their activities because of their illness. The primary outcome measure was total score on the 12 items (maximum score of 48).

Education and occupation

Highest educational attainment was separated into seven categories based on educational qualifications in the United Kingdom: 1) 11+ examinations; 2) CSE or equivalent; 3) GCSE or equivalent; 4) A-level or equivalent; 5) degree and 6) post-graduate degree. Occupations were categorised based on the Office for National Statistics’ classifications [416] into the following groups: 1) managers and senior officials; 2) professional occupations; 3) associate professional and technical occupations; 4) administrative and secretarial occupations; 5) skilled trade occupations; 6) personal, sales and customer service occupations; 7) process, plant and machinery operatives and 8) elementary occupations. Participants who were currently employed were asked to indicate if they were working full-time or part-time. Participants who were not working were classified as: 1) unemployed; 2) not working due to sickness and 3) voluntary work.

Data from parent studies

Data on lifetime diagnosis, age of onset and history of hospital admissions were obtained from the parent studies, CoMPaSS and NCMH. The methods for determining lifetime diagnoses have been described in the “Sample” section of this chapter. In CoMPaSS, age of onset was defined as the age at which the participant’s symptoms caused impairment in their life. Impairment was defined as: 1) disruption in work or social life more or less completely, 2) fights or other

violence, 3) job loss or unable to work, 4) police involvement, 5) family separation, 6) hospital admission or 7) receiving specific treatment. This was rated according to participants' responses to the SCAN interview and review of clinical records. In NCMH, participants were asked to report the age at which they first developed mental health problems and the age at which these problems caused impairment in their life. Age of first impairment was taken as the main measure of age of onset. Finally, participants were categorised according to whether they had ever been admitted to a psychiatric unit (yes/no) based on data from CoMPaSS (number of admissions) and NCMH (ever admitted to hospital).

5.3.3 Statistical analysis

All statistical analyses were performed using R version 3.3.0.

Analysis 1: Response rates

Response rates were calculated as the number of participants who completed the study (or at least parts of the study) as a percentage of the total number of participants who were invited. This was further broken down by recruitment strategy to allow specific response rates to be calculated for each parent study and split into email and letter invitations. Response rates were also broken down by diagnostic groups to determine whether participants with certain diagnoses were more likely to take part in the study.

Analysis 2: Demographic and clinical characteristics

Summary statistics or proportions were generated to examine the demographic and clinical characteristics of the internet sample. The variables examined were age, gender, education level, current occupation and currently taking psychiatric medication. In the NCMH cohort, the demographic and clinical characteristics of the participants (N=317) were compared to invited individuals who did not participate in the study (N=3145).

Proportions (gender, occupation, ever admitted to hospital, diagnosis and recruitment method into NCMH) were analysed using chi-square tests. Chi-square was used to examine the proportion of participants who: 1) had a degree and 2) did not have any qualifications. For contingency tables larger than 2x2, standardised residuals were calculated for each cell to determine the strength of the differences

between observed and expected values. Standardised residuals have an approximate normal distribution (mean of 0 and standard deviation of 1) and so can be used to identify cells that contribute to a significant chi-square statistic [417, 418]. Standardised residuals are calculated using the formula:

$$\text{Standardised Residual} = \frac{(\text{Observed cell count} - \text{Expected value})}{\sqrt{\text{Expected value}}}$$

Given that standardised residuals have an approximate normal distribution, they can be interpreted in the same way as z-scores, such that a standardised residual of ± 2 indicates that the cell's observed frequency is significantly less than or greater than expected at $p < 0.05$. A more conservative cut-off was selected for the standardised residuals of ± 3 to adjust for multiple comparisons. Thus, cells with a standardised residual of greater than 3 or less than -3 were considered significant.

For continuous variables, normal distribution was determined through visual inspection of histograms and an F test was used to compare the variances between the two groups. Age was normally distributed and the variance was homogeneous between groups so a t-test was conducted to compare the groups. Non-normally distributed and ordinal variables (age of onset and education) were analysed using the Wilcoxon rank sum test.

Logistic regression was conducted to determine the association between demographic and clinical variables and participation in the study. The outcome measure was participation in the study, a binary variable coded as "yes" or "no". The predictor variables were diagnosis, recruitment method into NCMH, age of onset, highest educational attainment and lifetime occupation. Variance inflation factors were calculated to identify collinearity between the predictors.

Analysis 3: Completion rates

Completion rates were calculated for each individual task. Completion rates were also calculated for each diagnostic group. Participants were grouped into three categories based on the number of tasks they had completed: full data (9 tasks, N=224), partial data (1-8 tasks, N=82) or no data (0 tasks, N=36). These three

groups were compared on the following variables: age, gender, HADS depression score, HADS anxiety score, highest educational attainment, diagnosis and WHODAS disability scores.

Proportions (gender and diagnosis) were analysed using chi square tests. Standardised residuals were calculated for each cell to determine the strength of the differences between observed and expected values [417, 418]. Standardised residuals have an approximate normal distribution (mean of 0 and standard deviation of 1) and so can be used to identify cells that contribute to a significant chi-square statistic. A critical value of ± 3 was selected to adjust for multiple comparisons (see above for full details and formula). For the diagnosis variable, 20 out of 39 cells had expected counts under 5 thus violating an assumption of chi-square tests. Therefore, Fisher's exact test was performed in R to produce a simulated p-value [419, 420]. As this method does not produce a chi-square statistic, data was resampled using the Monte-Carlo method and an approximate chi-square statistic and corresponding p-value were calculated [421].

For continuous variables, normal distribution was determined through visual inspection of histograms and Levene's test was used to compare the variances between the groups. Age was normally distributed and the variance was homogeneous between groups so analysis of variance was conducted to compare the groups. Non-normally distributed and ordinal variables (HADS depression scores, HADS anxiety scores, highest educational attainment and WHODAS disability scores) were compared between the three groups using Kruskal-Wallis tests.

Analysis 4: Factor analysis

The structure of the online cognitive battery was examined by conducting correlations between all the tasks. These analyses were followed up with exploratory factor analysis. The number of factors was identified using scree plots and parallel analysis. Principal axis factoring with oblique rotation (direct oblimin) was conducted to identify the factors. These analyses were conducted using all available data collected online to ensure a sufficient sample size and included data collected as part of the validation study (see Chapter 4, total N=382). The analyses were first conducted on all participants with complete data (N=292). Missing data

were then imputed using the methods described in the “Scoring and imputation” section above, and the analyses were repeated (N=321).

The correlations between each online task and measures of ‘g’ taken from scores on the online battery were examined. Measures of ‘g’ were derived for participants who had completed at least 5 tasks (N=321). Principal components analysis (PCA) was conducted including all the online tasks except for the task of interest. For example, in the correlation between ‘g’ and Digit Symbol Coding, ‘g’ was derived by conducting a PCA including all the tasks except Digit Symbol Coding. The first principal component score for each participant was taken as a measure of ‘g’. PCA was conducted on complete data and then repeated including the participants with imputed scores. Classical multidimensional scaling (MDS) was conducted on a Euclidean distance matrix to derive a third measure of ‘g’. MDS is an analogous approach to PCA but an advantage to this approach is that it can accommodate missing data [422, 423]. The ‘g’ derived using MDS was highly correlated with the ‘g’ derived using complete data ($r=0.997$) and the ‘g’ derived including imputed data ($r=0.987$). Correlations were conducted between each task and the three measures of ‘g’. Pearson’s correlations were used when task performance was normally distributed, whilst Spearman’s correlations were used for tasks that were not normally distributed.

5.4 Results

5.4.1 Analysis 1: Response rates

The response rates for each recruitment strategy are shown in Table 5-3. The initial advertisement in the NCMH newsletter resulted in 18 participants completing the study. Between June and September 2017, invitations (emails or letters) were then sent to 3463 individuals who had taken part in NCMH. Participation rates were higher for email invitations than letter invitations (10% and 5% respectively). Letters were sent to 127 individuals from CoMPaSS. The response rate was lower from these participants than NCMH participants (4%) although of note the CoMPaSS sample were recruited up to 10 years ago in comparison to 5 years for NCMH. Forty-one individuals responded to express an interest in the study but did not have access to the internet. The majority of these individuals lived in areas outside of Cardiff (N=32) so were unable to travel to participate in a clinical testing

room within the Division of Psychological Medicine and Clinical Neurosciences at Cardiff University and did not take part in the study. The remaining nine participants were located within the city of Cardiff. Of these nine individuals, one participated in the study by accessing the internet using facilities at a local community centre and the remaining eight individuals did not take part because they did not wish to travel (N=2), wanted to be re-contacted at a later date (N=1), could not be contacted due to an incorrect telephone number (N=1) or did not respond to attempts to contact them (N=4).

In total, 324 participants consented to the study from invitations. Therefore, the total number of participants was 342 once the 18 participants who responded to the newsletter advertisement are included. The sample included 297 participants with a mental health diagnosis and 45 healthy controls.

Table 5-3 Response rates broken down by recruitment strategy

Recruitment Method	Number of invitations sent	Number of refusals	Number of interested participants without internet¹	Number of participants consented	Response rate
NCMH Emails	2772	3	N/A	288	10%
NCMH Letters	691	43	40	31	5%
CoMPaSS Letters	127	5	1	5	4%
Total	3590	51	41	324	9%

¹Of these individuals, one participant was consented into the study

The response rates were broken down by diagnostic categories for participants recruited from the NCMH sample, as these participants have a variety of psychiatric diagnoses (see Table 5-4). Diagnoses were ascertained from participants' responses to the question, "Has a doctor or health professional ever told you that you have any of the following diagnoses?" Participants were given a list of diagnoses and asked to indicate all diagnoses that apply. They were then asked to indicate which of the diagnoses they have ticked would they consider to be their primary, secondary and tertiary diagnoses and whether their doctor would agree with this. Only primary diagnoses are included in this analysis. Of the 3463 participants who were sent invitations, 3457 either reported that they had been given a diagnosis by a health professional or were healthy controls. The diagnoses of the remaining six participants were listed as "unknown". The highest response rates were observed for participants with obsessive-compulsive disorder, although only a small number of participants with this disorder were invited. Other groups with high response rates included the healthy controls and participants with anxiety disorders, personality disorders and eating disorders. Participants with schizophrenia, other psychotic disorders and post traumatic stress disorder had the lowest response rates.

Table 5-4 Response rates for participants sent invitation emails or letters from NCMH

Diagnosis	Number of invitations sent	Number of participants consented	Response rate
Healthy controls	250	44	17.6%
Unipolar mood disorders ¹	1031	94	9.1%
Bipolar spectrum disorders ²	861	85	9.9%
Schizophrenia spectrum disorders ³	355	15	4.2%
Post traumatic stress disorder	321	18	5.6%
Anxiety disorders ⁴	179	20	11.2%
Autism spectrum disorders ⁵	96	10	10.4%
Attention deficit hyperactivity disorder	77	7	9.1%
Personality disorders ⁶	67	9	13.4%
Other psychotic disorders ⁷	52	1	1.9%
Eating disorders ⁸	40	5	12.5%
Obsessive compulsive disorder	22	5	22.7%
Other psychiatric disorders ⁹	106	6	5.7%
Total	3457	319	9.2%

¹Single episode or recurrent major depressive disorder and depressive disorder not otherwise specified (NOS);

²Bipolar disorder type I, type II, manic or hypomanic episode, cyclothymia and bipolar NOS; ³Schizophrenia and schizoaffective disorder; ⁴Panic disorder, agoraphobia, specific phobias, social phobias, generalised anxiety disorder, anxiety NOS; ⁵Autism, Asperger's syndrome; ⁶Borderline personality disorder and other personality disorders; ⁷Delusional disorder, psychosis NOS, substance induced psychotic disorder; ⁸Anorexia, bulimia, binge eating disorder and eating disorder NOS; ⁹This category included invited participants rated as having a behavioural or developmental disorders with onset in childhood or adolescence (N=18), Alzheimer's or other types of dementia (N=17), Parkinson's disease (N=1), intellectual disability (N=4), organic psychosis (N=2), other psychiatric disorder (N=39), other mood disorder (N=6), other psychological illness (N=7), alcohol misuse or dependence (N=6), mood disorder in pregnancy (N=1), post natal depression (N=3) or tic disorder (N=2).

The NCMH has been recruiting participants since 2012 so response rates were further broken down by year of participation (see Figure 5-1). Response rates were higher for participants who had taken part in NCMH in the last two years (2016: 10.7%; 2017: 11.4%).

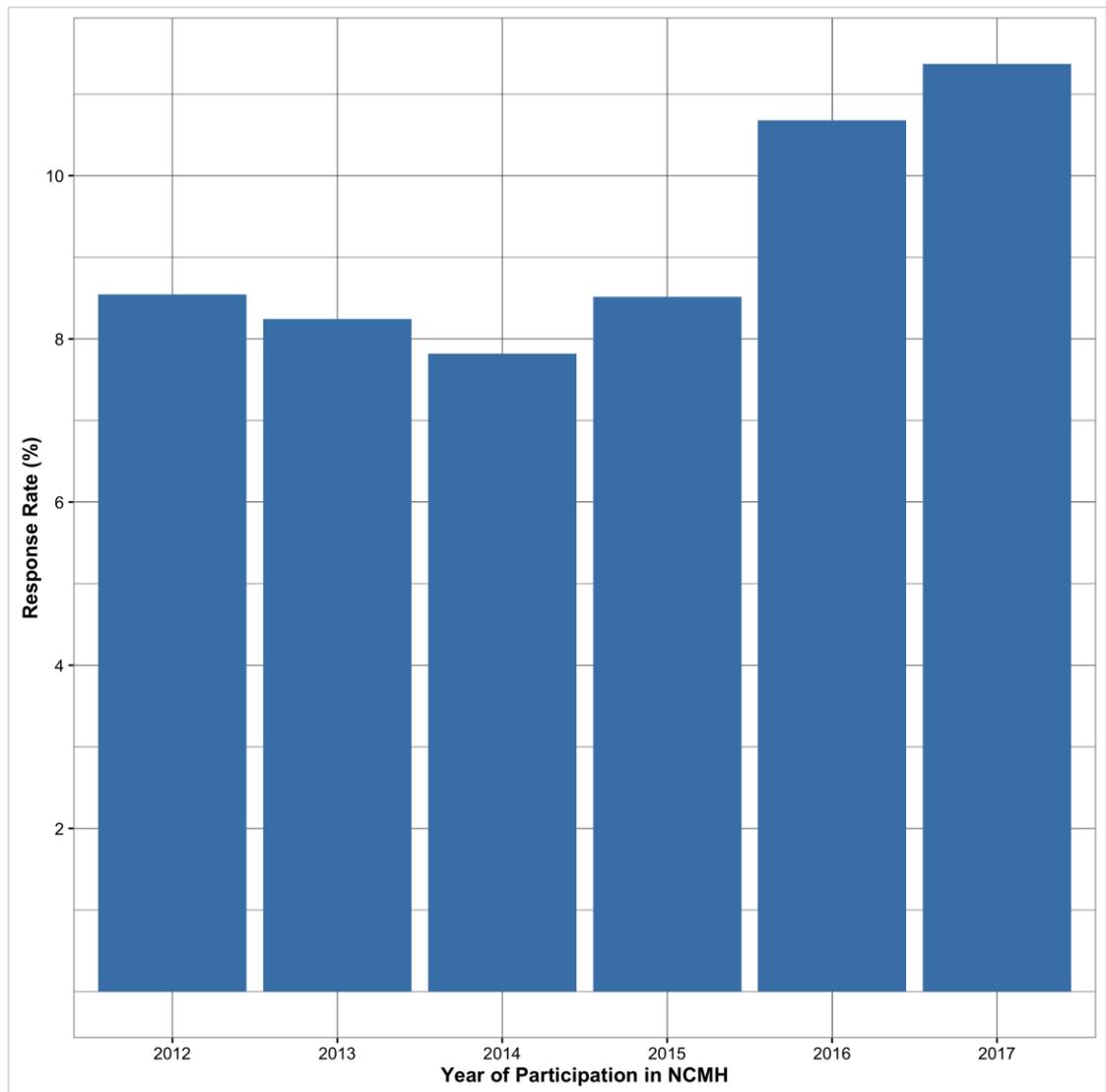


Figure 5-1 Response rate by year of participation in NCMH

5.4.2 Analysis 2: Demographic and clinical characteristics

The demographic and clinical characteristics of the cases and controls are shown in Table 5-5. The age range of the internet sample was 18 to 83 years old (mean=46.95, standard deviation=14.77). Most participants were female (64%). The percentage of participants that were educated to at least degree level was 41%. Almost half of the participants (43%) were in paid employment at the time of assessment. Current occupations were varied with the largest proportion of employed participants working in professional roles (18%). Of those in employment (N=162), 65% worked full time. The remaining participants were mainly retired (17%) or not working due to sickness or disablement (18%).

Table 5-5 Characteristics of the internet sample

Demographic and Clinical Characteristics	Cases	Controls
N	297	45
Age	46.4 (14.1)	50.6 (18.4)
Number of females (% Female)	191 (64.3)	29 (64.4)
Number of participants currently taking psychiatric medication (%)	232 (78.1)	N/A
Highest qualification		
None	11	0
11+	1	0
CSE or equivalent	13	0
GCSE or equivalent	43	1
A-level or equivalent	89	9
Degree	72	17
Postgraduate degree	36	14
Other	13	2
Current occupation		
Senior official	5	1
Professional	42	18
Technical	18	2
Administration	18	4
Service work	19	1
Trade work	5	2
Factory or plant work	1	0
Elementary occupation	2	0
Not working due to sickness	56	1
Full-time student	23	3
Homemaker	15	0
Unemployed	17	1
Voluntary work	15	0
Retired	43	10

N/A: not applicable

Given the majority of those who participated originated from the NCMH cohort, NCMH participants were chosen to examine whether those that participated differed from non-responders. These analyses were conducted amongst cases only and then repeated in the sample of healthy controls.

Cases

The demographic and clinical characteristics of the NCMH participants (N=275) were compared to invited individuals from the NCMH cohort who did not participate in the study (N=2936, see Table 5-6). Participants who consented to the study did not differ from non-participants in age ($t(3205)=-0.24$, $p=0.81$) or gender ($\chi^2(1)=1.59$, $p=0.21$). There were differences in the proportion of diagnoses between the two groups ($\chi^2(11)=28.9$, $p=0.002$). Examination of the standardised residuals indicated the participant group had fewer participants with schizophrenia spectrum disorders (standardised residual = -3.1) than would be expected. The groups differed on lifetime occupation ($\chi^2(8)=29.9$, $p=2.2 \times 10^{-4}$). In the participant group, there were more participants who had worked in a professional occupation than would be expected (standardised residual = 4.3). There was a significant difference in highest educational attainment between the participant and non-participant groups (Wilcoxon (3351)= 4413331, $Z=-3.8$, $p=1.5 \times 10^{-4}$). A higher proportion of the participant group had a degree (42%) compared to the non-participant group (34%, $\chi^2(1)=6.72$, $p=0.01$). A lower proportion of the participant group did not have any qualifications (4%) compared to the non-participant group (10%, $\chi^2(1)=7.77$, $p=0.005$). Methods of recruitment into the original NCMH study were compared and indicated differences between the two groups ($\chi^2(9)=35.21$, $p=5.5 \times 10^{-5}$). A higher proportion of the participant group had been recruited through the media (standardised residual = 3.62) and referrals from other research studies (standardised residual = 3.05) and fewer participants had been recruited from secondary and specialist psychiatric services (standardised residual = -3.98) than the non-participant group. There were no differences in the proportion of participants who had ever been admitted to hospital between the groups (36%, $\chi^2(1)=1.24$, $p=0.27$). Participants had a younger age of onset than non-participants, which was marginally significant (Wilcoxon (3010)=363081, $Z=-2.21$, $p=0.03$).

Diagnosis, method of NCMH recruitment, highest educational attainment, lifetime occupation and age of onset were entered as predictors in a logistic regression with participation as the outcome measure. In this model, diagnosis, age of onset, educational levels and occupations were not associated with participation. Participants who had been recruited into NCMH through secondary or specialist psychiatric services were less likely to participate than participants recruited through media advertisements (OR=0.62, 95% CIs: 0.43-0.88, p=0.008).

Table 5-6 Demographic and clinical characteristics of participants and non-participants from NCMH

Demographic and Clinical Characteristics	Participants	Non-participants
N	275	2936
Age	46.9 (14.3)	46.6 (14.2)
Number of females (%)	178 (64.7)	1789 (60.9)
Highest qualification		
None	12	282
11+	1	29
CSE or equivalent	3	97
GCSE or equivalent	46	582
A-level or equivalent	94	901
Degree	79	652
Postgraduate degree	30	251
Lifetime occupation		
Senior official	15	182
Professional	87	602
Technical	53	476
Administration	34	408
Service work	57	789
Trade work	10	144
Factory or plant work	2	72
Elementary occupation	5	56
Never worked due to sickness ¹	0	28
Never worked ¹	1	25
Voluntary work ¹	0	28
Diagnoses		
Unipolar mood disorders ²	94	937
Bipolar spectrum disorders ³	85	776
Schizophrenia spectrum disorders ⁴	15	340
Post traumatic stress disorder	18	303
Anxiety disorders ⁵	20	159
Autism spectrum disorders ⁶	10	86
Attention deficit hyperactivity disorder	7	70
Personality disorders ⁷	9	58
Other psychotic disorders ⁸	1	51
Eating disorders ⁹	5	35
Obsessive compulsive disorder	5	17
Other psychiatric disorders ¹⁰	6	100
Number of participants with ≥1 admission (%)	90 (32.7)	1055 (35.9)
Age of Onset¹¹	16 (14)	18 (15)

Numbers indicate mean and standard deviation for continuous data, counts are shown for highest qualification (ordinal data) proportion data. ¹These groups were combined into a “Never worked” group for analyses; ²Single episode or recurrent major depressive disorder and depressive disorder NOS; ³Bipolar disorder type I, type II, manic or hypomanic episode, cyclothymia and bipolar NOS; ⁴Schizophrenia and schizoaffective disorder; ⁵Panic disorder, agoraphobia, specific phobias, social phobias, generalised anxiety disorder, anxiety NOS; ⁶Autism, Asperger’s syndrome; ⁷Borderline personality disorder and other personality disorders; ⁸Delusional disorder, psychosis NOS, substance induced psychotic disorder; ⁹Anorexia, bulimia, binge eating disorder and eating disorder NOS; ¹⁰Full details of this category can be found in the “Diagnostic categories” on page 209; ¹¹Median and interquartile range shown due to non-normal distribution

Controls

The demographic and clinical characteristics of the healthy control participants from NCMH (N=44) were compared to invited healthy controls from the NCMH cohort who did not participate in the study (N=206, see Table 5-7). Participants who consented to the study did not differ from non-participants in gender ($\chi^2(1)=1.3 \times 10^{-30}$, $p=1$) or lifetime occupation ($\chi^2(8)=6.93$, $p=0.53$). The groups differed in age ($t(248)=-2.64$, $p=0.009$), as the mean age of the participant group was older than the non-participant group. There was a significant difference in highest educational attainment between the participant and non-participant groups ($W(3351)=20305$, $Z=-2.49$, $p=0.01$). A higher proportion of the participant group had a degree (71%) compared to the non-participant group (50%, $\chi^2(1)=5$, $p=0.03$).

Table 5-7 Demographic and clinical characteristics of participants and non-participants from NCMH (healthy controls)

Demographic and Clinical Characteristics	Participants	Non-participants
N	44	206
Age	50.9 (18.3)	43.5 (16.4)
Number of females (%)	29 (65.9)	138 (67)
Highest qualification		
None	0	3
11+	0	1
CSE or equivalent	1	3
GCSE or equivalent	1	18
A-level or equivalent	10	68
Degree	20	68
Postgraduate degree	8	22
Lifetime occupation		
Senior official	7	17
Professional	14	55
Technical	7	33
Administration	7	23
Service work	5	46
Trade work	0	2
Factory or plant work	0	1
Elementary occupation	0	3
Never worked due to sickness ¹	0	0
Never worked ¹	0	1
Voluntary work ¹	0	1

Numbers indicate mean and standard deviation for continuous data, counts are shown for highest qualification (ordinal data) and proportion data. ¹These groups were combined into a "Never worked" group for analyses.

5.4.3 Analysis 3: Completion rates

In total, 342 participants were consented into the study and completed the first stage (questionnaire). Of these participants, 306 completed at least 1 cognitive task. Of the 306 participants who completed any cognitive tasks, 35 participants completed the tasks over at least two separate days. Completion rates for each task can be found in Table 5-8. Overall, complete data was available for 224 participants (65.5%), partial data was available for 82 participants (24%) and 36 participants did not complete any tasks (10.5%). Figure 5-2 shows the completion rates for each task in order of administration, including the learning phase of the Verbal Paired Associates task. The largest loss of participants is between the Digit Symbol Coding and the learning phase of the Verbal Paired Associates where 21 participants discontinued. The second largest drop off point was between the Balloon Analogue Risk Task and Multiple Object Tracking where 15 participants discontinued.

Table 5-8 Completion rates for the cognitive tasks

Task	Number of Participants	Percentage of Missing Data
Digit Symbol Coding	302	12
Morphed Emotion Identification Task	271	21
Verbal Paired Associates Task	265	23
Backward Digit Span	257	25
Hartshorne Visual Working Memory	248	28
Matrix Reasoning Test	244	29
Balloon Analogue Risk Task	244	29
Multiple Object Tracking	229	33
Vocabulary	234	32

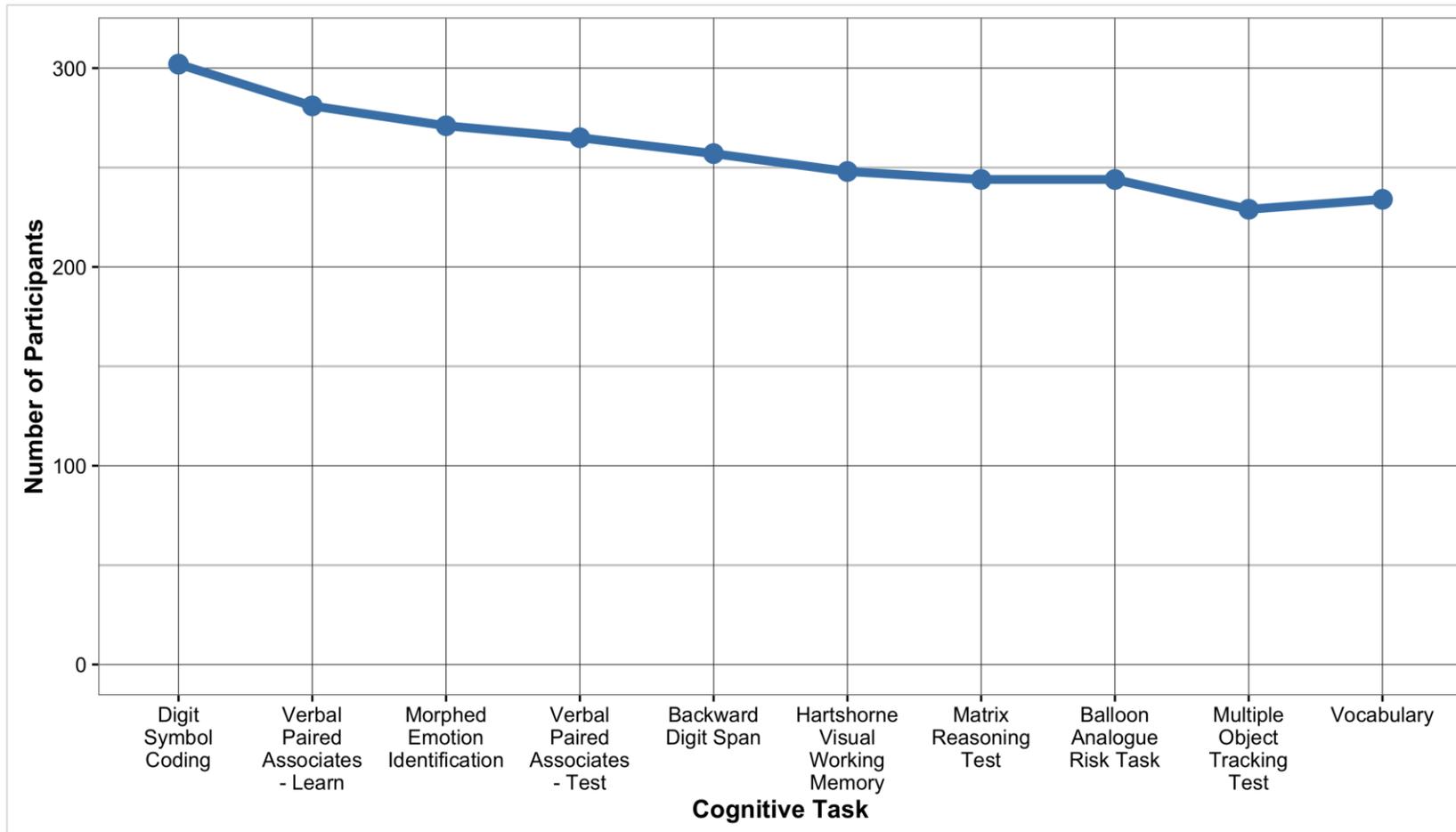


Figure 5-2 Completion rates for each task in order of administration

Verbal Paired Associates – Learn and Verbal Paired Associates – Test refer to the learning and test phases of the Verbal Paired Associates task respectively

Table 5-9 displays completion rates broken down according to diagnostic categories. The diagnostic groups did not differ on proportions of participants with complete, partial or no data ($\chi^2(24)=26.04$, $p=0.36$; *Fisher's exact test*: $p=0.49$).

Table 5-9 Completion rates by diagnostic group

Diagnosis	N	Complete Data Available (%)	Partial Data Available (%)	No Data Available (%)
Healthy controls	45	28 (62.2)	10 (22.2)	7 (15.6)
Unipolar mood disorders ¹	100	67 (67)	24 (24)	9 (9)
Bipolar spectrum disorders ²	87	54 (62.1)	28 (32.2)	5 (5.7)
Anxiety disorders ³	20	13 (65)	4 (20)	3 (15)
Post traumatic stress disorder	20	12 (60)	4 (20)	4 (20)
Schizophrenia spectrum disorders ⁴	24	18 (75)	3 (12.5)	3 (12.5)
Autism spectrum disorders ⁵	10	6 (60)	4 (40)	0 (0)
Personality disorders ⁶	10	8 (80)	1 (10)	1 (10)
Other psychiatric disorders ⁷	6	6 (100)	0 (0)	0 (0)
Attention deficit hyperactivity disorder	7	4 (57.1)	2 (28.6)	1 (14.3)
Eating disorders ⁸	6	4 (66.7)	1 (16.7)	1 (16.7)
Obsessive compulsive disorder	6	4 (66.7)	1 (16.7)	1 (16.7)
Other psychotic disorders ⁹	1	0 (0)	0 (0)	1 (100)
Total	342	224 (65.5)	82 (24.0)	36 (10.5)

¹Single episode or recurrent major depressive disorder and depressive disorder NOS; ²Bipolar disorder type I, type II, manic or hypomanic episode, cyclothymia and bipolar not otherwise specified (NOS); ³Panic disorder, agoraphobia, specific phobias, social phobias, generalised anxiety disorder, anxiety NOS; ⁴Schizophrenia and schizoaffective disorder; ⁵Autism, Asperger's syndrome; ⁶Borderline personality disorder and other personality disorders; ⁷Participants were rated as having an "other psychiatric disorder" (N=3), "other mood disorder" (N=1), postnatal depression (N=1) and Alzheimer's disease (N=1). More details on this category can be found in "Diagnostic categories" on page 209; ⁸Anorexia, bulimia, binge eating disorder and eating disorder NOS; ⁹Delusional disorder, psychosis NOS, substance induced psychotic disorder

Participants were grouped into three categories based on the number of tasks they had completed: full data (9 tasks, N=224), partial data (1-8 tasks, N=82) or no data (0 tasks, N=36). The three groups did not differ on age ($F(2,339)=0.93$, $p=0.4$), HADS depression score ($H(2)=1.86$, $p=0.4$), HADS anxiety score ($H(2)=0.72$, $p=0.7$), highest educational attainment ($H(2)=1.8$, $p=0.41$) or WHODAS disability scores ($H(2)=1.73$, $p=0.42$). However, there was a significant effect of gender ($\chi^2(2)=6.32$, $p=0.04$), as fewer males and more females had full data than would be expected.

Technical difficulties

All participants who did not complete the full battery were contacted via email and asked if they had experienced technical difficulties. Eleven participants reported technical difficulties with completing the cognitive tasks. Four participants reported the same issue so eight technical issues were reported in total. The issues reported are shown in Table 5-10. Three of the eight technical issues were resolved at the time of writing. One of the issues reported was due to the participants responding using the mouse instead of the keyboard. Another issue was resolved by adjusting the cookie settings on the participant's browser and another was resolved after the participant reloaded the tasks and tried using different keys on their keyboard. Three of the eleven participants were using touchscreen devices. Of the participants who reported technical difficulties, eight participants went on to complete all the tasks, two participants completed additional tasks and one participant did not complete any more tasks.

Table 5-10 Technical difficulties reported by participants

Problem Reported	Resolved or Ongoing?	Number of Participants	Touchscreen Device?	Solution
Participant was being redirected to the main “testmybrain.org” domain.	Resolved	1	No	The cookie settings on the participant’s browser needed to be turned on.
Tasks were not responding to touchscreen presses on Samsung Galaxy phone.	Ongoing	1	Yes	Unable to obtain further information from participant.
Digit Symbol Coding was not responding to mouse.	Resolved	1	No	Participants needed to use the keyboard rather than the mouse.
Address bar on browser was partially obstructing the view of the tasks.	Ongoing	1	Yes	Developers unable to locate the issue and may have been a specific setting on the participant’s phone.
Tasks were not responding to participant’s keyboard	Resolved	1	No	Participant was using the number pad so reloaded and used the other number keys, which worked.
Touchscreen responses would not register on multiple object tracking.	Ongoing	1	Yes	
Digit symbol coding was not responding to keyboard.	Ongoing	4	No	
Verbal Paired Associates task would not load.	Ongoing	1	No	Unable to obtain further information from participant.

When vocabulary was included, examination of the scree plot and parallel analysis indicated 2 factors with eigenvalues above 1. The factor loadings are shown in Table 5-11. All the measures except Vocabulary and Balloon Analogue Risk Task loaded onto the first factor. Only Vocabulary had a high loading on the second factor. The analysis was repeated excluding Vocabulary given the fact this task had low correlations with the other tasks (all $r < 0.25$). Examination of the scree plot and parallel analysis indicated 1 factor with an eigenvalue above 1. However, the second factor had an eigenvalue of 0.95 so principal axis factoring was conducted specifying two factors. The factor loadings are shown in Table 5-11. The Multiple Object Tracking task, Digit Symbol Coding and the Hartshorne Visual Working Memory Test loaded onto the first factor. The Matrix Reasoning Test and Balloon Analogue Risk Task loaded onto the second factor. The results of the factor analysis were similar when imputed data was included (see Table 5-11). The correlations between vocabulary and the other tasks were higher in the dataset with imputed missing values (r ranged between 0.15 and 0.36). When vocabulary was excluded, examination of the scree plot and parallel analysis indicated 1 factor with an eigenvalue above 1.

Table 5-11 Factor loadings of the online tasks

	With Vocabulary		Without Vocabulary		Imputed Data	
	Factor 1	Factor 2	Factor 1	Factor 2	Factor 1	Factor 2
Multiple Object Tracking	0.72	0.04	0.69	0.07	0.73	0.03
Vocabulary	-0.03	0.74			-0.03	0.68
Digit Symbol Coding	0.80	-0.10	0.70	0.10	0.81	-0.07
Morphed Emotion Identification	0.60	0.00	0.39	0.25	0.60	0.03
Hartshorne Visual Working Memory	0.67	-0.15	0.75	-0.11	0.70	-0.16
Matrix Reasoning Test	0.61	0.23	0.13	0.63	0.58	0.27
Backward Digit Span	0.45	0.22	0.27	0.27	0.44	0.20
Verbal Paired Associates	0.41	0.20	0.20	0.29	0.40	0.21
Balloon Analogue Risk Task	0.25	0.30	-0.14	0.52	0.23	0.34
Proportion of variance explained	0.77	0.23	0.65	0.35	0.78	0.22

Loadings >0.4 are shown in bold. PCA: Principal Components Analysis.

Correlations between online tasks and 'g'

In a final analysis, the correlations between each task and measures of 'g' derived from the online battery (excluding the relevant task) were examined. In the complete sample, eight out of nine tasks were correlated with 'g' at the Bonferroni-corrected alpha level of 0.00556 (r ranged from 0.42 to 0.65). These tasks included Digit Symbol Coding ($r=0.65$, 95% CIs: 0.59-0.71), Verbal Paired Associates ($r=0.42$, 95% CIs: 0.31-0.52), Morphed Emotion Identification ($r=0.53$, 95% CIs: 0.44-0.61), Backward Digit Span ($r=0.46$, 95% CIs: 0.37-0.55), Hartshorne Visual Working Memory ($r=0.53$, 95% CIs: 0.46-0.61), Matrix Reasoning Test ($r=0.58$, 95% CIs: 0.50-0.66), Multiple Object Tracking ($r=0.64$, 95% CIs: 0.58-0.70) and the Balloon Analogue Risk Task ($r=0.25$, 95% CIs: 0.13-0.35). The results were equivalent when 'g' was derived using imputed data and MDS (see Table 5-12).

Table 5-12 Correlations between each task and a measure of ‘g’ derived from the online battery

Online Task	PCA – Complete Data			PCA – Including Imputed Values			Multidimensional Scaling		
	r	95% CIs	p	r	95% CIs	p	r	95% CIs	p
Digit Symbol Coding	0.65	0.59-0.71	8.7×10^{-37}	0.67	0.60-0.73	3.6×10^{-42}	0.66	0.60-0.72	2.9×10^{-41}
Verbal Paired Associates*	0.42	0.31-0.52	5.2×10^{-14}	0.43	0.33-0.52	1.1×10^{-15}	0.42	0.33-0.52	5.2×10^{-15}
Morphed Emotion Identification	0.53	0.44-0.61	2.7×10^{-22}	0.54	0.46-0.61	1.3×10^{-25}	0.54	0.45-0.62	7.6×10^{-26}
Backward Digit Span	0.46	0.37-0.55	1.5×10^{-16}	0.47	0.39-0.54	1.2×10^{-18}	0.47	0.38-0.54	1.6×10^{-18}
Hartshorne Visual Working Memory	0.53	0.46-0.61	1.8×10^{-22}	0.54	0.46-0.61	2.3×10^{-25}	0.55	0.48-0.61	3.5×10^{-26}
Matrix Reasoning Test*	0.58	0.50-0.66	5.5×10^{-28}	0.59	0.50-0.66	9.4×10^{-31}	0.59	0.50-0.66	2.1×10^{-30}
Balloon Analogue Risk Task*	0.25	0.13-0.35	1.7×10^{-5}	0.24	0.12-0.34	2.2×10^{-5}	0.24	0.14-0.33	2.5×10^{-5}
Multiple Object Tracking	0.64	0.58-0.70	4.9×10^{-35}	0.64	0.58-0.70	3.1×10^{-36}	0.64	0.58-0.70	4.3×10^{-36}
Vocabulary*	0.14	0.02-0.26	0.02	0.15	0.03-0.26	0.009	0.15	0.03-0.26	0.007

*Spearman’s rank correlation rho shown instead due to non-normal distribution for these tests.

5.5 Discussion

In this chapter, participants from two studies within the MRC Centre for Neuropsychiatric Genetics and Genomics were invited to complete the online cognitive battery. The aims of this chapter were to evaluate whether online cognitive testing is a suitable method for mental health research and to examine the structure of the cognitive battery. Participants with a broad range of psychiatric disorders were invited to take part. The results of the four analyses indicated:

- 1 Response rates were 2-23% across the diagnostic groups. The lowest response rates were observed for participants with schizophrenia, other psychotic disorders and post-traumatic stress disorder (PTSD).
- 2 Comparisons between responders and non-responders indicated differences in diagnoses, lifetime occupations, educational attainment, method of recruitment into NCMH and age of onset. However, the results of logistic regression analysis indicated that only method of recruitment into NCMH predicted participation in the online study.
- 3 Two-thirds of the participants completed all nine tasks in the battery. There were no differences between participants who completed all the tasks and those who did not, except that fewer males had full cognitive data.
- 4 An exploratory analysis of the structure of the battery indicated that the majority of tasks were correlated with one another and the battery could be reduced to two factors.

5.5.1 Recruitment rates and characteristics of the internet sample

The online cognitive battery was an effective method for recruiting a large sample of participants within a short timeframe. During the three-month period of sending invitations (1st June to 30th September 2017), 325 individuals participated in the study. The response rate for participants from CoMPaSS was just 4%, which was lower than the response rate from NCMH. One reason for this may be that the CoMPaSS study has been recruiting participants for ten years (compared to five years of recruitment for NCMH) and therefore participants are more likely to have moved addresses and be difficult to contact. The response rate from participants with schizophrenia in the NCMH sample was 4.2%, which is comparable to the

response rate from participants in CoMPaSS. This suggests that participants with schizophrenia were less likely to participate.

In NCMH, the response rate was 5% for letter invitations and 10% for email invitations. This is lower than the response rates that NCMH have recorded for previous follow-up questionnaires (30-33%). However, the protocol of the online study is more demanding than previous follow-up questionnaires and requires a substantial time commitment (one hour compared to a questionnaire that takes 20 minutes to complete). In addition to this, previous follow-up with participants has been through postal questionnaires and so response rates for letter invitations were expected to be lower in this study due to the requirement of access to a computer and the internet.

The response rates were between 2% and 23% across the diagnostic groups. The lowest response rates were for participants with schizophrenia, other psychotic disorders and PTSD. These results suggest online cognitive testing may be less suitable for recruitment of patients with schizophrenia and PTSD. However, the recruitment methods employed by NCMH were shown to have an effect on participation in the online study. Participants who took part in the online study were less likely to have originally been recruited into NCMH through secondary services and more likely to have been recruited through media campaigns or have been referred to NCMH from another study in the department. Participants recruited through the latter methods may be particularly motivated to take part in research. Most participants with schizophrenia and PTSD in the NCMH sample were originally recruited through secondary psychiatry services or services for veterans. Participants recruited from secondary services may have a more severe illness, which could affect their access to the internet and their ability to use a computer. There is evidence that patients with psychosis are less likely to have access to the internet [270].

An examination of the demographic and clinical characteristics of the participants indicated that these participants were more highly educated and more likely to have worked in professional jobs during their lifetime than invited individuals who did not participate. Lack of money or knowledge of computers and internet have been shown to be barriers to using the internet for patients with psychiatric disorders

[270]. Participants with higher levels of education and professional occupations may be more likely to be able to afford internet access and have computing abilities. However, the results of the logistic regression analysis indicated that recruitment methods but not diagnosis, education or occupation predicted participation in the study. As noted above, recruitment methods may reflect the severity of a participant's illness. Therefore, the differences in education and occupation between participants and non-participants may be explained by differences in illness severity, as patients with a chronic disorder are less likely to be employed or have a high level of education.

The demographic and clinical characteristics of the healthy control group were analysed separately to ensure that differences between participants and non-participants were not driven by the higher proportion of controls in the online study. This also allowed me to assess whether the controls were representative of those included in NCMH. Controls who participated in the online study were older than the non-participants. This may be explained by the fact that 22% of the control participants were retired at the time of the online assessment. Retired individuals may be more willing to allocate time to completing the online study. The participant group was also more educated than the non-participant group. These findings have important implications for the interpretation of any comparisons between cases and controls, as both age and education are associated with cognitive ability.

It should be noted that the recruitment rates reported here are restricted to a given period (1st February to 30th September). Recruitment to the study is ongoing and some of the individuals in the non-participant group will go on to participate in the study. Each participant received one invitation to the study and therefore sending reminders may further enhance recruitment. The response rates of participants with certain diagnoses may also be increased through targeting the recruitment methods; for example, by using language in the emails and letters that targets specific diagnoses. The current invitations refer generally to mental illness, which may lead participants to think that the research may not be applicable to them.

5.5.2 Completion rates of the online cognitive battery

Completion rates give an indication of the tolerability of the cognitive battery. Of the 342 participants that consented to take part in the study, 89% completed at least one task, which is comparable to the 87% reported by Lumsden et al. [410]. Most participants who consented to take part in the study completed all nine tasks in the cognitive battery (66%). This figure is comparable to the completion rates reported by the TED study for their online battery of eight tasks (65%), although the study assessed children [274]. This figure is lower than those reported for face-to-face cognitive studies of participants with psychiatric disorders [389, 411]. However, a lower completion rate was expected given that the participants are unsupervised because they would not have the encouragement from a research assistant to continue with the study, would not have assistance if they have questions or encounter problems and therefore they be more likely to leave the study early.

There were three main drop-off points in the study: before the first task, after the first task and between the Balloon Analogue Risk Task and Multiple Object Tracking. Once a participant has completed the first task, they have a better understanding of what is involved in taking part in the study and may decide at that point that they do not wish to continue. It takes approximately 35-40 minutes to complete all tasks up to and including the Balloon Analogue Risk Task. Forty minutes may be the maximum amount of time that a proportion of the participants were willing or able to tolerate the tasks. Therefore, the third drop-off point may be the result of fatigue. Alternatively, aspects of certain tasks may discourage participants from continuing, although feedback from participants in the validation study did not indicate this (see Chapter 4). Another potential explanation for the loss of participants is technical issues. All participants who did not complete the tasks were contacted by email and asked if they had experienced any technical issues. Eleven participants reported issues with the website. Five participants reported problems with the first task, Digit Symbol Coding. This may explain why some participants did not complete any of the tasks. If a participant encountered a problem with the first task, then they may be discouraged from continuing with the study. One participant reported that the second task, Verbal Paired Associates, would not load and another reported a problem with inputting responses on the Multiple Object Tracking. If more participants had encountered these issues, then

this may explain the second and third drop-off points. However, it should be noted that the number of technical issues reported was small and technical issues are to be expected given the vast number of different devices and hardware, operating systems and internet browsers that the website needs to be compatible with. Despite the diverse range of devices used, the majority of participants completed all the tasks and eight of the eleven participants who reported technical difficulties went on to complete all the tasks.

There were no differences in the clinical and demographic characteristics of participants who completed the full battery and those who did not, with the exception that fewer males had full data than would be expected. Completion rates were comparable across the diagnostic groups suggesting that participants with a variety of mental health diagnoses do not differ in their ability to tolerate the battery. Levels of disability were also similar between participants with full, partial or no cognitive data suggesting that more severe disability is not a barrier to completing the tasks once the participants has started. However, it is possible that participants with the most severe levels of disability do not participate in the study but data on disability in the non-participant group was not available so this could not be assessed.

5.5.3 Factor structure of the online cognitive battery

An exploratory factor analysis was conducted to examine the structure of the battery and identify separable domains. There was evidence that the tasks loaded onto two factors. The first factor included all the tasks except Vocabulary, which uniquely loaded onto the second factor. This first factor explained a high proportion of the variance (77%), which is consistent with previous studies showing that a large proportion of the variance in cognitive performance can be explained by a single factor [206, 412]. Vocabulary is a verbal task and was designed to assess crystallised intelligence, whilst the remaining tasks are predominantly nonverbal tasks designed to assess fluid intelligence. This may explain the low correlations between this task and all other online tasks. When Vocabulary was excluded, the tasks loaded onto two factors. The first factor explained 65% of the variance in cognitive scores. Multiple Object Tracking, Digit Symbol Coding and Hartshorne Visual Working Memory loaded onto the first

factor. There are similarities between these three tasks; in particular, all three tasks require attention and memory for abstract objects [195, 374, 376]. Visual scanning and tracking abilities are also required to complete these tasks [195, 374, 376]. Matrix Reasoning and Balloon Analogue Risk Task loaded onto the second factor. Both tasks assess executive processes, including reasoning and strategic problem solving [375, 424].

The tasks in the online battery loaded predominantly onto a single factor, whereas studies have shown that tasks from the MCCB load onto three or seven factors [390-392]. Results from the validation study showed that each online task was correlated with multiple tasks from the MCCB, not just tasks measuring the same domain of cognition. Taken together, these results confirm the non-specificity of many of the tasks in the online battery and suggest that it may be more suitable as a general measure of cognitive function (similar to the BACS) rather than a comparable online version of the MCCB.

Most of the tasks were at least moderately correlated with three measures of general cognitive function ($r > 0.4$), with the exceptions of Balloon Analogue Risk Task ($r = 0.24-0.25$ across three measures of 'g') and Vocabulary ($r = 0.14-0.15$ across three measures of 'g'). This is consistent with research showing that cognitive tasks are related to a higher order factor of general cognitive ability ('g') [204, 205]. The finding that Balloon Analogue Risk Task is not correlated with 'g' mirrors the findings of Chapter 4, which showed a low correlation between this task and a measure of 'g' derived from the MATRICS Consensus Cognitive Battery. As noted in Chapter 4, Balloon Analogue Risk Task is a behavioural measure rather than a cognitive measure. This could explain the low correlations found between this task and measures of 'g', as well as low correlations between this task and other tasks in the online battery (r ranged between 0.13 and 0.31).

Given that a high proportion of the variance in the online battery was explained by a single factor ('g'), a shorter version of the battery may be suitable for assessing cognition whilst reducing the amount of missing data. The task with the highest correlations with measures of 'g' was Digit Symbol Coding ($r = 0.65-0.67$). This relatively simple task has been shown to be a robust measure of cognitive function [195]. Its short administration time and previous studies indicating a relationship

between this measure and functional outcome [368, 369] suggest this measure would be a strong contender for inclusion in a brief version of the battery. The second highest correlations were observed for the Multiple Object Tracking ($r=0.64$). This task may be beneficial for keeping participants engaged as it measures active attention and was selected as the best task by a quarter of participants in Chapter 4. Therefore, it is another potential candidate for inclusion in a brief battery. Three other tasks had correlations greater than $r=0.5$ with measures of 'g': Matrix Reasoning Test ($r=0.58-0.59$), Morphed Emotion Identification ($r=0.53-0.54$) and Hartshorne Visual Working Memory ($r=0.53-0.55$). Future research should examine the relationship between each of these tasks and functional outcome. This will further inform which tasks would be most beneficial to include in a briefer version of the battery. However, it should be noted that the online battery in its current form has been validated against the MATRICS Consensus Cognitive Battery and the psychometric properties of a brief version of the battery would need to be evaluated.

5.5.4 Generalizability of the results

The results presented in this chapter highlight a number of important issues about the generalizability of findings from online cognitive testing in psychiatric samples. The response rate was lower from participants with schizophrenia, which indicates that online cognitive testing may not be suitable for this patient group. Future studies should examine the characteristics of their sample when recruiting participants with schizophrenia using online methods to determine whether the sample is representative of patients with schizophrenia, particularly given the findings here that the online sample was more highly educated and more likely to be professionals. These latter findings highlight further issues with the representativeness of the online sample and suggest that participants recruited using online cognitive testing may be less likely to be cognitively impaired. This could potentially lead to studies under-estimating the degree of cognitive impairment in patients with these disorders. The finding that differences in recruitment methods between the online and NCMH cohort can account for differences in diagnosis, education and occupation does not diminish the issue with recruitment bias in this sample. However, it suggests that sample representativeness may be improved through employing better recruitment

strategies, such as utilising online testing methods in clinical settings to recruit the most difficult to reach participants. This strategy would eliminate the need for all participants to have access to the internet and a computer but reintroduces some of the problems associated with traditional cognitive studies, such as travel and expenses.

5.5.5 Concluding statements

This study has demonstrated that it is possible to use online cognitive testing to gather a large sample of data for mental health research within a relatively short timeframe. A strength of the study is the availability of demographic and clinical data on individuals who did not participate. This allowed me to identify factors that may impact participation in an online cognitive study. Invitations were sent to participants with a range of diagnoses from NCMH, so it was possible to examine the response rates across diagnoses.

Several limitations should be noted. Missing data was an issue for the factor analysis, as 24% of participants were missing data for at least one task. The analysis was repeated with imputed scores, but imputation assumes that data is missing at random and can affect the statistical properties of the data, such as mean and variance [425]. However, the results were similar when the factor analysis was conducted with complete data and with imputed scores. The online sample was compared to the NCMH sample but NCMH will also have ascertainment bias so these results do not indicate how representative the online sample is compared to the wider population of patients with psychiatric disorders. It should be noted that the NCMH has been recruiting participants since 2012 so data may be out of date for some participants. For example, participants may have gone on to obtain a higher qualification or have had a hospital admission since they participated in the NCMH study. It is also possible that invited individuals did not respond because they did not receive their invitation due to a change in contact details. Invitations were sent to over 3500 people, so it was not possible to contact each individual and confirm they had received their invitations. The NCMH study consists of a brief interview (30 minutes) so another interpretation of these results is that individuals who took part in the online study are simply more likely to take part in more in-depth, longer studies. Even if this is the case, the results indicated that online

participants are largely representative of the original cohort, except for fewer participants with schizophrenia and PTSD. Therefore, online cognitive testing appears to be a suitable method for research of most psychiatric disorders. However, if participants with schizophrenia and PTSD are discouraged from taking part due to length of the study rather than the fact it is online, then recruitment rates within these groups may be higher with a brief cognitive battery. This should be explored in future research. A final limitation is that there were an insufficient number of participants from the CoMPaSS study (N=5) to compare the demographic and clinical characteristics of these participants to the original CoMPaSS cohort. This was due to a smaller response rate (4%) and the fact that recruitment from this study was in the initial stages at the time of writing. Recruitment from this study is ongoing and there will be sufficient numbers to examine the characteristics of this sample in the future.

In conclusion, this chapter describes the recruitment of 342 participants to complete an online cognitive battery. There was evidence of differences in the diagnoses between those who participated and those who did not. Online cognitive testing may not be suitable for recruiting patients with schizophrenia and PTSD, although it is possible that more targeted recruitment strategies or a shortened version of the battery may encourage individuals with schizophrenia and PTSD to participate in the study. This should be examined in future research. Rates of participation amongst other diagnoses were higher suggesting that online cognitive testing is effective for recruiting large samples of participants with a range of psychiatric disorders, including bipolar disorders, unipolar depressive disorders, anxiety disorders, eating disorders and personality disorders. The battery was well tolerated with most participants completing all the tasks. There were no differences between participants who completed all the tasks and those who did not, except that fewer males had full cognitive data. An examination of the structure of the battery indicated a high proportion of the variance in cognitive performance across tasks was accounted for by the first factor. A brief version of the battery could improve participation rates further and may be particularly beneficial for males who were less likely to complete the full version of the battery. The most promising tasks for a shorter version of the battery included Digit Symbol Coding,

Multiple Object Tracking, Matrix Reasoning Test, Morphed Emotion Identification and Hartshorne Visual Working Memory.

Chapter 6: Examining Cognition across Psychiatric Disorders using an Online Cognitive Battery

6.1 Introduction

Psychiatric disorders are leading causes of disability worldwide with schizophrenia, bipolar disorder and major depressive disorder ranked in the top ten disabling conditions in young people [37, 38]. Current treatments have shown efficacy in alleviating affective and psychotic symptoms, but patients continue to exhibit impairment in social and occupational functioning. The presence of cognitive impairments has been established in patients with schizophrenia [191] and bipolar disorder [238]. These impairments have been shown to predict functional outcome [182, 183]. There is emerging evidence of cognitive impairments in patients with major depressive disorder, although effect sizes are smaller than those reported in meta-analyses of schizophrenia and bipolar disorder [426-429]. Like bipolar disorder and schizophrenia, these deficits persist during periods of remission [428, 429] and are apparent in patients experiencing their first episode of depression [427]. Few studies have examined the relationship between cognitive deficits and functional outcomes in major depressive disorders but there is evidence that cognitive dysfunction is associated with poor occupational outcomes [430].

To date, few studies have compared the nature and extent of cognitive impairments between major depressive disorder, bipolar disorder and schizophrenia or examined the impact of these impairments on functional outcomes across these three disorders. In a study of older adults (50 years or older) examining the effects of gender and diagnosis on cognition, males with bipolar disorder and females with depression performed better in memory tasks and had better overall cognitive function than males with schizoaffective disorder and females with schizophrenia [311]. Higher performance on cognitive tasks was associated with better social skills in the schizophrenia and depression groups but not in the bipolar disorder group. Another study found that participants with schizophrenia exhibited poorer performance on memory tasks than participants with depression [431]. There were no other differences between participants with schizophrenia, other psychotic disorders, bipolar disorder or depression, although all participants were currently

hospitalised. One study of participants with a first episode of schizophrenia, psychotic bipolar disorder or psychotic depression found similar cognitive profiles between the groups [432]. All diagnostic groups were impaired compared to controls. Participants with schizophrenia exhibited the poorest performance on cognitive tasks relative to controls. Performance in the bipolar disorder and depression groups was intermediate between healthy controls and schizophrenia. There were no differences between participants with bipolar disorder and depression. However, all participants had a lifetime history of psychosis, which has been associated with poorer cognitive function [241, 324, 433]. Similar findings were reported in a longitudinal study of adolescents and young adults (aged 12 to 35 years) with recent-onset psychosis, bipolar disorder or depression [186]. Participants with psychosis were more cognitively impaired than participants with bipolar disorder and depression, whilst participants with bipolar disorder and depression did not differ on any cognitive measure. Participants were reassessed between 12 and 36 months after their initial assessment. Improved verbal memory and sustained attention were associated with greater reductions in disability.

Cognitive function is impaired in some but not all patients with major depressive disorder, bipolar disorder and schizophrenia. For example, one study estimated that 16-45% of those with schizophrenia, 42-64% of those with bipolar disorder and 42-77% of those with major depressive disorder in their sample could be defined as cognitively normal [314]. Thus, there is individual variation within each diagnostic group. However, previous studies comparing cognitive function between these disorders have not included potential explanatory factors as covariates or explored the associations between clinical factors and cognition across disorders [186, 311, 431, 432]. Clinical factors that have been shown to be associated with cognitive performance in previous studies are summarised in Table 6-1.

Table 6-1 Clinical variables associated with poorer cognitive performance

Major Depressive Disorder	Bipolar Disorder	Schizophrenia
History of psychosis [433]	History of psychosis [241]	Earlier age of onset [438]
More severe depressive symptoms [426, 434]	More severe depressive symptoms [258, 435]	More severe negative symptoms [358, 439, 440]
Late onset (after 50 years old) [429]	Earlier age of onset [436] Longer duration of illness [258, 436, 437] Higher number of episodes and hospitalisations [436] Antipsychotic medication after accounting for psychotic symptoms [258, 346, 435, 437]	More severe depressive symptoms [363]

In the current study, the associations between three clinical variables and cognitive function across disorders were examined: age of onset, depressive symptoms and anxiety symptoms. Current depressive symptoms and age of onset have been shown to be associated with cognitive function in all three disorders but these variables are not well studied in a cross-disorder sample. An earlier age of onset has been found to be associated with more severe cognitive impairments in studies of bipolar disorder [436] and schizophrenia [438]. Conversely, late onset (after 50 years old) has been shown to be associated with lower cognitive performance in participants with depression [429]. More severe depressive symptoms have been found to be associated with more severe cognitive impairments in studies of major depressive disorder [426, 434] and bipolar disorder [258, 435]. There is conflicting evidence regarding the relationship between depressive symptoms and cognition in schizophrenia. Whilst some studies have shown an association between depressive symptoms and attention [363], psychomotor speed [363] and semantic encoding in memory, other studies have not found an association [440, 441].

The impact of anxiety symptoms on cognitive function has not been studied in participants with major depressive disorder, bipolar disorder and schizophrenia. Anxiety symptoms are common in patients with depression [442], bipolar disorder [443] and schizophrenia [444]. In studies of healthy older adults, increased anxiety has been shown to be associated with poorer cognitive function [445, 446].

Cognitive impairments have been found in participants with generalised anxiety disorder [447-449], obsessive-compulsive disorder [450] and social phobia [450]. Thus, anxiety symptoms were included as the final cross-disorder clinical variable.

6.2 Chapter aims and hypotheses

In this chapter, cognitive function was examined in a cross-disorder sample recruited using an online cognitive assessment. The main diagnoses of interest were major depressive disorder, bipolar disorder and schizophrenia. However, cross-disorder analyses were also conducted including all participants with a psychiatric diagnosis. This chapter had three aims:

1. To compare cognitive function between participants with major depressive disorder, bipolar disorder and schizophrenia. It was hypothesised that the schizophrenia group would exhibit greater cognitive impairments than the bipolar disorder and major depressive disorder groups.
2. To examine the associations between clinical factors (current symptoms of depression and anxiety, and age of onset) and cognitive function both within and across disorders. It was hypothesised that more severe depressive symptoms, more severe anxiety symptoms and earlier age of onset would be associated with lower cognitive performance.
3. To examine the associations between cognitive performance and functional outcome both within and across disorders. It was hypothesised that poorer cognitive performance would be associated with poorer functional outcome.

6.3 Method

6.3.1 Sample

In order to maximise the sample numbers, the validity of combining the study samples from Chapters 4 and 5 was examined. There were few differences in cognitive performance between the two samples so these were combined for the analyses in this chapter (see Appendix M for comparisons). Full details of the recruitment for these studies have been described in Chapters 4 and 5. All participants gave informed consent by selecting a tick-box on the website. The study received ethical approval from the School of Medicine Research Ethics Committee at Cardiff University (SMREC reference number: 15/64).

Participants were recruited from the databases of two studies: Cognition in Mood, Psychosis and Schizophrenia Study (CoMPaSS) and the National Centre for Mental Health (NCMH). These studies have been described in detail elsewhere (see Chapters 3 and 4) but brief details of recruitment and diagnoses are provided here. Both studies include confirmation of consent from participants to be approached for other research within the centre. Inclusion criteria were aged 16 or above, able to understand written and spoken English and no uncorrected deficits in sight or hearing. There were no specific exclusion criteria given the practical difficulties involved in pre-screening participants for an online study but data was collected on current substance use, history of neurological conditions and whether participants had been admitted to hospital or had a change in their medication in the last three months. Overall, cognitive data was available for 381 participants including 62 healthy controls and 314 participants with a range of mental disorders. Further details of CoMPaSS, NCMH and recruitment of healthy controls are provided below.

NCMH recruitment

Cognitive data was available for 294 participants from NCMH, including 31 participants who had been recruited as part of the validation study and 263 who had been recruited during the main study phase. In NCMH, diagnoses are determined through self-report using a brief clinical interview. Participants are asked the question, “Has a doctor or health professional ever told you that you have any of the following diagnoses?” Participants are given a list of diagnoses and asked to indicate all diagnoses that apply. They are then asked to indicate which of the diagnoses they have ticked they would consider to be their primary, secondary and tertiary diagnoses. Finally, they are asked, “If we were to speak to your clinical team or general practitioner, would they agree with that?” Their diagnosis is then confirmed with their clinical team where possible.

CoMPaSS recruitment

Cognitive data was available for 20 participants from CoMPaSS, including 15 participants who had been recruited as part of the validation study and 5 who had been recruited during the main study phase. In CoMPaSS, consensus lifetime DSM-IV diagnoses were determined based on a clinical interview (Schedule for

Clinical Assessment in Neuropsychiatry, SCAN [331]) and review of available clinical records.

Healthy controls

There were 62 healthy controls with cognitive data, including 9 participants from the pilot study, 19 from the validation study and 34 participants recruited from NCMH during the main study phase. Initially, 39 participants were recruited as healthy controls from NCMH. However, 5 participants reported that they had been prescribed antidepressant medication since their participation in NCMH and so these participants were excluded from the study.

Diagnoses

The final sample included 62 healthy controls and 314 participants with a psychiatric disorder. The main diagnoses of interest in this study were major depressive disorder, bipolar disorder and schizophrenia (total N=227). There were 106 participants with a diagnosis of major depressive disorder, including 96 with recurrent depressive episodes and 10 with a single episode. Participants with recurrent and single episodes of major depression were combined, as there was no significant difference in their overall cognitive performance ($p=0.38$). Of the 106 participants with a self-reported diagnosis of major depressive disorder, 69 participants were currently taking antidepressant medication and 93 participants had been prescribed antidepressant medication in the past. Of the remaining 14 participants who had never been prescribed antidepressant medication, 2 had previously received a combination of mood stabilisers and psychotherapy, 1 had received cognitive behavioural therapy (CBT) and 7 had received a talking therapy other than CBT.

The bipolar disorder group included 88 participants with bipolar disorder – type I (N=51) and bipolar disorder – type II (N=37). Participants with the subtypes of bipolar disorder were combined, as there was no significant difference in their overall cognitive performance ($p=0.44$). Of these 88 participants, 27 participants had also been interviewed with the Mini-International Neuropsychiatric Interview (MINI, [334]) as part of another study and their diagnosis of bipolar disorder was

confirmed. A further 2 participants had completed the SCAN interview as part of an in depth NCMH assessment and their diagnoses were confirmed.

The schizophrenia group included 33 participants with schizophrenia (N=31) and schizoaffective disorder – depressive type (N=2). Participants with schizophrenia and schizoaffective disorder – depressive type were combined on the basis of previous findings indicating that cognitive performance between these groups is comparable (see Chapters 2 and 3). Of the 33 participants included in this group, 17 participants had completed the SCAN interview and their diagnoses were confirmed according to DSM-IV criteria.

The remaining participants (N=87) had a primary diagnosis of post traumatic stress disorder (N=16), generalised anxiety disorder (N=9), emotionally unstable personality disorder (N=9), Asperger’s syndrome (N=9), other bipolar affective disorder (N=7), other anxiety disorder (N=7), attention deficit hyperactivity disorder (N=6), obsessive compulsive disorder (N=5), anorexia (N=5), schizoaffective disorder – bipolar type (N=4), cyclothymia (N=2), social phobia (N=1), postnatal depression (N=1), autism (N=1), Alzheimer’s disease (N=1), other mood disorder (N=1) and three were rated as having an “other psychiatric disorder” (N=3).

6.3.2 Measures

Cognitive assessment

Full details of the online cognitive battery can be found in Chapter 4. The battery comprises of 9 tasks that each assess a separate domain of cognition. The domains are speed of processing, verbal learning, working memory, visual learning, reasoning and problem solving, attention, social cognition, strategic risk taking and premorbid IQ. The tasks are shown in order of administration in Table 5-2.

Participants clicked on a study-specific website link to access the tasks. Each task loads in the participant's internet browser and the data is stored locally until the task ends then the data is encrypted and uploaded to a secure server. The battery takes 45-60 minutes to complete.

Table 6-2 Descriptions of the tasks included in the online battery

Domain	Task	Description	Outcome Scoring
Speed of Processing	Digit Symbol Coding	P uses the key to assign the correct numbers to a series of symbols.	Number of correct responses in 90 seconds.
Social Cognition	Morphed Emotion Identification	P decides whether a face looks angry, fearful, happy or disgusted.	Number of correct responses out of 60 faces.
Verbal Learning	Verbal Paired Associates	P must memorise word pairs and select the word that was shown with each target word.	Number of correct responses out of 25 word pairs.
Working Memory	Backward Digit Span	P recalls a sequence of numbers in reverse order.	Maximum length of number sequence the participant was able to recall backwards.
Visual Learning	Hartshorne Visual Working Memory	P decides whether an object is the same or different from the previous object in that location.	Number of correct responses out of 42 trials.
Reasoning and Problem Solving	Matrix Reasoning Test	P selects the image that best completes a pattern.	Number of correct responses out of 35 patterns.
Strategic Risk Taking	Balloon Analogue Risk Task	P collects as many points as possible by blowing up balloons but no points are given if the balloon pops.	Number of points collected by inflating 30 balloons. Higher scores indicate more effective strategic risk-taking.
Attention	Multiple Object Tracking	P follows multiple targets as they move amongst identical objects.	Number of correct responses over 30 trials. Within a trial, each correctly identified target is 1 point.
Premorbid IQ	Vocabulary	P select which word is closest in meaning to the target word.	Number of correct responses out of 20 words.

Scoring and imputation

The outcome measure for each task can be found in Table 5-2. For each task, z scores were derived using the mean and standard deviation of the healthy controls (N=62). Missing data was imputed using the method described in the manual of the MATRICS Consensus Cognitive Battery (MCCB) [338]. Full details of the imputation methods including formulas can be found in Appendix C. Imputed data was used solely to derive general cognitive performance scores (g). Imputed scores were not included in analyses of individual tasks given that the imputation algorithms rely on information from other tasks for that participant and so are not suitable for domain or task specific analyses. Data was imputed for participants that had completed at least 5 tasks of the battery, which is consistent with the approach used for MCCB data in Chapter 3, meaning that those with data for less than five tests were not included in the analysis calculating 'g'.

Three measures of general cognitive performance ('g') were derived using the approaches described in Chapter 5. Measures of 'g' were derived for participants who had completed at least 5 tasks (N=321). All the tasks from the battery were included. Principal component analysis (PCA) was conducted on complete data (N=292) and repeated in a dataset where missing scores had been imputed (N=321). The first component of the PCA was taken as a measure of 'g'. Classical multidimensional scaling (MDS) was conducted on a Euclidean distance matrix to derive a third measure of 'g'. MDS is an analogous approach to PCA but an advantage to this approach is that it can accommodate missing data [422, 423]. The 'g' derived using MDS was highly correlated with the 'g' derived using complete data ($r=0.997$) and the 'g' derived including imputed data ($r=0.987$). Therefore, the results for analyses using 'g' derived using MDS are presented in this chapter. The results for analyses using 'g' derived by conducting PCA on imputed scores can be found in Appendix M.

Clinical questionnaire

Participants completed an online questionnaire prior to completing the cognitive battery. This questionnaire included questions about current diagnosis, medication, medical history, substance use, education, occupation, functional outcome and current mood. Current psychotic and negative symptoms were not assessed due to

the lack of reliable, valid self-report questionnaires. Current symptoms of depression and anxiety were assessed using the Hospital Anxiety and Depression Scale (HADS) [379]. Further details of the main variables included in these analyses are provided below.

Depression and anxiety

The HADS is a brief self-assessment scale, which was developed to identify cases of anxiety and depression among patients in hospital clinics [379]. The scale is separated into two subscales, depression and anxiety. The HADS consists of 14 questions relating to non-physical symptoms of depression and anxiety. Each answer is scored on a scale of 0-3 with higher scores indicating greater severity of symptoms. Current depression and anxiety symptoms were recorded as total scores on the HADS depression and anxiety subscales respectively (maximum score for each subscale is 21).

Age of onset

Data on age of onset was taken from the parent studies, CoMPaSS and NCMH. In CoMPaSS, age of onset was defined as the age at which the participant's symptoms of their diagnosed disorder caused impairment in their life. Impairment was defined as: 1) disruption in work or social life more or less completely, 2) fights or other violence, 3) job loss or unable to work, 4) police involvement, 5) family separation, 6) hospital admission or 7) receiving specific treatment. This was rated according to participants' responses to the SCAN interview and review of clinical records. In NCMH, participants were asked to report the age at which they first developed mental health problems and the age at which these problems caused impairment in their life. Age of first impairment was taken as the main measure of age of onset. There is greater uncertainty in reporting ages of onset less than 10 years old thus those who reported an age of onset of 1-9 years old were recorded as 10.

Functional outcome

The 12-item self-report version of the World Health Organisation Disability Assessment Schedule Version 2 (WHODAS 2.0) was included as a measure of functional outcome [415]. Participants completed the WHODAS 2.0 online prior to completing the cognitive assessment. The WHODAS 2.0 asks participants to rate

how much difficulty they have had in the last 30 days completing everyday tasks. It covers six domains of functioning: cognition (understanding and communicating), mobility, self-care, social interactions, life activities (domestic responsibilities, leisure and work) and participation in the community. Items were rated on a difficulty scale from none, mild, moderate, severe to extreme / cannot do and each item is allocated a score of 0-4 based on these respective ratings. The maximum score on the 12-item questionnaire is 48 and higher scores indicate poorer functional outcome. Participants were asked to record the number of days the difficulties were present in the last 30 days. They were also asked how many days they were either “totally unable” to carry out their activities or had to “cut back or reduce” their activities because of their illness. The primary outcome measure was total score on the 12 items (maximum score of 48).

6.3.3 Statistical analysis

Comparing cognition between diagnostic groups

Statistical analyses to compare the groups were performed using R version 3.3.0. The groups included in these analyses were healthy controls (N=62), major depressive disorder (N=106), bipolar disorder (N=88) and schizophrenia (N=33). For each cognitive domain and across diagnostic groups, performance was compared using analysis of covariance (ANCOVA) with age and gender as covariates and followed up with Tukey’s HSD for pairwise comparisons. Pairwise comparisons were conducted between the following groups:

1. Healthy controls and major depressive disorder
2. Healthy controls and bipolar disorder
3. Healthy controls and schizophrenia
4. Major depressive disorder and bipolar disorder
5. Major depressive disorder and schizophrenia
6. Bipolar disorder and schizophrenia

Bonferroni correction was used to adjust for multiple comparisons resulting in an alpha of 0.005 (0.05/10, 9 domains and ‘g’). The alpha was not corrected further for the number of pairwise comparisons, as Tukey’s HSD is already a conservative test that corrects for family-wise error rate. Hedges’ g effect sizes were calculated

by dividing mean group difference by the pooled standard deviation [344] (see Appendix A for formulas). Repeated measures analysis of variance was used to compare profiles of cognitive performance between groups. The within-subject factor was cognitive domain. This is consistent with the approach used in previous studies to compare cognitive profiles [266, 314].

The assumptions of ANCOVA include normal distribution of the residuals and homogeneity of variances across groups. Visual inspection of Q-Q plots revealed overall normal distributions. Homogeneity of variance was assessed with Levene's test and by calculating the variance ratios (highest variance divided by lowest variance). The variances were homogeneous across the groups with no variance ratios exceeding a value of 2.

Sensitivity analyses

Sensitivity analyses were conducted excluding participants diagnosed with bipolar disorder – type II, as there is evidence that these individuals have better cognitive functioning than participants with bipolar disorder – type I [245, 345]. Sensitivity analyses were also conducted excluding participants with major depressive disorder who had only one episode of depression, as there is evidence that cognitive impairments worsen with recurrent episodes of depression [451].

Cross disorder clinical variables and cognitive performance

The relationship between each predictor and cognitive performance was examined by conducting linear regressions analyses using R version 3.3.0. These analyses were conducted for cases only. In each analysis, the outcome measure was 'g' and age and gender were included as covariates. Three sets of analyses were conducted with one of the following as predictors: 1) HADS depression scores, 2) HADS anxiety scores or 3) age of onset. For the analyses of current mood, participants were only included if they completed the cognitive tasks on the same day as the mood questionnaires.

For each predictor, the linear regressions were conducted in the following groups:

1. The whole sample including all participants with any psychiatric diagnosis
2. A subset including all participants with a diagnosis of either major depressive disorder, bipolar disorder or schizophrenia
3. Major depressive disorder only
4. Bipolar disorder only
5. Schizophrenia only

Bonferroni correction was used to adjust for multiple comparisons resulting in an alpha of 0.0033 (0.05/15 analyses).

Analyses of age of onset were also repeated in a subset of participants who only had one psychiatric diagnosis (N=89), as the onset of comorbid disorders may differ from the onset of a participant's primary disorder.

Two further sets of analyses were conducted to model the effects of diagnosis and mood symptoms on cognitive function. Either HADS depression or anxiety scores were included as covariates, along with age and gender, in an ANCOVA comparing cognitive performance between diagnostic groups (healthy controls, major depressive disorder, bipolar disorder and schizophrenia). HADS depression and anxiety were analysed separately, as scores on these scales were highly correlated ($r=0.78$) and thus violated the assumption of lack of collinearity between predictors. The ANCOVAs were followed up with Tukey's HSD for pairwise comparisons. Bonferroni correction was used to adjust for multiple comparisons resulting in an alpha of 0.005 (0.05/10, 9 domains and composite score). The alpha was not corrected further for the number of pairwise comparisons, as Tukey's HSD is already a conservative test that corrects for family-wise error rate.

Inspections of Q-Q plots confirmed that the residuals for all analyses were normally distributed. Residuals and standardized residuals were plotted against fitted values to ensure homoscedasticity of the errors. Standardized residuals were plotted against leverage to identify potential outliers. Variance inflation factors were calculated to identify collinearity between the predictors.

Cognitive performance and functional outcome

Linear regressions analyses were conducted using R version 3.3.0 to determine if measures of general cognitive performance ('g') and performance on each cognitive task were associated with functional outcome. These analyses were conducted with cases only, including all diagnoses and did not include participants from the pilot and validation study, as the WHODAS 2.0 was added to the website after these stages. Cognition scores were entered into linear regressions as predictors with total score on the WHODAS as the outcome and age and gender as covariates.

Linear regressions with 'g' as the predictor and WHODAS scores as the outcome (with age and gender as covariates) were also conducted for the following groups:

1. A subset including all participants with a diagnosis of either major depressive disorder, bipolar disorder or schizophrenia (N=133)
2. A subset of participants with other disorders, excluding major depressive disorder, bipolar disorder and schizophrenia (N=67)
3. Major depressive disorder only (N=67)
4. Bipolar disorder only (N=53)
5. Schizophrenia only (N=13)

Bonferroni correction was used to adjust for multiple comparisons resulting in an alpha of 0.0033 (0.05/15 analyses). Inspections of Q-Q plots confirmed that the residuals for all analyses were normally distributed. Residuals and standardized residuals were plotted against fitted values to ensure homoscedasticity of the errors. Standardized residuals were plotted against leverage to identify potential outliers. Variance inflation factors were calculated to identify collinearity between the predictors.

6.4 Results

6.4.1 Sample size and completeness of data

Of the 381 participants in the sample, 293 participants had complete cognitive data. Data was available for the following number of participants on each task: Digit Symbol Coding (N=377), Morphed Emotion Identification (N=346), Verbal Paired Associates (N=338), Backward Digit Span (N=332), Hartshorne Visual Working Memory (N=321), Matrix Reasoning (N=318), Balloon Analogue Risk Task (N=317), Multiple Object Tracking (N=302) and Vocabulary (N=308). For participants with missing data, 'g' was calculated for participants who had completed at least five tasks (N=321). The number of available scores for each task for each diagnostic group (healthy controls, major depressive disorder, bipolar disorder and schizophrenia) can be found in Appendix L.

6.4.2 Comparison of cognition between diagnostic groups

Demographic and clinical characteristics

The demographic and clinical characteristics of the full sample have been provided in Chapters 4 and 5. However, the demographic and clinical characteristics of the healthy control group and participants with major depressive disorder, bipolar disorder and schizophrenia are displayed in Table 6-3. There were no differences in age between the groups ($F(3, 285)=1.06, p=0.37$). Groups differed on the proportion of females ($\chi^2(3)=11.47, p=0.01$), with fewer females observed in the schizophrenia group; therefore gender was used as a covariate in all analyses. There were differences in highest educational attainment between the groups (Kruskal Wallis $H(3)=36.22, p=6.7 \times 10^{-8}$), as all diagnostic groups had lower educational attainment than the healthy control group. Participants with schizophrenia had lower educational attainment than participants with bipolar disorder. Amongst the cases, there were no differences between groups in current HADS depression (Kruskal Wallis $H(2)=0.01, p=1$), current HADS anxiety scores (Kruskal Wallis $H(2)=0.63, p=0.73$) or age of illness onset (Kruskal Wallis $H(2)=2.95, p=0.23$). The groups differed on the proportion of individuals who had ever been admitted to hospital ($\chi^2(2)=81.5, p<2.2 \times 10^{-16}$), as a higher proportion of the schizophrenia and bipolar disorder groups had been admitted to hospital and a lower proportion of the depression group had been admitted. Scores on the

functional outcome scale (WHODAS) did not differ between the groups (Kruskal Wallis $H(2)=3.89$, $p=0.14$).

Representativeness of online sample

The demographic and clinical characteristics of each diagnostic group were compared to participants with the same diagnosis from the original parent studies (NCMH or CoMPaSS) to examine whether the online participants were representative of the original cohorts. The online depressive disorder group did not differ from NCMH participants with major depressive disorder in age ($t(1038)=-0.75$, $p=0.45$), sex ($\chi^2(1)=0.09$, $p=0.76$), education (Wilcoxon $W=48022$, $p=0.43$) or age of onset (Wilcoxon $W=48606$, $p=0.45$). The online bipolar disorder group did not differ from NCMH participants with bipolar disorder on age ($t(123.1)=0.12$, $p=0.91$), sex ($\chi^2(1)=0.37$, $p=0.54$) or age of onset (Wilcoxon $W=30369$, $p=0.44$). However, the cohorts differed on education, as the online participants with bipolar disorder were more highly educated than participants with bipolar disorder from NCMH (Wilcoxon $W=23392$, $p=7.6 \times 10^{-4}$). The online participants with schizophrenia were compared with participants with schizophrenia from the NCMH cohort and then those from the CoMPaSS cohort. The online schizophrenia group did not differ from NCMH participants with schizophrenia in age ($t(355)=0.97$, $p=0.33$), sex ($\chi^2(1)=1.6 \times 10^{-31}$, $p=1$), education (Wilcoxon $W=4141$, $p=0.24$) or age of onset (Wilcoxon $W=4488$, $p=0.48$). The online schizophrenia group did not differ from CoMPaSS participants with schizophrenia in sex ($\chi^2(1)=0.06$, $p=0.8$), age of onset (Wilcoxon $W=11290$, $p=0.88$) or education (Wilcoxon $W=9634.5$, $p=0.21$). However, the online schizophrenia group differed from the CoMPaSS participants in age ($t(766)=-2.15$, $p=0.03$), as the online participants were older.

Table 6-3 Demographic and clinical variables

ICD-10 Diagnosis	Healthy Controls	Major Depressive Disorder	Bipolar Disorder	Schizophrenia	Test Statistic	P Value	Pairwise Comparison
N	62	106	88	33			
Age	48 (18.8)	47.1 (14.2)	50.7 (11.4)	47.9 (11.9)	1.06	0.37	NS
Number of females (%)	43 (69.4)	70 (66)	62 (70.5)	13 (39.4)	11.47	0.01	SZ < HC SZ < BD SZ < MDD
Highest qualification							
None	0	3	0	2			
11+	0	1	0	1			
CSE or equivalent	0	5	2	4	36.22	6.7 x 10 ⁻⁸	MDD < HC BD < HC SZ < HC SZ < BD
GCSE or equivalent	1	17	17	5			
A-level or equivalent	10	35	25	10			
Degree	20	22	27	2			
Postgraduate degree	18	14	10	3			
Number of participants with ≥1 admission (%)		13 (12.6)	49 (60.5)	29 (93.5)	81.5	<2.2 x 10 ⁻¹⁶	MDD < SZ MDD < BD
Age of Onset*		18 (14.5)	17 (12)	21 (7)	2.95	0.23	NS
HADS depression score*		8 (6)	8 (8.5)	7 (8)	0.01	1.00	NS
HADS anxiety score*		11 (7)	10 (9.25)	10 (9)	0.63	0.73	NS
AMS score*		2 (4)	1 (4)	2 (3)	3.64	0.3	NS
WHODAS score*		11.5 (14.75)	17 (20.25)	19 (19)	3.89	0.14	NS

Figures represent means and standard deviations, except for proportions, ordinal scales and scores with non-normal distributions. *Median and interquartile range shown due to non-normal distribution. Test statistic is F (ANOVA) or H (Kruskal-Wallis Analysis of Variance) for continuous variables and X² for proportions. Pairwise comparisons significant to p<.05. AMS, Altman Mania Scale; HADS, Hospital Anxiety and Depression Scale; WHODAS, World Health Organisation Disability Assessment Scale; NS, Not Significant.

Comparison of cognition between diagnostic groups

There was a significant main effect of diagnosis for overall cognitive function ‘g’ ($F(3, 239) = 10.71, p=1.3 \times 10^{-6}$). Cognitive performance (‘g’) did not differ between participants with major depressive disorder and controls (Hedge’s $g=0.25, p=0.47$). Participants with bipolar disorder had impaired cognitive performance compared to controls, although this does not withstand correction for multiple testing ($g=0.56, p=0.01$). Participants with schizophrenia had impaired cognitive performance compared to controls ($g=1.17, p<0.001$). Participants with schizophrenia were more impaired than participants with major depressive disorder ($g=0.93, p<0.001$) and bipolar disorder ($g=0.61, p=0.02$), although the latter comparison did not withstand correction for multiple testing. Participants with bipolar disorder and major depressive disorder did not differ in their cognitive performance ($g=0.31, p=0.2$). Equivalent results were found when general cognitive function was derived using PCA on complete data and imputed data (see Appendix M).

Comparison of cognitive profiles between diagnostic groups

The main effects of diagnosis on each cognitive domain are displayed in Table 6-4. After correction for multiple testing, there was a significant main effect of diagnosis on speed of processing ($F(3, 282)=7.01, p=1 \times 10^{-4}$), social cognition ($F(3, 257)=11.26, p=5.8 \times 10^{-7}$) and reasoning and problem solving ($F(3, 240)=4.88, p=0.003$).

Table 6-4 Effect of diagnosis on each cognitive domain

Domain	F^{df}	p	Partial η^2
Speed of Processing	F ^{3, 282} =7.01	0.0001	0.07
Verbal Learning	F ^{3, 251} =2.11	0.1	0.02
Social Cognition	F ^{3, 257} =11.26	5.8 x 10 ⁻⁷	0.12
Working Memory	F ^{3, 249} =4.14	0.007	0.05
Visual Learning	F ^{3, 241} =3.18	0.02	0.04
Reasoning & Problem Solving	F ^{3, 240} =4.88	0.003	0.06
Strategic Risk Taking	F ^{3, 239} =1.56	0.22	0.02
Attention	F ^{3, 225} =3.72	0.01	0.05
Vocabulary	F ^{3, 230} =4.16	0.007	0.05

Partial η^2 indicates the proportion of variance in cognitive scores that is associated with diagnosis.

Effect sizes are displayed for each pairwise comparison in Figure 6-1. After correction for multiple testing, participants with schizophrenia were more impaired than controls on speed of processing ($d=0.91$, $p<0.001$), social cognition ($d=1.23$, $p<0.001$) and reasoning and problem solving ($d=0.76$, $p=0.004$). The schizophrenia group were more impaired than participants with major depressive disorder on speed of processing ($d=0.67$, $p=0.0049$) and social cognition ($d=1.04$, $p<0.001$). Finally, the schizophrenia group were more impaired than participants with bipolar disorder on the social cognition task ($d=0.89$, $p<0.001$). No other comparisons were significant after correction for multiple testing.

MDD	0.25	0.19	0.25				Speed of Processing	Social Cognition	Verbal Learning
	-0.1	-0.07	0.21				Working Memory	Visual Memory	Reasoning & Problem Solving
	0.05	0.31	0.07				Strategic Risk Taking	Attention	Vocabulary
BD	0.49	0.33	0.21	0.24	0.14	-0.04			
	0.34	0.05	0.48	0.44	0.12	0.27			
	0.18	0.5	0	0.14	0.19	-0.07			
SZ	0.91	1.21	0.56	0.67	1.03	0.32	0.42	0.88	0.36
	0.44	0.57	0.76	0.55	0.64	0.55	0.1	0.52	0.28
	0.42	0.66	0.71	0.38	0.35	0.64	0.24	0.16	0.71
	HC			MDD			BD		

Figure 6-1 Pairwise comparisons

Each 3x3 section displays the Cohen's d effect sizes for the difference between two diagnostic groups for each domain of cognition. Positive effect sizes indicate that the group on the horizontal bottom row performed better than the group on the left-hand vertical column. Lighter shade $p < 0.05$, darker shade $p < 0.005$.

Figure 6-2 displays the mean z scores for each diagnostic group and the control group. Means for the control group are not exactly zero as the scores have been adjusted for age and gender (marginal means). Cognitive profiles were compared between diagnostic groups (excluding controls) using repeated measures analysis of variance, with cognitive domain included as the within-subject factor, to test whether between group differences were qualitative or merely quantitative. Mauchly's test indicated that the assumption of sphericity had been violated ($\chi^2(35)=82.49$, $p=1.1 \times 10^{-5}$) therefore degrees of freedom were corrected using Huynh-Feldt estimates of sphericity. The diagnosis-by-domain interaction was not significant ($F=1.43$, $df=15.54$, 1243.52 , $p=0.12$) indicating that patterns of cognitive ability did not differ by diagnostic group but rather differed quantitatively.

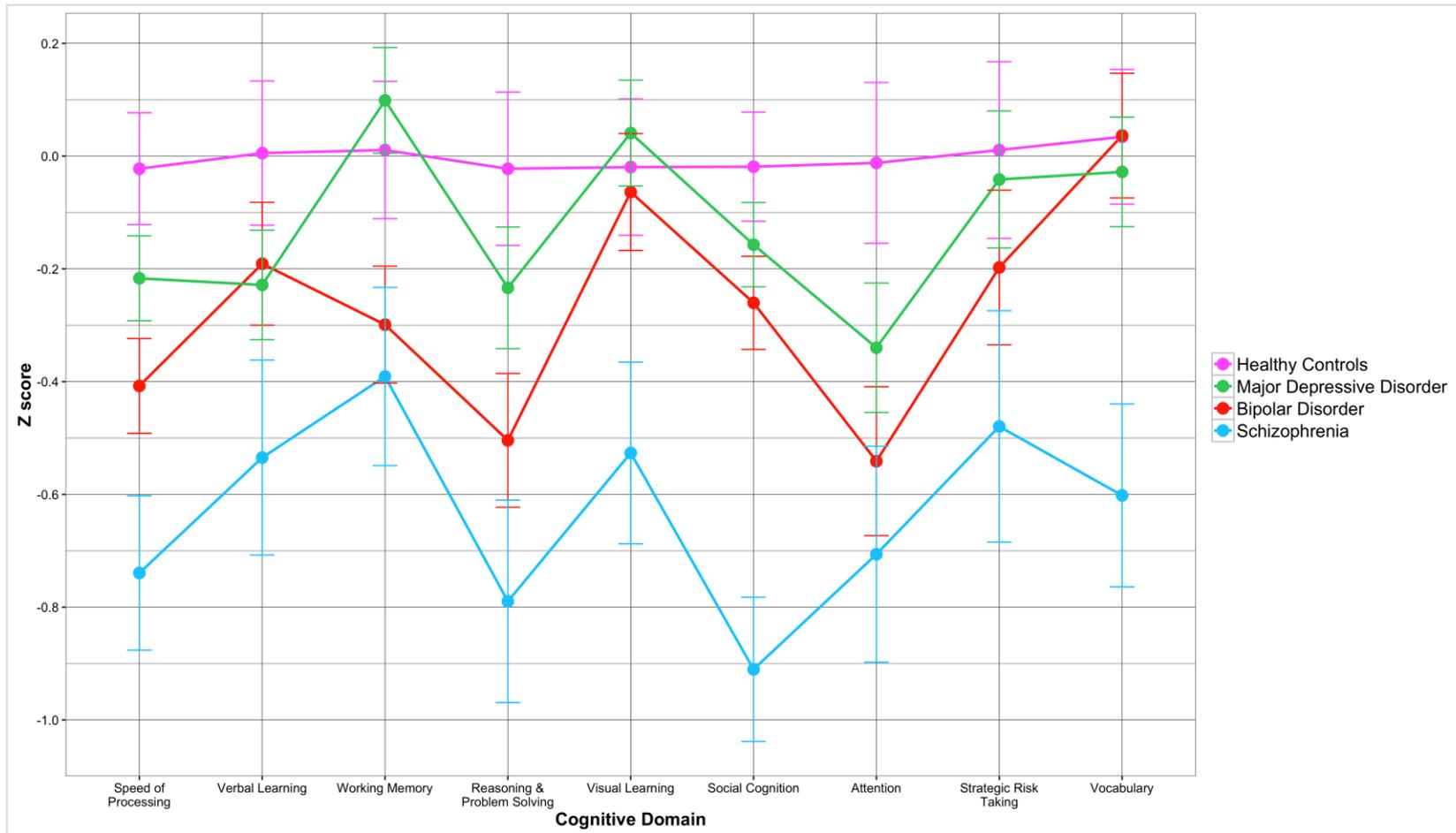


Figure 6-2 Cognitive profiles for participants with major depressive disorder, bipolar disorder and schizophrenia

Error bars indicate ± 1 standard error

Sensitivity analyses

Bipolar disorder - type I only

Given that there is some evidence to suggest patients with bipolar disorder – type II are less cognitively impaired than those with bipolar disorder – type I [245, 345], the analysis was repeated including only participants with bipolar disorder – type I (N=51). There were no significant differences between the bipolar disorder and schizophrenia groups on ‘g’ and vocabulary once participants with bipolar disorder – type II were excluded. Participants with bipolar disorder – type I were significantly more impaired than the healthy controls on attention. The remaining results did not differ from the main analysis (see Table 6-5).

Table 6-5 Comparisons of cognitive performance when only bipolar disorder - type I was included

Domain	Effect of Diagnosis			Pairwise Comparisons
	F ^{df}	p	Partial η^2	
General Cognitive Ability ('g')	F ^{3, 205} =11.70	4.2 x 10 ⁻⁷	0.15	BD<HC ¹ SZ<HC ² SZ<MDD ²
Speed of Processing	F ^{3, 245} =7.35	9.8 x 10 ⁻⁵	0.08	BD<HC ¹ SZ<HC ² SZ<MDD ¹
Verbal Learning	F ^{3, 216} =2.79	0.04	0.04	NS
Social Cognition	F ^{3, 222} =11.33	6.1 x 10 ⁻⁷	0.13	SZ<HC ² SZ<MDD ² SZ<BD ²
Working Memory	F ^{3, 215} =3.65	0.01	0.05	SZ<MDD ¹
Visual Learning	F ^{3, 207} =3.94	0.009	0.05	SZ<HC ¹ SZ<MDD ¹
Reasoning & Problem Solving	F ^{3, 207} =5.48	0.001	0.07	SZ<HC ¹ SZ<MDD ¹ BD<HC ¹
Strategic Risk Taking	F ^{3, 206} =1.48	0.22	0.02	NS
Attention	F ^{3, 196} =5.50	0.001	0.08	BD<HC ² SZ<HC ¹
Vocabulary	F ^{3, 200} =3.64	0.01	0.05	SZ<HC ¹ SZ<MDD ¹

Partial η^2 indicates the proportion of variance in cognitive scores that is associated with diagnosis. BD, Bipolar Disorder; HC, Healthy Controls; MDD, Major Depressive Disorder; SZ, Schizophrenia.

Major depressive disorder – recurrent only

Given evidence that cognitive impairments worsen with recurrent episodes of depression [451], the analysis was repeated including only participants with recurrent episodes of depression (N=96). This did not change the results or post hoc comparisons (see Table 6-6).

Table 6-6 Comparisons of cognitive performance when only participants with major depressive disorder - recurrent were included

Domain	Effect of Diagnosis			Pairwise Comparisons
	F ^{df}	p	Partial η^2	
General Cognitive Ability ('g')	F ^{3, 232} =10.84	1.1 x 10 ⁻⁶	0.12	BD<HC ¹ SZ<HC ² SZ<MDD ² SZ<BD ¹
Speed of Processing	F ^{3, 272} =6.96	1.6 x 10 ⁻⁴	0.07	BD<HC ¹ SZ<HC ² SZ<MDD ¹
Verbal Learning	F ^{3, 244} =2.06	0.11	0.02	NS
Social Cognition	F ^{3, 250} =11.51	4.4 x 10 ⁻⁷	0.12	SZ<HC ² SZ<MDD ² SZ<BD ²
Working Memory	F ^{3, 242} =4.35	0.005	0.05	BD<MDD ¹ SZ<MDD ¹
Visual Learning	F ^{3, 234} =3.10	0.03	0.04	SZ<MDD ¹
Reasoning & Problem Solving	F ^{3, 233} =4.87	0.003	0.06	SZ<HC ² SZ<MDD ¹ BD<HC ¹
Strategic Risk Taking	F ^{3, 232} =1.36	0.26	0.02	NS
Attention	F ^{3, 218} =3.77	0.01	0.05	BD<HC ¹ SZ<HC ¹
Vocabulary	F ^{3, 223} =4.27	0.006	0.05	SZ<HC ¹ SZ<MDD ¹ SZ<BD ¹

Partial η^2 indicates the proportion of variance in cognitive scores that is associated with diagnosis. BD, Bipolar Disorder; HC, Healthy Controls; MDD, Major Depressive Disorder; SZ, Schizophrenia.

6.4.3 Cross disorder clinical variables and cognitive performance

Across diagnostic groups

Figure 6-3 displays cognitive scores ('g') plotted against HADS depression scores across the whole sample and within the subgroups: major depressive disorder, bipolar disorder and schizophrenia. Figure 6-4 displays 'g' plotted against HADS anxiety scores across the whole sample and within the subgroups. Across the whole sample (cases only), higher HADS depression scores ($B=-0.08$, $SE=0.02$, $p=2.1 \times 10^{-4}$) and higher HADS anxiety scores ($B=-0.08$, $SE=0.02$, $p=4.7 \times 10^{-5}$) at the time of cognitive testing were associated with lower cognitive performance ('g'). Age of onset was not associated with cognitive performance ($B=-0.009$, $SE=0.01$, $p=0.4$). As a number of participants had two or more psychiatric diagnoses with different ages of onset, the analysis was repeated restricting the sample to participants with one diagnosis ($N=89$). As previously, age of onset was not associated with cognitive performance ($B=-0.002$, $SE=0.02$, $p=0.92$). The results were equivalent when the analyses were repeated with 'g' derived from imputed data using PCA (see Appendix M).

The analyses were then repeated and restricted to the three main diagnoses of interest: major depressive disorder, bipolar disorder and schizophrenia. Across these three disorders, higher HADS depression scores ($B=-0.08$, $SE=0.02$, $p=6.5 \times 10^{-4}$) and higher HADS anxiety scores ($B=-0.08$, $SE=0.02$, $p=1.7 \times 10^{-4}$) were associated with lower cognitive performance. Age of onset was not associated with cognitive performance ($B=-0.001$, $SE=0.01$, $p=0.95$). As previously, the analysis was restricted to participants with one diagnosis only ($N=69$) and there was no association between age of onset and cognitive performance ($B=0.008$, $SE=0.02$, $p=0.72$).

Within diagnostic groups

The associations between the clinical variables and cognitive performance within each diagnostic group are shown in Table 6-7. In the bipolar disorder group, higher HADS depression and anxiety scores were associated with lower cognitive performance (*HADS Depression*: $B=-0.08$, $SE=0.04$, $p=0.04$; *HADS Anxiety*: $B=-0.07$, $SE=0.04$, $p=0.046$). Higher HADS depression and anxiety scores were also associated with lower cognitive performance in the major depressive disorder

group (*HADS Depression*: $B=-0.07$, $SE=0.04$, $p=0.046$; *HADS Anxiety*: $B=-0.08$, $SE=0.04$, $p=0.03$). In the schizophrenia group, higher scores on the HADS anxiety subscale were associated with lower cognitive performance ($B=-0.10$, $SE=0.04$, $p=0.03$). However, none of the results were significant after correction for multiple testing.

Table 6-7 Associations between the clinical variables and cognitive performance

	N	General Cognitive Function		
		B	SE	p
Bipolar Disorder				
HADS depression	71	-0.08	0.04	0.04
HADS anxiety	71	-0.07	0.04	0.046
Age of onset	69	0.001	0.02	0.95
Major Depressive Disorder				
HADS depression	75	-0.07	0.04	0.046
HADS anxiety	75	-0.08	0.04	0.03
Age of onset	84	-0.01	0.02	0.61
Schizophrenia				
HADS depression	28	-0.11	0.05	0.05
HADS anxiety	28	-0.10	0.04	0.03
Age of onset	32	0.02	0.03	0.49

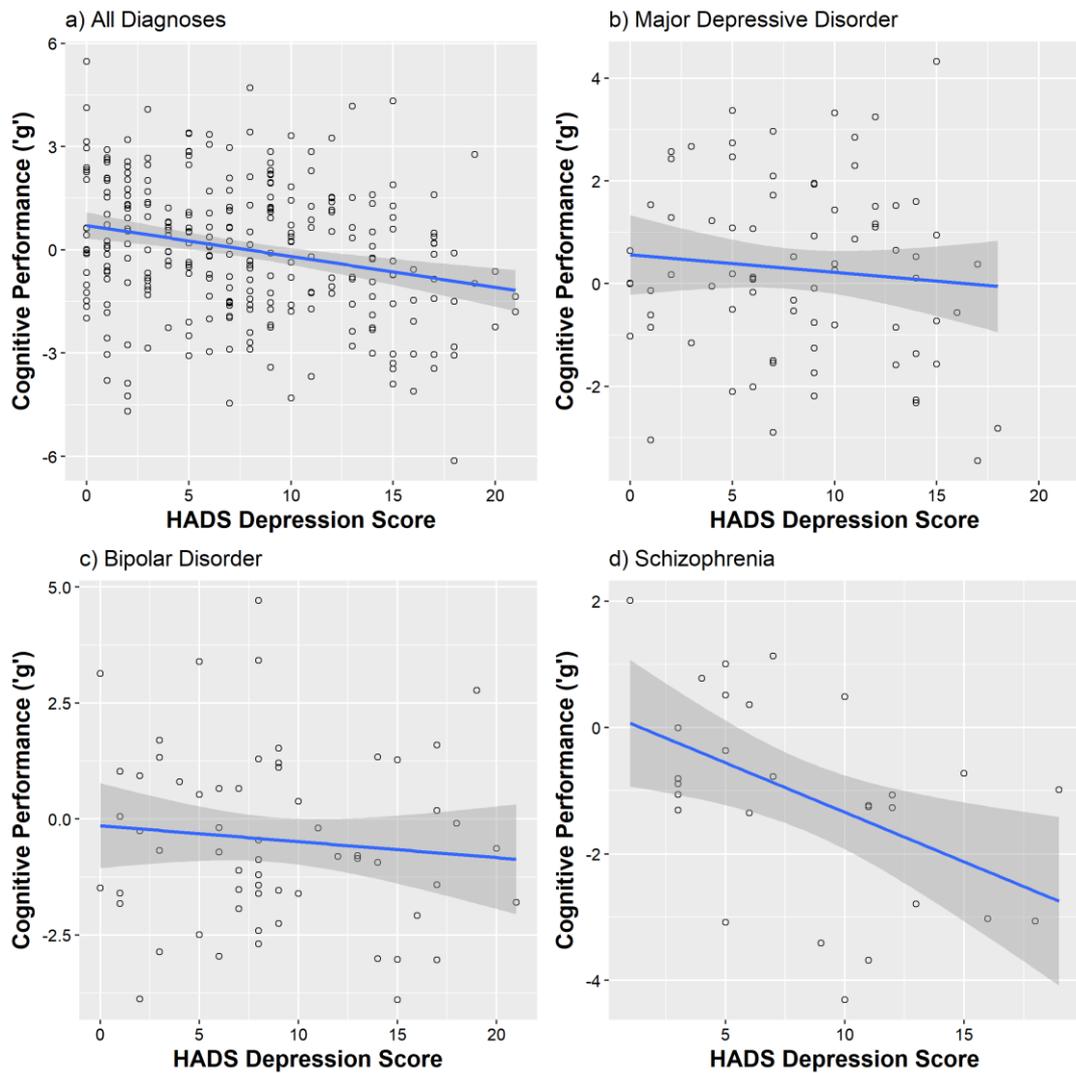


Figure 6-3 HADS depression scores and cognitive performance ('g')

From top left to bottom right: a) all diagnoses, b) major depressive disorder, c) bipolar disorder, d) schizophrenia. Line represents the regression line and the shaded region indicates 95% confidence intervals

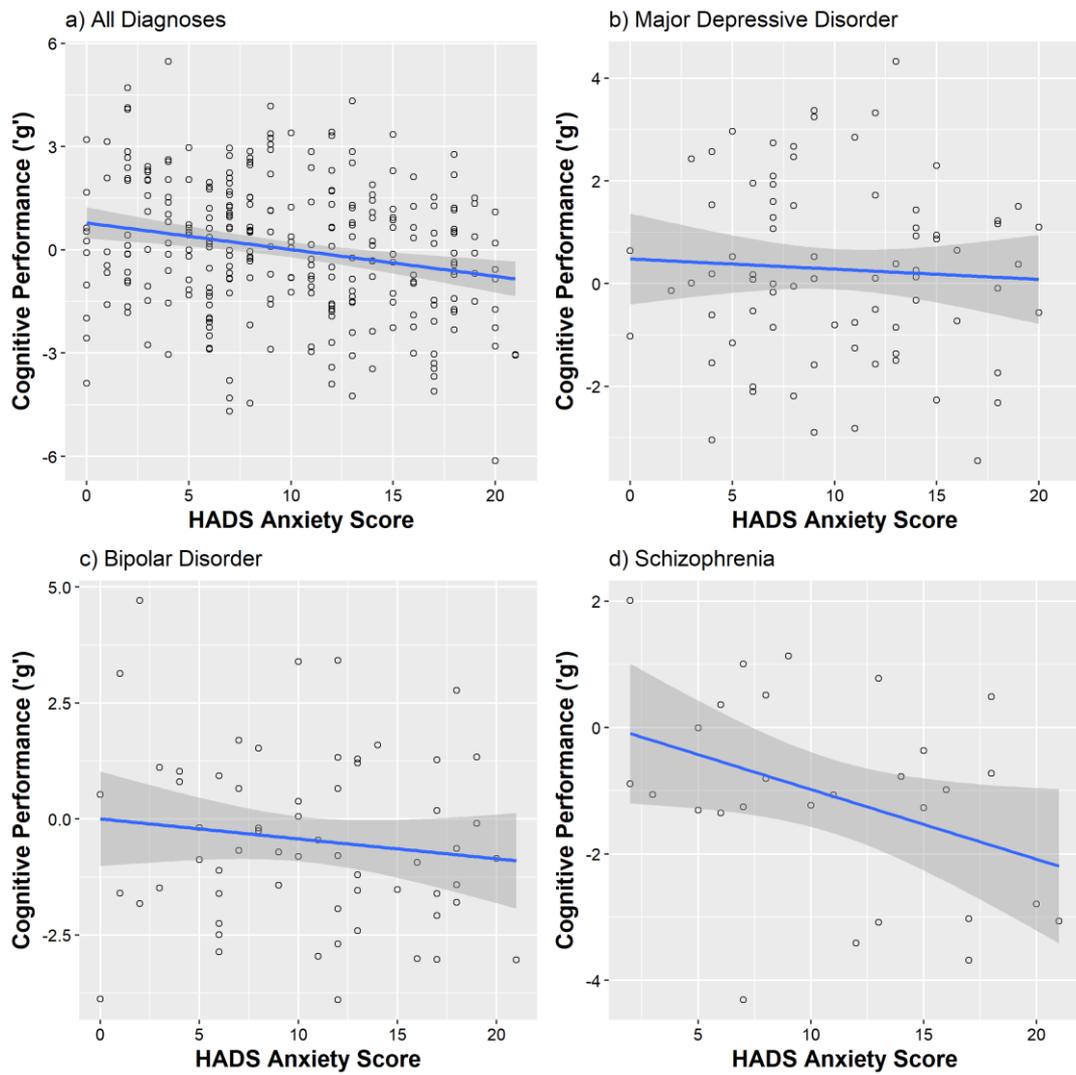


Figure 6-4 HADS anxiety scores and cognitive performance ('g')

From top left to bottom right: a) all diagnoses, b) major depressive disorder, c) bipolar disorder, d) schizophrenia. Line represents the regression line and the shaded region indicates 95% confidence intervals

Modelling the contributions of mood symptoms and diagnosis

Current anxiety symptoms were associated with performance on speed of processing ($F(1, 222)=18.44, p=2.6 \times 10^{-5}$), verbal learning ($F(1, 198)=16.57, p=6.8 \times 10^{-5}$) and 'g' ($F(1, 188)=15.31, p=1.3 \times 10^{-4}$, see Table 6-8 for full results). The estimated proportion of variance in cognitive scores explained by current anxiety symptoms was 0.08. The effect of diagnosis on speed of processing ($F(2, 222)=5.96, p=0.003$) and 'g' ($F(2, 188)=11.30, p=2.3 \times 10^{-5}$) remained significant after adjusting for anxiety symptoms. Current depressive symptoms were associated with speed of processing ($F(1, 222)=19.81, p=1.4 \times 10^{-5}$), attention ($F(1, 173)=8.02, p=0.005$) and 'g' ($F(1, 188)=13.20, p=3.6 \times 10^{-4}$, see Table 6-9 for full results). The estimated proportion of variance in cognitive scores explained by current depressive symptoms ranged from 0.05 to 0.08. The effect of diagnosis on speed of processing ($F(2, 222)=5.70, p=0.004$) and 'g' ($F(2, 188)=11.60, p=1.8 \times 10^{-5}$) remained significant after adjusting for depressive symptoms.

Table 6-8 The effects of diagnosis and HADS anxiety scores on cognitive performance

Domain	Effect of Diagnosis			Effect of Current Anxiety Symptoms			Pairwise Comparisons
	F ^{df}	p	Partial η^2	F ^{df}	p	Partial η^2	
Speed of Processing	F ^{2, 222} = 5.96	0.003	0.05	F ^{1, 222} = 18.44	2.6 x 10 ⁻⁵	0.08	SZ<MDD ²
Verbal Learning	F ^{2, 198} = 1.13	0.32	0.01	F ^{1, 198} = 16.57	6.8 x 10 ⁻⁵	0.08	NS
Social Cognition	F ^{2, 202} = 13.75	2.6 x 10 ⁻⁶	0.12	F ^{1, 202} = 0.32	0.57	0.002	SZ<BD ² SZ<MDD ²
Working Memory	F ^{2, 196} = 6.05	0.003	0.06	F ^{1, 196} = 2.69	0.1	0.01	BD<MDD ¹ SZ<MDD ¹
Visual Learning	F ^{2, 189} = 4.16	0.02	0.04	F ^{1, 189} = 3.85	0.05	0.02	SZ<MDD ¹
Reasoning & Problem Solving	F ^{2, 187} = 4.30	0.01	0.04	F ^{1, 187} = 5.18	0.02	0.03	SZ<MDD ¹
Strategic Risk Taking	F ^{2, 187} = 2.32	0.1	0.02	F ^{1, 187} = 2.39	0.12	0.01	NS
Attention	F ^{2, 173} = 1.62	0.2	0.02	F ^{1, 173} = 4.83	0.03	0.03	NS
Vocabulary	F ^{2, 176} = 6.38	0.002	0.07	F ^{1, 176} = 5.22	0.02	0.03	SZ<BD ² SZ<MDD ¹
General Cognitive Function ('g')	F ^{2, 188} = 11.30	2.3 x 10 ⁻⁵	0.11	F ^{1, 188} = 15.31	1.3 x 10 ⁻⁴	0.08	SZ<MDD ² SZ<BD ¹

Partial η^2 indicates the proportion of variance in cognitive scores that is associated with each variable. BD, bipolar disorder; HADS, Hospital Anxiety and Depression Scale; HC, healthy controls; MDD, major depressive disorder; SZ, schizophrenia; ¹p<0.05; ²p<0.005 (Bonferroni-corrected)

Table 6-9 The effects of diagnosis and HADS depression scores on cognitive performance

Domain	Effect of Diagnosis			Effect of Current Depressive Symptoms			Pairwise Comparisons
	F ^{df}	p	Partial η^2	F ^{df}	p	Partial η^2	
Speed of Processing	F ^{2, 222} = 5.70	0.004	0.05	F ^{1, 222} = 19.81	1.4 x 10 ⁻⁵	0.08	SZ<MDD ²
Verbal Learning	F ^{2, 198} = 1.39	0.25	0.01	F ^{1, 198} = 5.22	0.02	0.03	NS
Social Cognition	F ^{2, 202} = 13.81	2.4 x 10 ⁻⁶	0.12	F ^{1, 202} = 0.06	0.81	2.9 x 10 ⁻⁴	SZ<BD ² SZ<MDD ²
Working Memory	F ^{2, 196} = 5.96	0.003	0.06	F ^{1, 196} = 1.34	0.25	0.01	BD<MDD ¹ SZ<MDD ¹
Visual Learning	F ^{2, 189} = 4.23	0.02	0.04	F ^{1, 189} = 3.27	0.07	0.02	SZ<MDD ¹
Reasoning & Problem Solving	F ^{2, 187} = 4.40	0.01	0.05	F ^{1, 187} = 4.61	0.03	0.02	SZ<MDD ¹
Strategic Risk Taking	F ^{2, 187} = 2.37	0.10	0.03	F ^{1, 187} = 0.57	0.45	0.003	NS
Attention	F ^{2, 173} = 1.82	0.17	0.02	F ^{1, 173} = 8.02	0.005	0.05	NS
Vocabulary	F ^{2, 176} = 6.67	0.002	0.07	F ^{1, 176} = 4.09	0.04	0.02	SZ<BD ² SZ<MDD ²
General Cognitive Function ('g')	F ^{2, 188} = 11.60	1.8 x 10 ⁻⁵	0.11	F ^{1, 188} = 13.20	3.6 x 10 ⁻⁴	0.07	SZ<MDD ² SZ<BD ²

Partial η^2 indicates the proportion of variance in cognitive scores that is associated with each variable. BD, bipolar disorder; HADS, Hospital Anxiety and Depression Scale; HC, healthy controls; MDD, major depressive disorder; SZ, schizophrenia; ¹p<0.05; ²p<0.005 (Bonferroni-corrected)

6.4.4 Cognitive performance and functional outcome

Across diagnostic groups

Linear regression across the whole sample indicated that lower cognitive performance ('g') was associated with higher WHODAS scores, which indicates poorer functional outcome ($B=-1.69$, $SE=0.45$, $p=2.2 \times 10^{-4}$). The analyses were then repeated and restricted to the three main diagnoses of interest: major depressive disorder, bipolar disorder and schizophrenia. Across these three disorders, lower cognitive performance was associated with higher WHODAS scores ($B=-1.36$, $SE=0.59$, $p=0.02$) but this did not survive correction for multiple testing. In the subgroup of participants with other psychiatric disorders (excluding major depressive disorder, bipolar disorder and schizophrenia), lower cognitive performance was significantly associated with higher WHODAS scores ($B=-2.08$, $SE=0.64$, $p=0.002$).

Relationships between cognitive tasks and functional outcome

Four tasks were associated with functional outcome (see Table 6-10): Digit Symbol Coding, Backward Digit Span, Hartshorne Visual Working Memory Test and Balloon Analogue Risk Task. After correction for multiple testing, higher scores on three tasks were significantly associated with better functional outcome as measured by total WHODAS scores (*Digit Symbol Coding*: $B=-0.35$, $SE=0.08$, $p=4.1 \times 10^{-5}$; *Backward Digit Span*: $B=-1.40$, $SE=0.44$, $p=0.002$; *Hartshorne Visual Working Memory Test*: $B=-0.53$, $SE=0.17$, $p=0.003$).

Table 6-10 Associations between cognitive performance and functional outcome (WHODAS score)

Task	N	B	SE	p
Digit Symbol Coding	249	-3.39	0.81	4.1 x 10 ⁻⁵
Verbal Paired Associates	219	-1.01	0.89	0.26
Backward Digit Span	212	-2.60	0.82	0.002
Hartshorne Visual Working Memory Test	203	-2.49	0.82	0.003
Morphed Emotion Identification	223	-1.48	0.93	0.11
Matrix Reasoning Test	199	-1.34	0.80	0.09
Balloon Analogue Risk Task	199	-1.51	0.66	0.02
Multiple Object Tracking	185	-1.28	0.73	0.08
Vocabulary	189	-0.90	1.02	0.38

Within diagnostic groups

In analyses of individual diagnostic groups, lower cognitive performance was associated with poorer functional outcome in the depression group only (B=-2.8, SE=0.74, p=3.7 x 10⁻⁴, see Table 6-11 for full results). Results were comparable when the analysis was repeated with ‘g’ derived from imputed data (see Appendix M).

Table 6-11 Associations between ‘g’ and WHODAS score within diagnostic groups

	N	B	SE	p
Across Three Groups	133	-1.36	0.59	0.02
Bipolar Disorder	53	0.30	0.92	0.75
Major Depressive Disorder	67	-2.80	0.74	3.7 x 10 ⁻⁴
Schizophrenia	13	-3.12	1.72	0.1

6.5 Discussion

This chapter had three main aims: 1) to examine the nature and extent of cognitive impairments in participants with major depressive disorder, bipolar disorder and schizophrenia; 2) to examine the associations between clinical features (current depressive symptoms, current anxiety symptoms and age of onset) and cognitive performance both within and across disorders; 3) to determine whether cognitive impairments predict functional outcome both within and across disorders. There were three main findings of this study:

1. Cognitive impairments were present in participants with bipolar disorder and schizophrenia but participants with major depressive disorders did not exhibit impairments relative to controls. Differences between participants with bipolar disorder and healthy controls were not significant after correction for multiple testing.
2. Greater depressive and anxiety symptoms were associated with poorer cognitive performance but there was no association between age of onset and cognition.
3. Poorer cognitive performance was associated with poorer functional outcome across disorders.

Each of these findings is discussed in detail in the following sections.

6.5.1 Cognitive performance across disorders

Comparisons of cognitive performance between groups indicated that participants with bipolar disorder and schizophrenia exhibited overall cognitive impairment, whilst participants with major depressive disorder did not. However, the difference in 'g' between participants with bipolar disorder and healthy controls did not survive correction for multiple testing. Cognitive profiles did not differ between diagnostic groups. There were significant effects of diagnosis on only three domains after correction for multiple testing: speed of processing, social cognition and reasoning and problem solving.

The findings reported in this chapter replicate the findings of Chapter 3, which found similar cognitive profiles but greater cognitive impairment in the schizophrenia group than the bipolar group. However, the effect sizes reported in

this study are smaller than those reported in Chapter 3. Consequently, the difference in overall cognitive function between participants with bipolar disorder and healthy controls did not survive correction for multiple testing. The major depressive disorder group did not differ from the healthy control group. This is contrary to meta-analyses that have found small impairments in overall cognitive function, even in euthymic participants with major depressive disorder [426, 429]. In this study, major depressive disorder was broadly defined including both participants with single and recurrent episodes. The inclusion of participants with a single episode of depression may have obscured differences between the major depressive disorder group and healthy controls. However, only a small number of participants with a single episode were included (N=10), participants with single and recurrent episodes of depression did not differ in their cognitive performance and the results were equivalent when participants with single episodes of depression were excluded from analyses. This suggests the lack of impairments found in this study cannot be explained by the inclusion of a diverse group of participants with major depressive disorder.

One explanation for the smaller effect sizes reported in this study may be due to the use of online cognitive testing. Participants in the online study were less likely to have been recruited through secondary psychiatry services (see Chapter 5).

Therefore, participants with a more severe illness may be less likely to participate in an online study compared to the face-to-face interviews conducted in Chapter 3.

The characteristics of the online sample were compared with the parent studies to examine whether the online sample was representative of the original cohorts.

Online participants with bipolar disorder were more highly educated than participants with bipolar disorder from the NCMH cohort who did not participate.

Online participants with schizophrenia did not significantly differ in education levels from participants with schizophrenia in the NCMH or CoMPaSS cohort.

However, it should be noted that three participants in the online sample (9%) had post-graduate degrees compared to 2% of the CoMPaSS sample, which may be an indication that the online participants with schizophrenia are more highly educated than participants from CoMPaSS. This may explain why participants in this study exhibited smaller impairments and only analyses of three domains survived correction for multiple testing.

Participants did not differ in performance on two domains: verbal learning and strategic risk taking. The lack of significant differences in verbal learning between groups contradicts the findings of Chapter 3. In Chapter 3, verbal learning was assessed using the Hopkins Verbal Learning Test – Revised (HVLT-R) in a sample of participants with schizophrenia, schizoaffective disorder and bipolar disorder. The largest impairments across groups were exhibited on the HVLT-R. One plausible reason for the differences in results between these two studies is that the correlation between the Verbal Paired Associates task and HVLT-R was moderate ($r=0.41$, see Chapter 4). The two measures assess distinct aspects of verbal learning. The Verbal Paired Associates task assesses delayed associative learning (word pairs), whilst the HVLT-R assesses short-term free recall of a list [452]. It should also be noted that few participants obtained high scores on the Verbal Paired Associates task. For example, only 3% of participants obtained scores of 20 or above (out of 25) on this task. Therefore, another plausible explanation is a lack of variation in scores means the task is not sensitive enough to be able to detect differences between groups.

To my knowledge, this study was the first to examine whether scores on the Balloon Analogue Risk Task (BART) differs between diagnostic groups. Performance on the BART did not differentiate between cases and controls. Although performance on the BART was associated with functional outcome, the coefficient was small ($B=0.01$) and did not survive correction for multiple testing. This calls into question the usefulness of this measure in psychiatric populations.

Participants with schizophrenia exhibited impairments on the social cognition task (emotion identification), whilst participants with bipolar disorder and major depressive disorder did not. Previous studies have shown that participants with schizophrenia are more impaired on measures of emotion recognition than participants with mood disorders [370, 453]. Participants with bipolar disorder showed small, non-significant impairments in emotion identification. The effect size reported in this study ($g=0.33$) was comparable to that of a meta-analysis of studies comparing emotion identification between participants with bipolar disorder and healthy controls ($d=0.35$) [243]. Overall these findings are consistent with the findings of Chapter 3, which demonstrated that pronounced impairments

in social cognition are present in participants with schizophrenia and schizoaffective disorder but not bipolar disorder.

6.5.2 Clinical predictors of cognitive function

Current symptoms of depression and anxiety were associated with cognitive performance across disorders, although the effect of diagnosis remained significant when these variables were included as covariates. Pairwise differences between the groups did not change when anxiety or depression scores were included as covariates. Age of onset was not associated with cognitive performance either across or within diagnostic groups.

Higher scores on the HADS depression subscale were associated with poorer performance on measures of processing speed, attention and overall cognitive function. That depressive symptoms are associated with performance on tasks assessing processing speed and attention is not surprising given that symptoms of depression include poor concentration and psychomotor retardation [8].

Associations between depression scores and cognition were found in the depression and bipolar disorder groups, which is consistent with previous studies [258, 426, 434, 435]. There is conflicting evidence of the influence of depressive symptoms on cognitive impairment in schizophrenia. In the current study, the association between depression scores and cognitive performance was not significant in the schizophrenia group ($p=0.05$) so it was not possible to draw any firm conclusions in this group.

Higher scores on the HADS anxiety subscale were also associated with poorer cognitive performance both within and across diagnostic groups. To my knowledge, this is the first study to examine the association between current anxiety symptoms and cognitive performance across disorders. Previous studies have found cognitive impairments in participants with a primary diagnosis of an anxiety disorder and in older adults with anxiety symptoms [445-450]. This study expands on these findings by showing that increased anxiety symptoms are associated with poorer cognitive performance in participants with major depressive disorder, bipolar disorder and schizophrenia. Anxiety symptoms were associated with speed of processing, verbal learning and overall cognitive function. There are several explanations for this finding. Anxiety symptoms may directly affect cognitive

performance. For example, participants who are experiencing symptoms of anxiety may have greater difficulty concentrating resulting in poorer performance. Alternatively, a high score on the HADS anxiety scale may be an indicator that the participant has a more severe course of illness or experiencing a relapse of their symptoms. Another possibility is that this result may be confounded by participants' use of benzodiazepines, which may have a dulling effect on cognitive function [454]. Finally, the HADS depression and anxiety subscales were highly correlated in this study ($r=0.78$). Therefore, it was not possible to disentangle the effects of depression and anxiety in a single model, as this violated the assumption of no collinearity in regression analyses.

Age of onset was not associated with cognitive performance within or across diagnostic groups. There is evidence that earlier age of onset is associated with poorer cognitive function in participants with bipolar disorder and schizophrenia. A study of participants with bipolar disorder demonstrated that both age of first symptom and age of first treatment are positively correlated with cognitive performance [436]. A meta-analysis compared cognitive performance between participants with youth-onset schizophrenia (19 years or younger), late-onset schizophrenia (40 years or older) and first-episode schizophrenia (20-39 years) [438]. The youth-onset group were more cognitively impaired than the first-episode and late-onset groups. The first-episode group were was impaired than the late-onset group. In contrast, a meta-analysis of participants with major depressive disorder found poorer cognitive performance amongst participants with a late onset (defined as onset after 50 years) compared to participants with an earlier age of onset (18-50 years). These results suggest there may be a complex relationship between age of onset and cognitive performance across disorders. In the current study, age of onset was considered as a linear variable. An alternative approach would be to identify participants with an early onset and late onset and compare performance but there were an insufficient number of participants to do this. It should be noted that the majority of participants in this study were recruited from NCMH and so their age of onset was based on self-report and may not be as reliable as studies that have accessed clinical records. Age of onset was also higher (though not significantly different) in the schizophrenia group than the bipolar

disorder and major depressive groups, which may indicate participation bias. Therefore, caution is advised in the interpretation of this result.

6.5.3 Cognitive performance and functional outcome

In a cross-disorder analysis, poorer cognitive performance was associated with poorer functional outcome, as measured by the WHODAS. The WHODAS assesses six domains of functional outcomes, including cognition (understanding and communicating), mobility, self-care, social interactions, life activities (domestic responsibilities, leisure and work) and participation in the community. These results suggest that cognitive performance is an important indicator of overall functional outcome across a range of psychiatric diagnoses. This is consistent with an earlier prospective study that used the WHODAS to examine the association between cognitive performance and functional outcome in young participants with major depressive disorder, bipolar disorder and psychosis [186]. In the prospective study, improved verbal memory and sustained attention were associated with greater reductions in disability. The authors performed a cluster analysis and identified three cognitive subtypes associated with functional outcome. However, the clusters did not differ by diagnosis suggesting that cognitive improvement predicts functional outcome independent of diagnosis. This study expands on these findings by showing that cognitive performance is associated with functional outcome in a sample of adults with a broader range of psychiatric disorders.

In contrast to the study by Lee et al. [186], measures of verbal memory and attention were not associated with scores on the WHODAS. In this study, performance on Digit Symbol Coding, Backward Digit Span and Hartshorne Visual Working Memory were associated with scores on the WHODAS. Scores on Digit Symbol Coding were most strongly associated with functional outcome and this is consistent with the findings of previous studies examining functional outcomes in schizophrenia [369, 455]. Previous studies have shown that impairments in working memory are associated with poor functional outcomes in participants with first episode psychosis [456] and major depressive disorder [457]. Both Digit Symbol Coding and Backward Digit Span have short administration times (under five minutes) so may be particularly suited for brief assessments of cognition in a

clinical setting. Future studies should investigate whether interventions that target impairments in processing speed and working memory are beneficial for improving functional outcomes in patients with psychiatric disorders.

The analyses were repeated in three diagnostic groups: major depressive disorder, bipolar disorder and schizophrenia. Poorer cognitive performance was associated with poorer functional outcome in the major depressive disorder group only. In the schizophrenia group, the effect was in the expected direction but the sample size was small (N=13) and the analysis may have been inadequately powered to detect an association. In the bipolar disorder group, the regression coefficient was close to zero (B=0.3, 95% CI: -1.56-2.16) but the confidence intervals were wide, which suggests this analysis may also have been underpowered. It should be noted that functional outcomes did not differ between the three diagnostic groups, which may indicate that a certain level of functioning is required to complete the online tasks and the online sample may be a higher functioning sample.

The current study was cross-sectional so it was not possible to examine whether changes in cognitive function are associated with changes in functional outcome in cross-disorder samples. In addition, the WHODAS is a broad measure of functional outcome that assesses both occupational and social outcomes. Cognitive domains may differ in their associations with occupational and social outcomes. A seven-year longitudinal study of participants with schizophrenia found that individual cognitive domains predicted different aspects of functional outcome [184]. Verbal memory was associated with recreational activities, whilst attention predicted occupational outcomes. Future research should examine whether the association with cognitive performance differs for occupational and social outcomes across psychiatric disorders.

6.5.4 Generalizability of the results

The issue of recruitment bias in the online sample has been discussed extensively in section 5.5.4. However, the findings of this chapter expand on the issues highlighted in Chapter 5. The effect sizes reported in this chapter are smaller than those reported in Chapter 3 and previous meta-analyses. This may be the result of recruitment bias. There was some evidence that the schizophrenia and bipolar disorder groups were more highly educated than participants with the same

disorders in the NCMH and CoMPaSS cohorts (for further discussion, see section 6.5.1). Therefore, caution is advised in generalising the findings presented here to the population of people with these disorders.

6.5.5 Concluding statements

Several limitations of this study should be noted. Diagnosis was based on self-report rather than a structured clinical interview. Participants' diagnoses were confirmed with their clinical team where possible and they were asked to report diagnoses that they had been given by a health professional, which is consistent with the approach taken by other large studies with self-report measures of diagnosis, such as the UK Biobank [388]. In addition, most participants (N=244, 76% of cases) were taking psychiatric medication at the time of assessment. The schizophrenia group was smaller than the bipolar and depression groups due to a lower response rate from participants with schizophrenia. It should be noted that recruitment to this study is ongoing and participants recruited through secondary services who completed structured clinical interviews are currently being invited to the study. Due to the study being online, clinical symptom measures were based on self-report rather than objective assessments. However, the HADS anxiety and depression scores have been demonstrated to have good validity when compared with observer ratings of mood symptoms [458]. It was not possible to consider negative or psychotic symptoms in these analyses due to the lack of reliable, valid self-report questionnaires. Participants were grouped according to their primary diagnosis in this study and co-morbid psychiatric diagnoses were not considered. This is particularly relevant for participants with major depressive disorder, as depression is highly comorbid with other psychiatric disorders and is more likely to occur after the onset of another psychiatric disorder [459, 460]. Whilst participants with comorbid diagnoses were not excluded, participants were only included in the depression group if their primary diagnosis was major depressive disorder, as opposed to having a diagnosis of another psychiatric disorder and a secondary diagnosis of depression.

This study has several strengths. The sample is large and includes participants with a diverse range of psychiatric disorders. No single published study has compared cognition between adults with schizophrenia, bipolar disorder and depression,

examined factors associated with cognition and the relationship between cognition and functional outcome in a single cohort. The study included measures of current anxiety as well as current depression.

In conclusion, I have recruited a large sample of participants with a range of psychiatric disorders using an online cognitive assessment. These findings should be considered preliminary as recruitment to this study is ongoing and the schizophrenia group was small. This study replicated the earlier findings of Chapter 3 showing similar cognitive profiles but more severe impairment in the schizophrenia group compared to those with bipolar disorder. This study was the first to demonstrate that current symptoms of depression and anxiety are associated with cognitive performance in a cross-disorder analysis. Poorer cognitive performance was associated with poorer functional outcome across disorders. Self-reported functional outcome did not differ between diagnoses and was associated with cognitive performance even amongst participants with major depressive disorder, who did not differ from controls in their overall cognitive function. Overall, these results support a role for cognitive function in functional outcome that is independent of diagnostic boundaries.

Chapter 7: General Discussion

7.1 Overview

This thesis set out to characterise the nature and degree of cognitive impairment present in psychotic and affective disorders using large datasets and to develop an online cognitive battery for use in psychiatric research. Cognitive impairments are increasingly recognised as a core feature of psychotic and affective disorders and are a strong predictor of functional outcomes for patients [182, 183].

Understanding cognitive impairments across these disorders has implications for clinical practice and treatment, diagnostic classification of these disorders and to inform investigations of biology and genetics. Large cross-diagnostic datasets are needed to investigate the environmental and genetic factors that influence cognitive function.

The first approach was to conduct a systematic review and meta-analysis comparing cognitive performance in schizoaffective disorder to schizophrenia and bipolar disorder. Individual studies that have examined cognitive performance in schizoaffective disorder have produced conflicting results. This work indicated that schizoaffective disorder was associated with poorer overall cognitive performance than bipolar disorder and better cognitive performance than schizophrenia. This suggested a gradient of increasing impairment from bipolar disorder to schizoaffective disorder to schizophrenia. There was initial evidence to suggest differential cognitive performance in the subtypes of schizoaffective disorder but few studies had separated the subtypes. The systematic review also confirmed earlier findings that a lifetime history of psychosis is associated with the presence of cognitive impairments.

These findings were then built upon by examining cognition in a large and well-characterised cross-diagnostic sample. Using ordinal regression modelling, it was demonstrated that there is a gradient of increasing cognitive impairment from bipolar disorder to schizoaffective bipolar to schizophrenia and schizoaffective depressive. Comparisons between the diagnoses confirmed that the subtypes of schizoaffective disorder show differential cognitive performance. Regression

analyses also showed that a dimensional measure of lifetime psychosis is linearly associated with cognition. Despite quantitative differences in cognitive impairment, the cognitive profiles of the disorders were similar, which could indicate common underlying neurobiology.

An online cognitive battery was developed to gather data on a large cohort of participants for whom clinical and genetic data was already available. I developed the battery in collaboration with The Many Brains Project using their platform, “TestMyBrain.org”. Task selection was informed by the work of the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative. A pilot and validation study was then conducted. Sixty-five participants completed the new battery and the MATRICS Consensus Cognitive Battery on consecutive days. This study indicated that the online battery provided valid measurements of all the MATRICS domains except visual learning. The battery was well tolerated in the validation study with 58 out of 65 participants completing every task and the feedback was positive.

The online battery was then rolled out to participants from two studies within the MRC Centre for Neuropsychiatric Genetics and Genomics: National Centre for Mental Health (NCMH) and Cognition in Mood, Psychosis and Schizophrenia Study (CoMPaSS). Participants from these studies have been previously administered a clinical interview and provided a blood sample so phenotype and genotype data were available. Recruitment for this study is ongoing but data was analysed from the first 342 participants who took part in the study. Participants were representative of the original cohort in terms of demographic characteristics although participants with schizophrenia and post-traumatic stress disorder were underrepresented in the online sample (see Chapter 5). Two-thirds of the sample completed all the online tasks. An exploratory factor analysis indicated two factors with the first factor explaining a high proportion of the variance in cognitive performance and the Vocabulary task (a measure of crystallised intelligence) uniquely loading onto the second factor.

Finally, the data collected using the online cognitive battery was used to examine the nature and extent of cognitive impairments in participants with major depressive disorder, bipolar disorder and schizophrenia (Chapter 6). Findings from

this study mirrored those of Chapter 3, indicating that cognitive profiles are similar across disorders but participants with schizophrenia have more severe impairments than participants with bipolar disorder. Participants with major depressive disorder did not differ from healthy controls in their cognitive function. Regression analyses showed that concurrent symptoms of both depression and anxiety at the time of cognitive testing, are associated with cognitive performance across psychiatric disorders. An important concluding observation was that poorer cognitive performance was associated with poorer functional outcome across disorders.

The findings of this thesis add to a growing literature showing the importance of examining cognitive function across psychiatric disorders. To date, it is the first study to develop and utilise an online cognitive assessment for psychiatric research. The key findings and potential implications of this work are discussed in the next section.

7.2 Summary and context of findings

The following summary is divided into two main sections based on the central aims of this thesis. The first section describes the main findings of the studies examining the nature and degree of cognitive impairment across disorders (Chapters 2, 3 and 6). The second section describes the development of the online cognitive battery and the main findings from the validation and main recruitment phases of the study (Chapters 4 and 5).

7.2.1 Cognition across major psychiatric disorders

Cognition across the bipolar-schizophrenia diagnostic spectrum

A central finding of this thesis is that there is a gradient of increasing cognitive impairment from bipolar disorder through schizoaffective disorder – bipolar type to schizoaffective disorder – depressive type and schizophrenia. This was supported by the findings of the meta-analysis and analysis of the CoMPaSS sample.

Differences between the groups were smaller in magnitude in the meta-analysis. However, there was evidence of heterogeneity in the distribution of effect sizes for individual cognitive domains and few studies included data on the subtypes of schizoaffective disorder. The CoMPaSS study included a large, well-characterised sample assessed with a recognised gold-standard battery of cognitive tasks. The

sample was sufficiently large enough to separate the subtypes of schizoaffective disorder. In the CoMPaSS study, the differences between groups were larger in magnitude. The cognitive impairments observed in the bipolar disorder group were on average 0.5-1.25 standard deviations below the control group, this increased to 1-2 standard deviations in the schizoaffective disorder – bipolar type group and 1-2.5 standard deviations in the schizoaffective disorder – depressive type and schizophrenia groups. The effect sizes reported in Chapter 3 are consistent with findings of meta-analyses of cognitive performance in bipolar disorder [237-240] and schizophrenia [191-193].

The results of the meta-analysis and CoMPaSS studies expand on existing literature through three novel findings. Firstly, there was preliminary evidence in the meta-analysis that cognitive impairments were similar in schizophrenia and schizoaffective disorder – depressive type but in contrast the bipolar type of schizoaffective disorder was associated with less severe impairments than schizophrenia. These initial findings were borne out in the analysis of the CoMPaSS sample. These results raise a potential limitation of previous studies that combined the subtypes of schizoaffective disorder for cognitive analysis, and which may have had the effect of obscuring differences between schizoaffective subtypes. Secondly, a gradient of increasing cognitive impairment from bipolar disorder to schizoaffective disorder – depressive type and schizophrenia was demonstrated in the CoMPaSS sample using ordinal regression modelling. Finally, the study showed that lifetime psychosis is linearly associated with severity of cognitive impairments.

These results offer important insights for psychiatric nosology providing support for a dimensional model of psychotic and affective disorders. Diagnostic criteria such as DSM-5 and ICD-10 maintain Kraepelin's dichotomy between schizophrenia and bipolar disorder, although ICD-11 will incorporate symptom specifiers (including cognition) that can be utilised across certain disorders [461]. The National Institute for Mental Health's Research Domain Criteria (RDoC) encourages researchers to adopt a dimensional approach to measuring psychopathology (including cognition) rather than using existing categorical diagnoses [25, 28, 29]. The findings of Chapter 3 adds to a growing body of evidence showing overlap in the presentations of patients with schizophrenia and

bipolar disorder and demonstrates the value of examining psychopathology across disorders. Cognitive profiles were similar across the disorders and the groups differed chiefly on the severity of impairments (except for social cognition). This is consistent with dimensional models, including the model proposed by Owen et al. [24, 26, 27]. Owen and colleagues have proposed that intellectual disability, autism, schizophrenia, schizoaffective disorder and bipolar disorder occupy a gradient of neurodevelopmental impairment [24, 26, 27]. They argue that differences in cognitive impairment across the disorders are the result of quantitative rather than qualitative differences in neurobiological factors, such as polygenic risk, burden of copy number variants (CNVs) and neurobiological dysfunction. In support of this model, studies have identified overlapping polygenic risk between schizophrenia and bipolar disorder [73, 74]. Participants with schizophrenia show an increased burden of CNVs that are also associated with intellectual disability [65, 66] but such an increased burden is not found in studies of bipolar disorder [69-72]. There is evidence of reduced grey matter in similar regions of the brain across disorders (bipolar disorder, schizoaffective disorder and schizophrenia) [347, 348]. However, reductions in grey matter are less extensive in participants with bipolar disorder [347, 348]. These differences in genetic and neurobiological vulnerabilities may manifest in greater cognitive impairment for patients with schizophrenia. Genetic and neurobiological factors were not considered in this study but future studies should investigate whether these factors are associated with cognitive function in a cross-disorder sample. For example, the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) study has measured grey matter volume, sensorimotor reactivity and cognitive performance in their sample of participants with bipolar disorder, schizoaffective disorder and schizophrenia [462]. They utilised cluster analysis in their cross-disorder sample and identified three subgroups. Group 1 was impaired on measures of cognition, sensorimotor reactivity and social functioning and had widespread grey matter reduction. Group 2 had less severe impairments and regionally similar but smaller grey matter reductions compared to Group 1. Group 3 was cognitively normal with slight impairments in sensorimotor reactivity and modest localised reductions in grey matter. In both studies, diagnoses were represented across the groups but bipolar disorder was overrepresented in the cognitively normal group and schizophrenia

was overrepresented in the globally impaired group. Those with schizoaffective disorder were more evenly distributed across the clusters.

The finding that all patient groups are impaired relative to the healthy controls has implications for the development of cognition-enhancing therapies. Pharmaceutical approaches to improve cognitive function in psychiatric disorders have targeted a wide range of neurotransmitter systems, including dopaminergic, noradrenergic, serotonergic and glutamatergic systems, although studies have reported limited efficacy [463]. Non-pharmaceutical approaches that have been examined include repetitive transcranial magnetic stimulation and cognitive remediation therapy [463]. Application of repetitive transcranial magnetic stimulation over the dorsolateral prefrontal cortex has been shown to have modest effects on cognitive function in participants with schizophrenia [464] and depression [465]. Cognitive remediation therapy has been shown to be beneficial to participants with schizophrenia in improving task-specific cognitive performance, although smaller effect sizes are reported when the outcome measure is overall functioning or negative symptoms [466-469]. Cognitive remediation therapy also requires a regular commitment of time and motivation, which may be a barrier for some patients [463]. If similar mechanisms are involved in the development of cognitive impairments across disorders, then any therapy developed to improve cognitive functioning may be beneficial for patients with a variety of psychiatric disorders [463].

Examining cognition across disorders using an online cognitive battery

The study in Chapter 6 develops approaches such as those reported in Chapter 3 by applying online cognitive assessment to examine cognitive impairment in a sample of participants with a diverse range of psychiatric disorders. Cognitive performance was compared between participants with major depressive disorder, bipolar disorder and schizophrenia. The associations between a set of clinical variables (current depressive symptoms, current anxiety symptoms and age of onset) and cognitive performance were examined both within and across disorders. The relationship between cognitive performance and functional outcome (as assessed by the World Health Organisation Disability Assessment Scale 2.0) was also examined within and across disorders.

The results of this chapter mirror the findings of Chapter 3 by demonstrating greater cognitive impairment in participants with schizophrenia than participants with bipolar disorder. Cognitive profiles did not differ between groups. However, this study expanded on these findings by including participants with major depressive disorder. Participants with major depressive disorder did not exhibit cognitive impairments relative to controls (Hedges' g effect sizes ranged from -0.1 to 0.31). These results contradict the findings of previous meta-analyses that have identified mild to moderate impairments in memory, attention and executive function and reported effect sizes ranging from 0.32 to 0.97 across domains [426, 428, 429]. It was also noted that effect sizes for the bipolar disorder and schizophrenia groups were smaller in magnitude in this study compared to Chapter 3. Performance in the bipolar disorder group was on average 0.1 to 0.5 standard deviations below the control group across the domains (compared to -0.5 to -1.25 in Chapter 3). Performance in the schizophrenia group was on average 0.4 to 0.9 standard deviations below the control group (compared to -1 to -2.5 in Chapter 3). This may be explained by the use of online assessments, which may have resulted in participation bias (discussed further in the following sections). In addition to this, the major depressive disorder group were mainly recruited into NCMH non-systematically (primarily through media campaigns). Therefore, this group may not be as impaired as participants recruited through health services.

Current symptoms of depression and anxiety were associated with cognitive performance in a cross-disorder analysis. Previous studies have shown that severity of depressive symptoms is associated with severity of cognitive impairments in participants with either major depressive disorder [426, 434] or bipolar disorder [258, 435]. To my knowledge, this is the first study to demonstrate that higher levels of anxiety are associated with greater cognitive impairment across disorders. This finding has important clinical implications. It suggests that patients experiencing increased depression or anxiety may exhibit poorer cognitive function, irrespective of their diagnosis.

Another novel finding of this study was that poorer cognitive performance was associated with poorer functional outcome in a cross-disorder analysis. This expands on previous findings in schizophrenia [183], bipolar disorder [182] and major depressive disorder [430]. The result is consistent with a study of cognition

and functional outcome in young participants (aged 12-35 years) with recent-onset depression, bipolar disorder and psychosis [186]. Although the major depressive disorder group did not exhibit cognitive impairments on average, poorer cognitive performance was associated with poorer functional outcome in this group. This suggests that cognitive function is still clinically relevant in major depressive disorder. The association was also found when participants with a primary diagnosis of major depressive disorder, bipolar disorder or schizophrenia were excluded. However, it should be noted that the study was cross-sectional so it was not possible to establish the direction of causality.

Social cognition

Whilst deficits in neurocognitive domains were present across disorders, deficits in social cognition were associated with schizophrenia and schizoaffective disorder only. In Chapter 3, participants with bipolar disorder did not exhibit impairments on the Mayor-Salovey-Caruso Emotional Intelligence Test – Managing Emotions (MSCEIT-ME) subtest, whilst participants with schizophrenia and schizoaffective disorder were markedly impaired. Furthermore, current psychotic symptoms were associated with deficits in performance on the MSCEIT-ME but were not associated with any of the other domains. In Chapter 6, participants with schizophrenia exhibited impaired performance on the Morphed Emotion Identification task, whilst only small, non-significant impairments in performance were found in participants with bipolar disorder or major depressive disorder. These results are consistent with a recent meta-analysis that identified more severe deficits in facial emotion recognition and theory of mind in participants with schizophrenia than participants with bipolar disorder [265].

Participants with schizophrenia exhibit deficits in theory of mind, social perception, emotion perception and emotion processing [470]. The measures used in this thesis assess emotion processing (MSCEIT-ME) and facial emotion identification (Morphed Emotion Identification). The observation that social cognition was associated with positive symptoms may provide insights into the psychological modelling of psychotic symptoms. It has been proposed that social cognition may play a role in the development and maintenance of delusions [354]. Deficits in facial emotion recognition are apparent in participants at clinical high-risk for

schizophrenia and first-episode participants [471-473]. It has been proposed that an impaired ability to recognise emotions could predispose individuals to develop paranoid thoughts [474]. An alternative explanation could be that poor social functioning increases exposure to adverse environments that in turn increase risk for the development of psychosis [474]. One study did not find an association between deficits in emotion recognition and conversion to psychosis in at-risk individuals, although only 25 participants developed psychosis in the two-year follow-up period [472].

Other domains of social cognition were not considered in this thesis. For example, participants with schizophrenia exhibit pronounced deficits in theory of mind (ToM) [470]. These deficits are also present in ultra-high risk and first-episode participants [475]. Deficits in ToM have been shown to predict conversion to psychosis in participants at clinical high risk of psychosis [219]. ToM impairments are more severe in participants with schizophrenia than those observed in participants with bipolar disorder [265]. Future studies should examine whether other domains of social cognition follow the same pattern of findings, as those reported here for social processing and identification.

7.2.2 Development of an online cognitive battery

Cognitive data was collected using the MATRICS Consensus Cognitive Battery (MCCB) in Chapter 3. The MCCB is considered a gold standard assessment. However, administering the MCCB is labour intensive so gathering data on very large samples is logistically difficult and expensive. The battery requires a specially trained researcher to administer it [278]. All but one of the tasks are pen and paper tasks so presentation of the stimuli, scoring and recording the data is all done manually so there are potential experimenter effects [272]. The battery takes up to one and a half hours to administer so is time-consuming [277]. By contrast, an online battery is relatively inexpensive despite the initial setup costs, does not require specially trained administrators and data is scored and entered automatically [272]. At the time of writing, no online cognitive batteries had been shown to be suitable for collecting data from participants with psychiatric disorders.

One of the main aims of the PhD was to develop an online cognitive battery that measured the MATRICS domains and pilot this battery in a cross-disorder sample.

The online battery assessed 9 domains of cognition: speed of processing, verbal learning, visual learning, reasoning and problem solving, working memory, attention, social cognition, strategic risk taking and premorbid IQ. Participants with schizophrenia, bipolar disorder or major depressive disorder were recruited to complete the MCCB and the online battery in a pilot and validation study (Chapter 4). In Chapter 4, the convergent validity of the online tasks was evaluated. Convergent validity is measured by assessing the extent to which two tasks assumed to measure the same construct are correlated [476]. The results of these analyses indicated that seven out of eight online tasks were correlated with their MCCB equivalent, although scores on only four tasks had the highest correlations with their MCCB equivalents compared to other MCCB tasks. The online study was then rolled out to participants from two studies within the MRC Centre for Neuropsychiatric Genetics and Genomics at Cardiff University (Chapter 5). The data collected from these two chapters was used to examine cognitive impairments in a cross-disorder sample.

Overall the results of the three chapters indicate that the online battery is a useful tool for gathering cognitive data in large cohorts and across disorders. The battery itself had five main strengths: 1) good convergent validity with the MCCB; 2) moderate to high correlations with general cognitive ability ('g') across tasks; 3) was associated with a measure of functional outcome; 4) discriminated between cases and controls; 5) can be run on touchscreen devices as well as computers. The properties of each task are summarised in Table 7-1. The main strength of using online recruitment was the large amount of cognitive data collected in a short time period at an inexpensive cost. The online sample was representative of the original cohort in terms of age, gender and clinical variables (age of onset and history of hospital admission) but there was evidence that online participants were more highly educated, less likely to be diagnosed with schizophrenia or post-traumatic stress disorder and less likely to have been recruited from secondary services.

Table 7-1 Summary of results from Chapters 4-6

	Correlates with MCCB equivalent?	Correlates with measure of general cognitive ability ('g') derived from MCCB?	Associated with functional outcome?	Discriminates between cases and controls?
Digit Symbol Coding	Yes	Yes	Yes	Yes
Morphed Emotion Identification	Yes ¹	Yes	No	Yes
Verbal Paired Associates	Yes	Yes	No	Yes ¹
Backward Digit Span	Yes ¹	Yes	Yes	Yes ¹
Hartshorne Visual Working Memory	No	Yes ¹	Yes	Yes ¹
Matrix Reasoning	Yes	Yes	No	Yes
Multiple Object Tracking	Yes ¹	Yes	No	Yes ¹
Balloon Analogue Risk Task	N/A ²	No	Yes ¹	No
Vocabulary	Yes	Yes ¹	No	Yes ¹

¹Not significant after correction for multiple testing; ²There is no equivalent to the Balloon Analogue Risk Task in the MCCB. N/A, not applicable.

One shortcoming of the battery is the amount of missing data during later tasks. Excluding data collected during the pilot and validation, 66% of the sample had completed all tasks. In comparison, 89% of participants had full data on the MCCB in Chapter 3. This may be a consequence of unsupervised online testing, as studies utilising online cognitive assessments have reported similar completion rates [274, 410]. However, other factors differed between the two studies and this may have affected completion rates. For example, participants were reimbursed for their time in CoMPaSS and whilst this was not conditional on completing the MCCB, participants may have assumed that they needed to complete the full battery. In the validation study, completion rates were comparable for the MCCB and the online battery suggesting that the use of unsupervised online testing does not fully explain the difference in completion rates between the two studies.

The effect sizes were smaller in Chapter 6 compared to those found using the MCCB, which may indicate that participants with more severe cognitive impairment are less likely to take part in the online study. In Chapter 5, the results indicated that online participants were less likely to have been recruited into NCMH through secondary services, which may suggest that they have a less severe illness. The duration of the battery (45-50 minutes) may discourage certain groups from participating and result in high drop-out rates for the later tasks. This could be resolved by reducing the number of tasks in the battery to create a brief assessment. The results of the factor analysis in Chapter 5 indicated high correlations between tasks and only two factors were extracted. Therefore, a condensed version of the battery may be a useful alternative for particularly impaired populations and is one area of further development. Tasks should be selected systematically based on specified criteria. Based on the results of Chapters 4-6 (see Table 7-1), Digit Symbol Coding and Backward Digit Span would be suitable candidates for inclusion in a brief battery, as the tasks are highly correlated with their MCCB equivalents and 'g', associated with functional outcome, discriminate cases and controls and have short administration times. In contrast, the Balloon Analogue Risk Task (BART) was found to have little value in research of psychiatric populations. Performance on the BART was shown to have a small association with functional outcome but did not discriminate between cases and controls.

Another consideration in any online research is technical issues. Across the validation and main studies, 17 participants reported technical problems (4% of the total sample). Most participants went on to complete all online tasks. More work is needed to determine what impact technical issues have on performance.

Researchers utilising online assessments need to anticipate the occurrence of technical issues in their study design and consider how to account for these in analyses of the data. In the current study, participants who reported technical issues were included in all analyses. However, if there is evidence that technical issues adversely impact performance on the remaining tasks then it may be better to exclude the participant's scores on these tasks.

One psychometric property of the battery that has not been assessed is test-retest reliability. The correlation between two tasks cannot exceed the square root of the product of the test-retest reliabilities of both tasks [272]. Therefore, the

interpretation of the correlations between the online battery and MCCB depend on the test-retest reliability of the tasks. This does not affect the magnitude or significance of the correlations that were found between the tasks, although it would be helpful for interpretation. Future research should evaluate the test-retest reliability of the battery.

Existing cognitive batteries (including the MCCB) are predominantly under copyright and therefore expensive to administer. It is my intention to continue collaborating with The Many Brains Project to make the battery freely available to researchers and potentially healthcare providers, although this will require additional validation and impact studies. The findings so far indicate that the online battery is useful for collecting large samples of cognitive data from people with psychiatric disorders with some caveats. Access to the internet and a computer is essential for individuals who wish to take part and there is evidence of a digital divide between patients with psychiatric disorders and the general population [270, 271]. However, the online battery can be run on touchscreen devices, such as tablet computers and smart phones, which is important given evidence that patients with psychiatric disorders are increasingly using these devices to access the internet [270]. Participation in an online study is also likely to be influenced by the person's computing abilities and confidence in using the internet, although ability and confidence were not assessed in the current study. Based on the results of Chapter 5, there are a number of groups who are less likely to engage with an online cognitive assessment, including patients with schizophrenia, psychosis or PTSD and those with lower educational attainment. The most significant predictor of participation in the online study was recruitment method into NCMH, as participants originally recruited from secondary services were less likely to take part. This may indicate that online participants have a less severe illness but this was not formally assessed. However, providing additional support or motivation to participate may increase recruitment rates from these groups. The online battery can be used to measure general cognitive function and provides valid measurements of the majority of MATRICS domains. However, this online battery is not suitable for assessing free recall memory (particularly verbal memory) or reaction times.

7.3 Methodological considerations in cognitive research of psychiatric disorders

7.3.1 Influence of demographic and clinical variables

There are several demographic and clinical variables that may influence cognitive performance of participants with psychiatric disorders, including age, sex, current and lifetime symptoms and current and lifetime medication use. A strength of this PhD is the inclusion of covariates and the use of regression models to estimate the contributions of these factors to cognitive performance. In Chapter 3, the results of comparisons between groups were robust to the inclusion of age, sex, current psychotic symptoms, current negative symptoms, current dose of antipsychotic medication and duration of antipsychotic use as covariates. In Chapter 6, the results of comparisons were robust to the inclusion of age, sex, current depressive symptoms and current anxiety symptoms. The associations between symptoms and cognition were also examined in cross-disorder analyses. Overall, the results reported in this thesis indicate that factors associated with severity of cognitive impairments include: diagnosis, current and lifetime negative symptoms, lifetime history of psychosis, current dose of antipsychotic medication, duration of exposure to antipsychotic medication, current depressive symptoms and current anxiety symptoms. The relationship between diagnosis and cognitive impairments has been discussed in the previous section and the remaining factors are discussed in the remainder of this section. However, it should be noted that there are likely to be other unidentified confounding variables influencing the between-group comparisons.

Negative symptoms explained a larger proportion of the variance in cognitive scores than diagnosis, although there was no association between negative symptoms and cognition when the analyses were restricted to participants with bipolar disorder and schizoaffective disorder – bipolar type (see Chapter 3). A review of 58 studies showed that negative and disorganised symptoms are associated with neurocognitive impairment, whilst positive symptoms were not [440]. Whether there is a causal relationship between negative symptoms and cognitive performance is unclear and three potential explanations for the association are described here. Firstly, poor cognitive performance may be the result of negative symptoms such as reduced motivation and interest. Secondly,

certain negative symptoms may be a manifestation of poor cognitive function. For example, anhedonia may be the result of reduced attention and memory that hinders patients' ability to participate in and enjoy activities, whilst deficits in social cognition may make maintaining social relationships difficult. Thirdly, both cognitive impairments and negative symptoms may be manifestations of a single disease process. For example, dopamine hypoactivity in the prefrontal cortex has been associated with both negative symptoms and cognitive impairments [477].

Lifetime history of psychosis was associated with (decreased) cognitive function. Studies included in the systematic review reported milder or no cognitive impairments in participants with bipolar disorder and no history of psychosis [303, 316, 319, 321], whilst participants with bipolar disorder and a history of psychosis exhibited deficits closer in magnitude to schizoaffective disorder [295, 308, 314, 316]. In the CoMPaSS sample, greater frequency and severity of psychosis over the course of illness was associated with greater cognitive impairment across the diagnostic groups and within subgroups (see Chapter 3). A related finding was that participants who were taking higher doses of antipsychotic medication at the time of assessment or had longer duration of antipsychotic medication use showed more severe impairments. However, antipsychotic medication use did not fully account for the relationship between lifetime psychosis and cognitive performance. In addition, current psychosis was not associated with cognitive function, although it should be noted that the majority of participants were not acutely psychotic at the time of assessment so only chronic or residual psychotic symptoms were examined in this study. Other factors that might account for the relationship between more severe and frequent psychosis and greater cognitive impairments include younger age of onset, more frequent or prolonged hospitalisations or greater substance use. Alternatively, lifetime psychosis may be associated with cognitive function because both are markers of illness severity so participants with a more severe illness course exhibit greater cognitive impairment and more severe or frequent psychotic episodes.

In Chapter 6, higher scores on scales assessing current depressive and anxiety symptoms were associated with lower cognitive performance. These effects were observed in a cross-disorder analysis but did not explain differences between participants with major depressive disorder, bipolar disorder and schizophrenia.

There are several possible explanations for this finding. More severe symptoms of depression or anxiety may affect cognitive performance directly by reducing the participant's concentration or slowing psychomotor responses. An alternative explanation is that higher scores on the Hospital Anxiety and Depression Scale may indicate a more severe illness course or a relapse in the participant's illness resulting in greater cognitive impairment. The results may be confounded by medication use, which was not explored in this study. Symptoms of depression and anxiety are highly correlated, so it was not possible to disentangle the contributions of these symptoms.

Premorbid IQ was included as a covariate in a separate analysis to examine whether differences in IQ before onset of disorder could explain the differences between groups. However, caution is advised in the interpretation of these results. Cognitive deficits are present before the onset of schizophrenia and it has been argued that schizophrenia is a neurodevelopmental disorder [214, 215, 356]. As such, low premorbid IQ and schizophrenia are not independent. Covariates in analysis of covariance should be unrelated to the independent variable and controlling for premorbid IQ can result in over-correction for group differences [478]. The results of Chapter 3 suggested that cognitive decline is similar between participants with schizoaffective disorder and schizophrenia. Differences between schizoaffective disorder – bipolar type and bipolar disorder were larger after accounting for premorbid IQ suggesting that schizoaffective disorder – bipolar type is associated with greater cognitive decline than bipolar disorder. However, this was not empirically tested and should be investigated using a longitudinal design.

One confounder that was not addressed in this thesis was substance use. The most commonly used substances were alcohol and tobacco. Current alcohol use was reported by 32% of participants in the CoMPaSS sample and 55% of the online sample. Whilst alcohol use causes acute cognitive impairments [479, 480], most participants in the samples (CoMPaSS: 95%; online: 87%) had not consumed alcohol for at least 12 hours and so this seems unlikely to have affected the results. The percentages of current smokers in each sample were 58% of the CoMPaSS sample and 19% of the online sample. However, smoking cigarettes has been associated with small improvements in cognitive performance in participants with schizophrenia suggesting that studies including participants who have recently

smoked may be more likely to underestimate the degree of impairment rather than overestimate it [481].

The most commonly used illegal substance across the two samples was cannabis. Current cannabis use was reported by 6% of the CoMPaSS sample and 4% of the online sample. Cannabis use has been associated with acute impairments in memory [482], attention [483] and planning [483] in the general population. These impairments are transient with no differences found between non-users and cannabis-users who have abstained for at least 25 days [484]. A meta-analysis of cannabis use and cognitive function of participants with schizophrenia found superior performance in the user group compared to the non-user group [485]. The same authors found similar results amongst participants with first-episode psychosis. First-episode participants who used cannabis were impaired on 9 out of 16 tasks, whilst participants who did not use cannabis were impaired on 15 tasks. The authors propose several explanations for these surprising results, including misdiagnosis of substance-induced psychosis as schizophrenia, that cannabis use may induce psychosis in individuals who are less “cognitively vulnerable” or may alleviate psychotic symptoms thus improving cognitive performance [485]. However, a more recent meta-analysis found that current cannabis users with schizophrenia exhibited worse performance on measures of premorbid IQ, current IQ and working memory [486]. Few participants across the samples reported current use of illicit substances other than cannabis (2% of CoMPaSS participants and 1% of online participants). In conclusion, it is unlikely that illicit substance use affected the results reported, as substance use was low both in the CoMPaSS and online samples. However, illicit substance use may be under-reported.

Neither educational attainment nor socioeconomic status was included as a covariate in any analysis. Cognitive deficits are apparent before the onset of these disorders and onset is typically in late adolescence to early adulthood [214, 215, 356]. A consequence of this can be a reduced number of years in education. Similarly, current socioeconomic status is also affected by diagnosis. Therefore, educational attainment and socioeconomic status can be a consequence of the pathology of the disorder rather than confounders. For this reason, controlling for these variables can eliminate the variance in cognitive performance between diagnostic groups.

7.3.2 Representativeness of samples included

An important consideration in cognitive studies of participants with psychiatric disorders is recruiting representative samples. Participants should reflect the population of individuals with that disorder in the community. To encourage recruitment, tasks must be tolerable for participants and of reasonable duration and difficulty. Failure to recruit a representative sample can lead to an underestimation or overestimation of the extent of cognitive impairments in a patient group. The severity of cognitive impairments may be underestimated if participants with the most severe illness are unable or do not wish to participate. Conversely, the extent of impairments may be overestimated if the sample is underrepresented by participants with less severe illness courses. Individuals with a less severe illness course may be less likely to participate due to time constraints (such as work) or because they feel the study may be less relevant to them. They may also be harder to recruit if they have recovered and are no longer in contact with secondary services. The two studies described in this thesis used different recruitment methods and each has advantages and disadvantages.

CoMPaSS is a large UK-based study, which recruits participants from the community via outpatient clinics, clozapine and depot clinics, early intervention psychosis services and using posters, leaflets, website and voluntary organisations. A wide range of recruitment methods is employed to ensure the sample is representative of the population, which is predominantly from south Wales but also north and west Wales, west England, and the cities of Leeds and Hull. Most participants are outpatients at the time of assessment. The study protocol takes two to three hours to complete and requires a face-to-face interview either at the participant's home, local psychiatric clinic or at Cardiff University. This may be a barrier to participation for some individuals, particularly if they are more severely impaired or work full time. The main method of recruitment is through secondary services. As noted above, individuals who have shown good recovery may no longer be in contact with secondary services and therefore may be underrepresented in this study. The sample is also enriched for individuals with treatment-resistant schizophrenia due to recruitment from clozapine clinics. In contrast, the advantage of the online study is that individuals can take part at a time that best suits them. The study is also comparatively shorter taking approximately

one hour to complete. Results from Chapter 5 indicated that the study was largely representative of the original NCMH cohort but had lower response rates from participants with schizophrenia and post-traumatic stress disorder. A disadvantage of this study is that participants need computer skills and access to a computer and the Internet. Therefore, participants with more severe cognitive impairments may be underrepresented in this study.

Another important consideration when recruiting participants with mood disorders and schizophrenia is phase of illness. Mood disorders typically have an episodic course, whilst schizophrenia is a chronic condition. It is debatable whether patients with mood disorders should be recruited when they are in a mood episode or remission. Studies that recruit stabilised patients (such as CoMPaSS) are likely to include participants with differing levels of symptoms. Participants with mood disorders are likely to be experiencing few or no symptoms, whilst participants with schizophrenia are more likely to have negative symptoms and residual psychotic symptoms. Participants with schizoaffective disorder may be experiencing mood, psychotic or negative symptoms, a combination of these or no symptoms. However, only recruiting participants who are symptom free would not be representative of the population of patients with these disorders and thus the results would be less generalizable. Other studies have recruited acutely unwell patients (for example, Amann et al. [295]) but this may overestimate the level of impairment and is less generalizable to patients in the community.

7.3.3 Cognitive assessments

The selection of suitable cognitive assessments is another important consideration in research. The tasks selected should be tolerable for participants and show good validity and reliability. The tolerability, validity and reliability of the MCCB (used in Chapter 3) is well-established [203]. One of the aims of this thesis was to develop an online alternative to the MCCB and establish its validity by comparing the two batteries. Seven out of eight online tasks were correlated with their MCCB equivalent (correlations ranged between 0.26 and 0.73). Two-thirds of participants completed all tasks and feedback from participants was positive suggesting the tasks are tolerable for most participants.

More generally, there are limitations that apply to the use of cognitive assessments, such as the ones utilised in this thesis [487]. Cognitive tasks were scored based on the speed or accuracy of performance and do not directly measure specific neural processes [212]. Performance on any cognitive task requires numerous neural processes to interact to achieve the goal. It is not possible to assess using these tasks how these individual processes interact, for example whether they run in serial or parallel. Analyses of cognitive data ignore the relationship between different components of cognition because they focus on measuring one specific domain, such as working memory. In addition, analysis of cognitive data assumes that each person tackles a cognitive task in the same way.

All cognitive assessments require attention. Attention processes are influenced by numerous factors, including the nature and intensity of the stimuli and relevance of the stimuli to the individual's goals. In the real world, a person's attention can be drawn to aspects of the environment (stimulus-driven [488]) or driven by the person's behaviour (goal-directed [489]) and in turn that person's behaviour can change the stimuli around them. In cognitive assessments, the researcher rather than the participant manipulates the stimuli. Therefore, it has been argued that cognitive tasks lack ecological validity [487, 490].

Despite these limitations, performance on cognitive tasks predicts functional outcome in patients suggesting these tasks are functionally relevant and argues for their continued use in research of psychiatric disorders. In addition to this, cognitive performance is heritable [188] and studies have demonstrated polygenic overlap between cognitive performance and schizophrenia [491]. Stratifying participants by cognitive performance has also been shown to be useful in a study examining the burden of rare genetic variants in participants with schizophrenia [492].

7.3.4 General or specific cognitive impairments

Scores on pairs of cognitive tasks are moderately correlated. The fact that a portion of the variance in each task can be attributed to a general cognitive factor (known as 'g') was noted by Spearman [205]. Spearman described 'g' as the general intellectual function required for completing all cognitive tasks. This has remained a fundamental concept of cognitive psychology, although later theories of

intelligence posited a division between fluid and crystallised intelligence [493]. The implication of 'g' is that the deficits across cognitive domains seen in cases may be the result of a unitary deficit in general cognitive function. Approximately two-thirds of the difference in performance between participants with schizophrenia and healthy controls can be accounted for by 'g' [207, 208]. The results of Chapters 3 and 6 indicated that cognitive profiles across disorders were similar, which could indicate shared underlying neurobiology. An alternative explanation is that performance on the tasks depends on 'g'. Thus, variation in the extent of impairments between cognitive domains may be related to some aspect of the individual tasks, such as difficulty.

In Chapter 5, the factor structure of the online cognitive battery was examined and this provided further evidence that 'g' explains a large proportion of the variance in cognitive performance across domains. Performance on all the online tasks was at least moderately correlated (r ranged from 0.13 to 0.57). The first factor ('g') explained 77% of the variance in cognitive performance and all but two of the tasks loaded onto this first factor. This finding has several implications. If scores across the tasks are highly loaded on a single factor then this argues against using a large number of tasks to assess separate domains. Therefore, it may be more beneficial for studies to assess global cognition using a brief battery. This may reduce the amount of missing data and place less demand on participants, particularly amongst those with severe cognitive impairments. In addition to this, this suggests that unitary measures of 'g' can be combined from studies using different cognitive assessments, which is of particular importance in large genomic studies that aggregate genotype and phenotype data from multiple datasets [494]. A disadvantage of 'g' is it is a relatively non-specific measure and may not be useful for studies that seek to identify the specific underlying pathology that causes cognitive impairments. Tasks that assess specific cognitive mechanisms, such as those included in the Cognitive Neuroscience-Based Approaches to Measuring and Improving Treatment Effects on Cognition in Schizophrenia (CNTRICS) initiative [212], may be useful for identifying specific neurobiological mechanisms that contribute to the development of cognitive impairments.

7.4 Future work

The discussion above has highlighted several potential questions for future research. Work is ongoing to invite participants from NCMH (over 10,000 individuals) and CoMPaSS (over 1,200 individuals) to complete the online battery, as well as expanding ethical approval to other studies within the department. To date (March 2018), over 700 individuals have participated in the online cognition study. These participants have phenotype and genotype data available, which will enable us to examine a range of research questions. In Chapter 6, there were insufficient sample sizes of certain diagnoses to be able to examine cognitive function in participants with specific disorders and this could be explored in future analyses. There is currently limited phenotype data on the NCMH cohort but there is ongoing work to collect more in-depth data through questionnaires and structured clinical interviews. More extensive phenotype information could be used to examine whether the results of Chapter 3 can be extended to other disorders, such as major depressive disorder. These analyses could include examining whether there is a linear association between lifetime psychosis and cognition in depression and the impact of medications. There is also scope to examine whether genetic risk is associated with cognitive function.

The neurobiological basis of cognitive impairments in psychiatric disorders is not well understood. One barrier is the lack of large samples with cognitive data. Current efforts to determine genetic risk factors for cognitive impairments rely on collating data from studies that use a diverse range of cognitive measures. One solution is for studies to use the same standardised battery, such as the MCCB. However, administration of the MCCB can be time-consuming and expensive, which is prohibitive to the collection of cognitive data in large samples. Whether the MCCB is sensitive to cognitive impairments in more diverse cross-disorder samples (not limited to schizophrenia and bipolar disorder) has not been established. Another solution is to take advantage of existing large databases of participants with genetic data and utilise online cognitive assessments. The findings of this thesis indicate it is possible to recruit large samples within a short time period and at a relatively low cost. As genetic studies rely on very large samples for statistical power, combining large datasets that have measured the same domains using comparable tasks is likely to be the best solution. There is a need for

consensus in the domains of cognition that should be assessed across disorders. This exists in schizophrenia research due to the work of the MATRICS initiative [201] and there have been efforts to achieve a similar consensus in bipolar disorder [242]. As the online sample grows, we will be able to examine whether the cognitive battery developed in this thesis is suitable for use in research of other psychiatric disorders.

There are efforts to identify the specific cognitive processes affected in psychiatric disorders, such as the work of the Cognitive Neuroscience-Based Approaches to Measuring and Improving Treatment Effects on Cognition in Schizophrenia (CNTRICS) initiative [212]. The aim of the CNTRICS initiative was to use existing findings from cognitive neuroscience to select tasks for which the underlying neural systems involved are at least partly known. These tasks may be useful in identifying specific neural pathways involved in the aetiology of cognitive impairments.

One of the main statistical approaches taken in Chapters 3 and 6 focused on identifying between-group differences. However, this approach does not account for the individual differences in cognitive performance within diagnostic groups. For example, one study estimated that 16-45% of those with schizophrenia and 42-64% of those with bipolar disorder in their sample could be defined as cognitively normal [314]. This highlights the importance of cross-disorder analyses to identify associations between illness factors and cognitive performance, such as those undertaken in this thesis. There is increasing interest in using data-driven approaches to identify more homogeneous subgroups of participants. It is hoped that these neurocognitive subgroups may be more biologically and functionally relevant than current diagnostic classification and could be used in research of neurobiology and genetics, as well as in the development of cognition enhancing treatments or interventions [495]. Studies utilising cluster analysis across disorders (schizophrenia, schizoaffective disorder and bipolar disorder) have identified three to four clusters with differential patterns of impairment [462, 496]. Both studies included clusters of participants with normal cognitive function and diagnoses were represented across all clusters. This suggests that there is no clear boundary in cognitive performance between diagnoses. In addition, Clementz et al. [462] demonstrated that the clusters differed on measures of grey matter volume and

sensorimotor reactivity. The authors concluded that data-driven approaches could be used to identify neurobiologically distinct groups amongst patients with similar clinical phenotypes. Such approaches could be extended to the study of psychiatric genetics.

7.5 Summary

The main aims of this thesis were to examine cognitive impairment across the bipolar / schizophrenia diagnostic spectrum and develop a new online cognitive battery for use in large-scale studies of mental health disorders. The strengths of the methods utilised within this thesis have been discussed in previous chapters. However, the main strengths are briefly reiterated here. The main strengths of this thesis include: 1) the use of large datasets, including a large and well-characterised dataset of 927 participants in Chapter 3, 2) the use of cross-disorder datasets to examine the associations between clinical and cognitive factors that cross traditional diagnostic boundaries, 3) the inclusion of a range of demographic and clinical covariates in analyses, and 4) the development of a new cognitive battery based on the MATRICS domains.

The work described in this thesis builds on existing scientific knowledge in several ways. Through meta-analytic approaches (Chapter 2) and utilising regression models in a large, well-characterised dataset (Chapter 3), it has been shown that there is a gradient of increasing cognitive impairment from bipolar disorder to schizoaffective disorder – bipolar type to schizophrenia and schizoaffective disorder – depressive type. It has also been demonstrated that participants with the subtypes of schizoaffective disorder differ in the extent of their cognitive impairments. These findings also indicated that lifetime severity and frequency of psychosis is linearly associated with cognitive function across disorders. These results offer important insights for psychiatric nosology and add to a growing body of literature that supports dimensional models of psychotic and affective disorders.

In addition to analyses of existing data, I have developed a new online cognitive battery for use in research of psychiatric disorders. The battery assesses the domains outlined by the MATRICS initiative. To date, there have been no published studies that have examined whether online cognitive testing is suitable for collecting data from populations with psychiatric disorders. I have collected and

analysed cognitive data from a large number of participants with a wide range of psychiatric disorders, including but not limited to major depressive disorder, bipolar disorder, schizophrenia, anxiety disorders and post-traumatic stress disorder. This dataset presents new opportunities to examine the causes and impact of cognitive impairments across psychiatric disorders.

Overall, these findings support the use of cognitive assessments to study psychiatric disorders. Cognitive function is an important indicator of functional outcome and therefore has relevance to clinical practice. Further, it is hoped that the use of cross-disorder samples will aid understanding of the aetiology of psychiatric disorders, particularly in molecular genetic studies that rely on large samples. This would facilitate the development of new treatments and improve functional outcomes for patients.

Appendix A: Hedges g Effect Sizes

Hedges g effect sizes were calculated for each pair of comparisons using the formula described by Rosnow and Rosenthal [291] and Rosnow, Rosenthal and Rubin [292]. The formula for calculating Hedges g is:

$$d = \frac{\bar{X}_1 - \bar{X}_2}{SD_{pooled}}$$

\bar{X}_1 = Mean of group 1

\bar{X}_2 = Mean of group 2

SD_{pooled} = Pooled standard deviation

where the pooled standard deviation was weighted by each group's sample size using the formula:

$$SD_{pooled} = \sqrt{\frac{(n_1 - 1)SD_1^2 + (n_2 - 1)SD_2^2}{n_1 + n_2}}$$

n_1 = Number of participants in group 1

n_2 = Number of participants in group 2

SD_1^2 = Standard deviation of group 1

SD_2^2 = Standard deviation of group 2

Appendix B: Sensitivity analyses (Chapter 2)

Two sets of sensitivity analyses were performed. Firstly, the meta-analysis comparing bipolar disorder and schizoaffective disorder was repeated excluding papers that included bipolar disorder - type II in their sample. Secondly, the analyses were repeated excluding two studies that had samples with a mean age between 58 and 65 years.

Bipolar disorder – type I only

Composite cognition effect sizes were calculated for six studies comparing schizoaffective disorder and bipolar disorder – type I. Participants with schizoaffective disorder performed worse than participants with bipolar disorder ($g=-0.27$, $p<0.0001$, see Figure B-1).

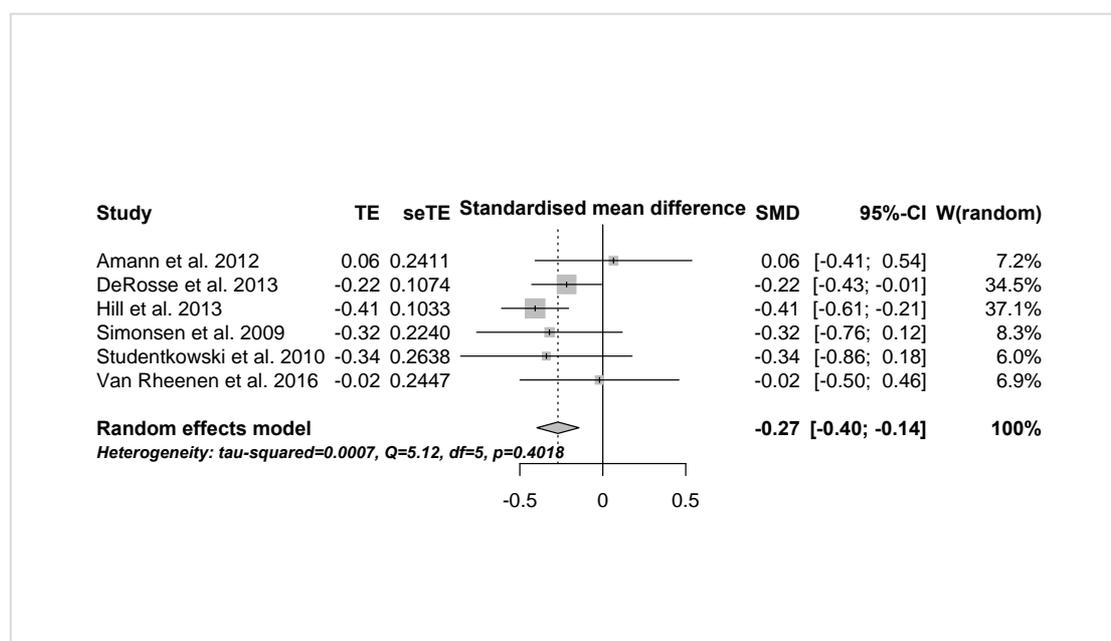


Figure B-1 Forest plot of individual and pooled random effect estimates of mean differences between schizoaffective disorder and bipolar disorder - type I

Positive effect sizes indicate better performance in the schizoaffective disorder group.

Older samples removed

Composite cognition effect sizes were calculated for seven studies comparing schizoaffective disorder and bipolar disorder. The study by Mueser et al. [311] was excluded for this analysis, as the sample included older adults (50 years and older). Participants with schizoaffective disorder performed worse than participants with bipolar disorder ($g=-0.28$, $p<0.0001$, see Figure B-2).

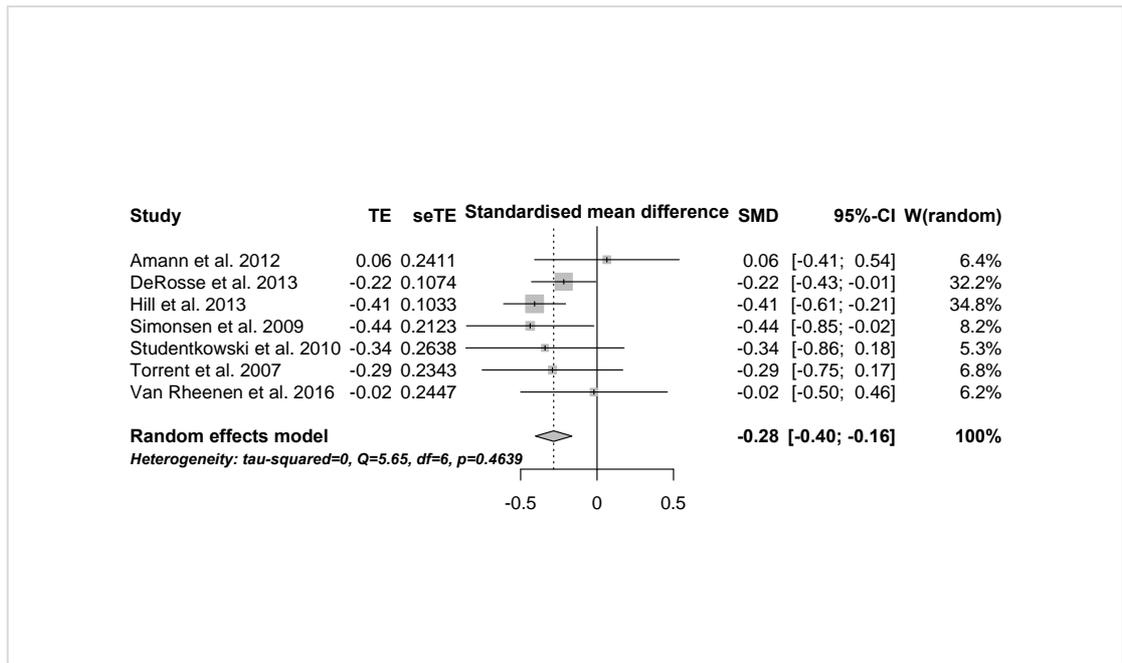


Figure B-2 Forest plot of individual and pooled random effect estimates of mean differences between schizoaffective disorder and bipolar disorder, excluding one study with an older sample

Positive effect sizes indicate better performance in the schizoaffective disorder group.

Composite cognition effect sizes were calculated for 18 studies comparing schizoaffective disorder and schizophrenia. The studies by Mueser et al. [311] and Evans et al. [300] were excluded as both studies had older samples. Participants with schizoaffective disorder performed better than participants with schizophrenia based on composite cognition scores ($g=0.20$, $p<0.0001$, see Figure B-3).

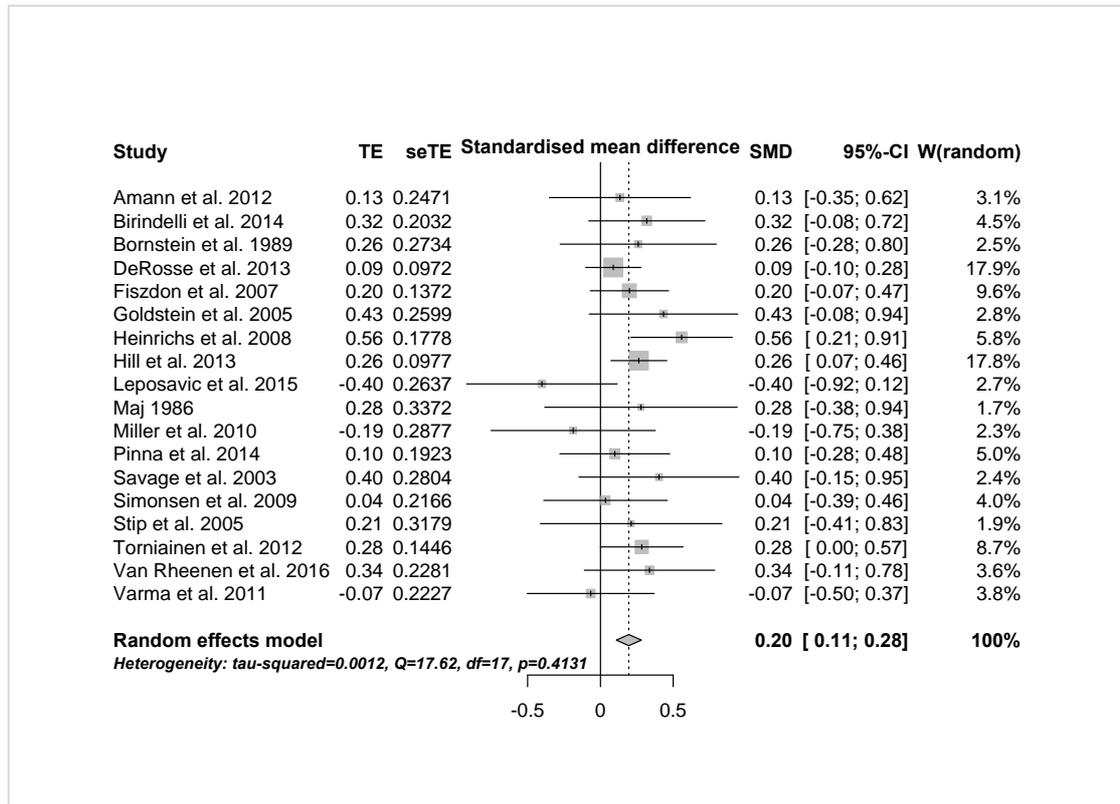


Figure B-3 Forest plot of individual and pooled random effect estimates of mean differences between schizophrenia and schizoaffective disorder

Positive effect sizes indicate better performance in the schizoaffective disorder group.

Appendix C: MCCB Imputation Method

Missing values were imputed using the formula described in the MCCB manual for all tests, with the exception of the CPT-IP, HVLTR and BVMT-R. Imputed composite scores were only used when an individual had completed 5 or more of the domains. The imputed score (Y_{di}) is calculated using the mean Z score of that test for all cases (Y_{d+}), the mean Z score of all completed tests for the individual (Y_{+i}) and the mean Z score of all tests for all individuals (Y_{++}). The formula is:

$$Y_{di} = (Y_{d+}) + (Y_{+i}) - (Y_{++})$$

CPT-IP, HVLTR and BVMT-R

Missing scores were imputed differently on tests with three trials, as there was more information to enable the trial scores to be imputed in a way that would better reflect the participant's performance on that particular test. To impute missing trials of the CPT-IP, the same formula was used but the mean z-scores were taken from CPT-IP trials only so did not include any other tests. Once the individual missing scores for the trials were imputed, the CPT-IP mean was calculated. If a participant was missing all of the trials then the mean score was imputed. To impute missing trials of the HVLTR and BVMT-R, cases were selected with the same total score for the completed trials as the participant with the missing score. For example, if a participant's scores on trials 1 and 2 were 3 and 5 respectively and they were missing trial 3, all cases with a total of 8 on trials 1 and 2 were selected. A mean z-score was calculated from the test totals of these selected cases. This mean z-score was used as the imputed total z-score for the participant with the missing score. This was then converted back into a raw total score and the missing value was filled in so that the total added up correctly. For example, if the participant described above had an imputed total score of 14 then their missing value on trial 3 would be 6.

Appendix D: Completeness of Data (Chapter 3)

Complete data was available on all tasks for the healthy control group. The number of scores available for each domain is shown in Table D-1.

Table D-1 Total number of scores available for each domain of the MCCB

Domain	Bipolar Disorder	Schizoaffective Disorder – Bipolar Type	Schizoaffective Disorder – Depressive Type	Schizophrenia	Complete Data for Cases
Verbal Learning	78	76	112	558	824
Reasoning & Problem Solving	78	76	112	558	824
Visual Learning	78	76	112	554	820
Social Cognition	75	75	110	544	804
Attention / Vigilance	77	72	102	518	769
Speed of Processing	78	76	112	558	824
Working Memory	78	76	112	558	824
Composite Score	78	76	112	557	823

Appendix E: Proportional Odds Assumption (Chapter 3)

Schizoaffective disorder – depressive type and schizophrenia as one

Ordinal regression analyses were conducted to test the hypothesis that cognition can be considered a dimensional phenotype showing increasing impairment from bipolar disorder to schizoaffective disorder – depressive type / schizophrenia. Participants were assigned scores from 0 to 2 based on their diagnosis (0 = schizoaffective disorder - depressive type / schizophrenia, 1 = schizoaffective disorder - bipolar type and 2 = bipolar disorder). Diagnosis was entered as the outcome variable with composite cognition scores as the predictor and age and sex as covariates.

The assumption of proportional odds was confirmed using the test of parallel lines ($\chi^2 = 4.97$, $df = 3$, $p = 0.174$) and by examining the coefficients for binary regressions for each cut-off point in the scale (see Table E-1).

Table E-1 Binary regressions for each threshold of the diagnostic scale

	B coefficients	95% Confidence Intervals	Odds ratios	95% Confidence Intervals
Lower categories vs. BD	0.83	0.6 to 1.06	2.29	1.82 to 2.89
SAD / SZ vs. higher categories	0.65	0.49 to 0.82	1.92	1.63 to 2.27

BD, Bipolar Disorder; SAD, Schizoaffective Disorder – Depressive Type; SZ, Schizophrenia.

All Groups

In the second ordinal model, participants were assigned scores from 0 to 3 based on their diagnosis (0 = schizophrenia, 1 = schizoaffective disorder – depressive type, 2 = schizoaffective disorder – bipolar type and 3 = bipolar disorder). The results of the parallel lines test indicated that the proportional odds assumption was violated in this model ($\chi^2 = 27.61$, $df = 6$, $p = 1.1 \times 10^{-4}$). This indicates that the logistic estimates are not equal across all levels of the dependent variable therefore the combined estimate for the model is not accurate. To investigate this further, I calculated the coefficients for binary regressions for each cut-off point in the scale. There are three cut-off points (thresholds) on this scale and therefore three binary regressions were conducted:

1. Schizophrenia vs. all higher categories
2. Schizophrenia and schizoaffective disorder – depressive type vs. schizoaffective disorder – bipolar type and bipolar disorder
3. All lower categories vs. bipolar disorder

The results of binary regressions examining each threshold of the diagnostic scale are shown in Table E-2. Overall, the coefficients were not equal across the analyses with the largest difference in coefficients between analysis 1 and analysis 3.

Table E-2 Binary regression results for each threshold of the diagnostic scale

	B coefficients	95% Confidence Intervals	Odds ratios	95% Confidence Intervals
1. SZ vs. higher categories	0.38	0.26 to 0.51	1.46	1.3 to 1.67
2. SAD and SZ vs. BD and SAB	0.65	0.49 to 0.82	1.92	1.63 to 2.27
3. Lower categories vs. BD	0.83	0.6 to 1.06	2.29	1.82 to 2.89

BD, Bipolar Disorder; SAB, Schizoaffective Disorder – Bipolar Type; SAD, Schizoaffective Disorder – Depressive Type; SZ, Schizophrenia.

Schizoaffective disorder as one

The final ordinal model included schizoaffective disorder as a single category (0 = schizophrenia, 1 = schizoaffective disorder and 2 = bipolar disorder). The test of parallel lines was significant indicating that the proportional odds assumption had been violated in this model ($\chi^2 = 20.03$, $df = 3$, $p = 1.7 \times 10^{-4}$). The results of individual binary regressions for each cut-off point on the scale are shown in Table E-3. The coefficients for these models were not similar indicating that the coefficient in the ordinal regression model may not be accurate.

Table E-3 Binary regression results for each cut-off point on the diagnostic scale

	B Coefficient	95% Confidence Intervals	Odds ratios	95% Confidence Intervals
Lower categories vs. BD	0.83	0.6 to 1.06	2.29	1.82 to 2.89
SZ vs. higher categories	0.38	0.26 to 0.51	1.46	1.3 to 1.67

BD, Bipolar Disorder; SZ, Schizophrenia.

Appendix F: Schizoaffective disorder as a single group

Previous studies comparing cognitive function between diagnoses have combined the subtypes of schizoaffective disorder. Therefore, a further set of ANCOVAs was conducted that included schizoaffective disorder as a single group (combining the bipolar and depressive subtypes). This allowed me to evaluate whether amalgamation of the subtypes of schizoaffective disorder as a single group could be masking differences between the diagnoses. As previously, there was a main effect of diagnosis for all domains of cognition. Post hoc tests revealed significantly greater impairment in the schizoaffective group compared to the bipolar group on all measures, except attention (composite cognition: $g=0.75$, $p<0.001$, see Table F-1 for full results). The schizophrenia group was significantly more impaired than the schizoaffective group (composite cognition: $g=0.29$, $p=0.005$).

Table F-1 Comparison of cognitive performance with schizoaffective disorder as a single group

Domain	Effect of Diagnosis			Pairwise Comparisons
	F ^{df}	p	Partial η^2	
Verbal Learning	F ^{3, 923} =81.08	<2.2 x 10 ⁻¹⁶	0.21	SA < BD ² SZ < BD ²
Reasoning & Problem Solving	F ^{3, 923} =55.41	<2.2 x 10 ⁻¹⁶	0.15	SA < BD ² SZ < BD ²
Visual Learning	F ^{3, 923} =68.42	<2.2 x 10 ⁻¹⁶	0.18	SA < BD ² SZ < BD ² SZ < SA ²
Social Cognition	F ^{3, 903} =33.37	<2.2 x 10 ⁻¹⁶	0.10	SA < BD ² SZ < BD ²
Attention / Vigilance	F ^{3, 868} =45.24	<2.2 x 10 ⁻¹⁶	0.14	SA < BD ² SZ < BD ² SZ < SA ¹
Speed of Processing	F ^{3, 923} =104.92	<2.2 x 10 ⁻¹⁶	0.26	SA < BD ² SZ < BD ² SZ < SA ¹
Working Memory	F ^{3, 923} =66.03	<2.2 x 10 ⁻¹⁶	0.18	SA < BD ² SZ < BD ²
Composite Score	F ^{3, 922} =120.71	<2.2 x 10 ⁻¹⁶	0.28	SA < BD ² SZ < BD ² SZ < SA ²

All case-control comparisons were significant ($p<0.001$), except for bipolar disorder on social cognition (no significant difference). Partial η^2 indicates the proportion of variance in cognitive scores that is associated with diagnosis. BD, bipolar disorder; SA, schizoaffective disorder; SZ, schizophrenia; ¹ $p<0.05$, ² $p<0.00625$ (Bonferroni-corrected)

Appendix G: Bristol Online Survey Questionnaire

Participants who are sent a letter with a username and password see the login page below. Participants who are sent an email with their unique website link included do not see this page, as their details are entered automatically when they click on the link. Each page of the BOS questionnaire is displayed below.

CoMPaSS Web

Please sign in below using the credentials supplied to you

Username

Password

[Sign in](#)

CoMPaSS Web

0% complete

Page 1: Cognition in Mood, Psychosis and Schizophrenia Study (CoMPaSS Web)

Welcome to the Cognition in Mood, Psychosis and Schizophrenia Study (CoMPaSS Web). Thank you for your interest in this research. The aim of this study is to examine whether memory and concentration problems are linked with a range of mental health disorders, including mood disorders, such as bipolar disorder and major depression, and psychotic disorders, such as schizophrenia.

The study should take no longer than one hour to complete. On the next page you will be given full information about the study and asked to give your consent to participate. You will then be asked to answer some brief questions about your mental health (no more than ten minutes) and complete some memory and concentration tasks (no more than fifty minutes).

All of your data will be kept securely and confidentially. If you would like to contact the team, please call 02920 688371 or email us at compass@cardiff.ac.uk.

Thank you.

CoMPaSS Web Team

[Next >](#)

[Finish later](#)

CoMPaSS Web

10% complete

Page 2: Study Information

Please read the following information carefully before deciding whether to participate in this study. If anything is unclear or you would like more information, please contact us using the information at the bottom of this page.

The consent form is located at the bottom of this page.

What is the purpose of the study?

Our team is interested in examining how people with a history of mental health problems perform on a set of cognitive tasks and how this may be influenced by genes and the environment. We will also use this data to investigate the finding that mental health conditions can impair memory and concentration skills and that this can have a major effect on people's functioning. Through this work we hope to describe the type of cognitive problems people may experience, their causes and effects. During this study, you will be asked to complete a series of memory and concentration tasks.

Why have I been invited?

You are being asked to take part because you have previously taken part in studies involving Cardiff University, such as the Cognition in Psychosis, Schizophrenia and Bipolar Disorder Study, the Bipolar Disorder Research Network (BDRN) or the National Centre for Mental Health (NCMH). You have given permission to be contacted about new research in the department.

Do I have to take part?

It is up to you to decide if you would like to take part. If you decide to take part you are still free to withdraw at any time and without giving a reason. This will not affect the standard of care you receive. If you wish to withdraw at any time please contact us. We will then discuss whether we can use the data collected or whether you would prefer for your details to be removed from the study.

What will I have to do?

We will ask you to complete a short questionnaire about your mental health. We will then ask you to complete a series of tasks that are similar to games or puzzles. You will receive specific instructions and complete a practice session before each task.

How long will this study take?

This study will take about 1 hour to complete.

What if I change my mind and don't want to do the study anymore?

Your participation is completely voluntary and you can withdraw from the experiment at any time by closing your browser window. You can leave blank questions you do not wish to answer in the questionnaire.

What will happen with my information?

All information that is collected about you during the course of the study will be kept strictly confidential. All of the data collected will be identified by an ID code rather than your name. A separate list of names and ID codes will be kept securely. The information will be stored securely at Cardiff University. Your data will be kept for 10 years in accordance with guidelines from the Medical Research Council. Only members of the research team who have signed confidentiality agreements will have access to the data on our servers. We will follow the rules of the Data Protection Act (1998).

We will also link the information from this study to the existing information that we collected about you in the original study you participated in. This includes genetic information collected from the blood sample you gave us. We can do this by using the ID number that was assigned to you in the first study you took part in.

A group called TestMyBrain from Harvard University, Boston, USA designed the cognitive assessments used in this study and hosts the website that is used to collect the cognitive data. We work closely with these researchers in designing the tests to be used. The cognitive test data will be uploaded to their secure servers. We will ensure that any data shared with TestMyBrain will not compromise your confidentiality. An ID number will be entered before you complete the cognitive tasks. TestMyBrain will only have access to this ID number and your scores on the cognitive tasks. The answers you give in the questionnaire will not be shared with TestMyBrain and they will not hold any information about you.

What are the possible disadvantages and risks of taking part?

The risks and disadvantages of taking part are minimal. The cognitive tasks are not thought to cause any psychological problems or lead to any mental health difficulties. If you have any concerns, you can contact the team on 02920 688043. If you remain unhappy and wish to complain formally, you can do this by contacting School of Medicine Research Ethics Committee at Cardiff University.

What are the possible benefits of taking part?

Participation in this study will not provide any direct benefit to you but it is hoped that this study will add to existing evidence about cognition in these conditions.

What will happen to the results of the research study?

It is hoped that the results will be published in scientific/medical journals and also presented at conferences related to mental health. The identity of all participants in the study will be kept strictly confidential when the results are presented. We will keep you updated of the results of the study through newsletters.

Who is doing the study?

Members of the Division of Psychological Medicine and Clinical Neurosciences, School of Medicine, Cardiff University have organized this study. This study is joint-funded by a Medical Research Council PhD studentship competitively awarded to Amy Lynham.

Who has reviewed the study?

All research is looked at by an independent group of people, called a Research Ethics Committee, to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given favourable opinion by the School of Medicine Research Ethics Committee at Cardiff University.

What if I have questions?

If you have any questions about participating in this study, please contact the research team on 02920 688043 or email us at compass@cardiff.ac.uk.

How do I agree to participate?

By ticking the box next to "I agree to participate..." you are saying that:

1. You have read and understood this information and have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.
2. You understand that your participation is voluntary and you are free to withdraw at any time, without giving reason and without your medical care or legal rights being affected.
3. You agree for your scores on the cognitive tasks to be shared with TestMyBrain. This will be done anonymously.
4. You agree to take part in this study.

I agree to take part in this study and know that I am free to leave the study at any point. *

Required

Yes

No

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Page 3

Please enter your age: * *Required*

Please select your gender: * *Required*

Female

Male

Prefer not to say

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CoMPaSS Web

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Page 4: Diagnosis, Medication and Admissions

Have you been given a diagnosis by your psychiatrist?

- Yes
- No

Please select your most recent main diagnosis from the list of options:

Please select

If you selected Other, please specify:

This part of the survey uses a table of questions, [view as separate questions instead?](#)

Have you ever been diagnosed with any of the following:

	Yes	No	Don't Know
Schizophrenia	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Psychosis	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Clinical / Major Depression	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Bipolar Disorder / Manic Depression	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

This part of the survey uses a table of questions, [view as separate questions instead?](#)

Please select your current psychiatric medications and include the dose and length of time you have been taking each medication:

	Medication	Dose (total mg per day)	How long have you been taking this medication?
1.	Please select		
2.	Please select		
3.	Please select		
4.	Please select		
5.	Please select		

Has your medication changed in the last month?

Yes
 No

If yes, please provide details:

Please list any other medications you are currently taking:

Have you been admitted to hospital because of your mental health in the last three months?

Yes

No



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Page 5: Alcohol, Smoking and Drugs

Do you currently smoke?

- Yes
- No

If yes, how long ago did you last smoke?

Do you currently drink alcohol?

- Yes
- No
- Prefer not to say

If yes, how long ago did you last drink alcohol?

Do you currently use cannabis?

- Yes
- No
- Prefer not to say

If yes, how long ago did you last use cannabis?

Do you currently use any other illicit or street drugs?

- Yes
- No
- Prefer not to say

If yes, how long ago did you last use street drugs?

Please select:

Please select

If you selected Other, please specify:

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CoMPaSS Web

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Page 6: Medical History

Have you ever been diagnosed with or experienced any of the following?

- Dyslexia
- Surgery on your head
- Dementia (of any type)
- Stroke / brain haemorrhage
- Head injury with loss of consciousness (that required hospital admission)
- Epilepsy
- Multiple sclerosis
- A brain tumour
- Learning disability
- Other neurological condition

Please provide details:

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Please select which of the following best **describes your work now**:

- Legislator / senior official / manager
- Professional
- Technician / associate professional / civil servant
- Clerk / office worker
- Service worker / shop & market worker
- Skilled agricultural / fishery worker
- Craft & related trade worker
- Plant & machinery operator / assembler
- Elementary occupation
- Armed forces
- Not working due to sickness / disablement
- Homemaker
- Full-time student
- Unemployed
- Retired
- Voluntary work
- Other / Unsure

Please write job title here:

If you are currently working, is this job full-time or part-time?

- Full-time
- Part-time

Please select which of the following types of jobs you have had **during your lifetime**:

- Legislator / senior official / manager
- Professional
- Technician / associate professional / civil servant
- Clerk / office worker
- Service worker / shop & market worker
- Skilled agricultural / fishery worker
- Craft & related trade worker
- Plant & machinery operator / assembler
- Elementary occupation
- Armed forces
- Never worked due to sickness / disablement
- Homemaker
- Never worked
- Full-time student
- Voluntary work
- Other / Unsure

Please write job title here:

[< Previous](#)

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[Finish later](#)

CoMPaSS Web

70% complete

Page 8: WHODAS

This questionnaire asks about **difficulties due to health conditions**. Health conditions include diseases or illnesses, other health problems that may be short or long lasting, injuries, mental or emotional problems, and problems with alcohol or drugs.

Think back over the **past 30 days** and answer these questions, thinking about how much difficulty you had doing the following activities. For each question, please select only **one** response.

This part of the survey uses a table of questions, [view as separate questions instead?](#)

In the past 30 days, how much difficulty did you have in:

	None	Mild	Moderate	Severe	Extreme or cannot do
Standing for long periods such as 30 minutes?	<input type="radio"/>				
Taking care of your household responsibilities?	<input type="radio"/>				
Learning a new task, for example, learning how to get to a new place?	<input type="radio"/>				
How much of a problem did you have joining in community activities (for example, festivities, religious or other activities) in the same way as anyone else can?	<input type="radio"/>				
How much have you been emotionally affected by your health problems?	<input type="radio"/>				
Concentrating on doing something for ten minutes?	<input type="radio"/>				
Walking a long distance such as a kilometre (or equivalent)?	<input type="radio"/>				
Washing your whole body?	<input type="radio"/>				
Getting dressed?	<input type="radio"/>				
Dealing with people you do not know?	<input type="radio"/>				
Maintaining a friendship?	<input type="radio"/>				
Your day-to-day work?	<input type="radio"/>				

Overall, in the past 30 days, **how many days** were these difficulties present?

In the past 30 days, for how many days were you **totally unable** to carry out your usual activities or work because of any health condition?

In the past 30 days, not counting the days that you were totally unable, for how many days did you **cut back** or **reduce** your usual activities or work because of any health condition?

This questionnaire was reproduced, with permission of WHO, from Measuring Health and Disability: Manual for WHO Disability Assessment Schedule (WHODAS 2.0). Geneva, World Health Organization, 2010 (WHODAS 2.0 12-item Self-Report Instrument www.who.int/classifications/icd/whodasii/en accessed 17th May 2017. The World Health Organization (WHO) does not endorse any specific companies, products or services.

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[Finish later](#)

CoMPaSS Web

80% complete

Page 9: HADS

Please select the reply that is closest to how you have been feeling in the past week. Don't take too long over your replies: your immediate is best.

I feel tense or 'wound up':

- Not at all
- From time to time, occasionally
- A lot of the time
- Most of the time

I still enjoy the things I used to enjoy:

- Definitely as much
- Not quite so much
- Only a little
- Hardly at all

I get a sort of frightened feeling as if something awful is about to happen:

- Not at all
- A little, but it doesn't worry me
- Yes, but not too badly
- Very definitely and quite badly

I can laugh and see the funny side of things:

- As much as I always could
- Not quite so much now
- Definitely not so much now
- Not at all

Worrying thoughts go through my mind:

- Only occasionally
- From time to time, but not too often
- A lot of the time
- A great deal of the time

I feel cheerful:

- Most of the time
- Sometimes
- Not often
- Not at all

I can sit at ease and feel relaxed:

- Definitely
- Usually
- Not often
- Not at all

I feel as if I am slowed down:

- Not at all
- Sometimes
- Very often
- Nearly all the time

I get a sort of frightened feeling like 'butterflies' in the stomach:

- Not at all
- Occasionally
- Quite often
- Very often

I have lost interest in my appearance:

- I take just as much care as ever
- I may not take quite as much care
- I don't take as much care as I should
- Definitely

I feel restless as I have to be on the move:

- Not at all
- Not very much
- Quite a lot
- Very much indeed

I look forward with enjoyment to things:

- As much as I ever did
- Rather less than I used to
- Definitely less than I used to
- Hardly at all

I get sudden feelings of panic:

- Not at all
- Not very often
- Quite often
- Very often indeed

I can enjoy a good book or radio or TV program:

- Often
- Sometimes
- Not often
- Very seldom

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[Finish later](#)

CoMPaSS Web

90% complete

Page 10: AMS

This questionnaire asks you about how you feel today.

1. On this questionnaire are groups of five statements. Please read each group of statements carefully.
2. Choose **one** statement in each group that *best* describes how you feel *today*.
3. Please note, the word "occasionally" when used here means once or twice. "Often" means several times or more. "Frequently" means most of the time.

Statement 1.

- I do not feel happier or more cheerful than usual.
- I occasionally feel happier or more cheerful than usual.
- I often feel happier or more cheerful than usual.
- I feel happier or more cheerful than usual most of the time.
- I feel happier or more cheerful than usual all of the time.

Statement 2.

- I do not feel more self-confident than usual.
- I occasionally feel more self-confident than usual.
- I often feel more self-confident than usual.
- I feel more self-confident than usual most of the time.
- I feel more self-confident than usual all of the time.

Statement 3.

- I do not need less sleep than usual.
- I occasionally need less sleep than usual.
- I often need less sleep than usual.
- I frequently need less sleep than usual.
- I can go all day and night without any sleep and still do not feel tired.

Statement 4.

- I do not talk more than usual.
- I occasionally talk more than usual.
- I often talk more than usual.
- I frequently talk more than usual.
- I talk constantly and cannot be interrupted.

Statement 5.

- I have not been more active (either socially, sexually, at work, home or school) than usual.
- I have occasionally been more active than usual.
- I have often been more active than usual.
- I have frequently been more active than usual.
- I am constantly active or on the go all the time.

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[Finish ✓](#)

[Finish later](#)

CoMPaSS Web

100% complete

Thank you for completing part 1 of the study. Please click the link to go on to part 2.

The next stage of the study will be the memory and concentration tasks.

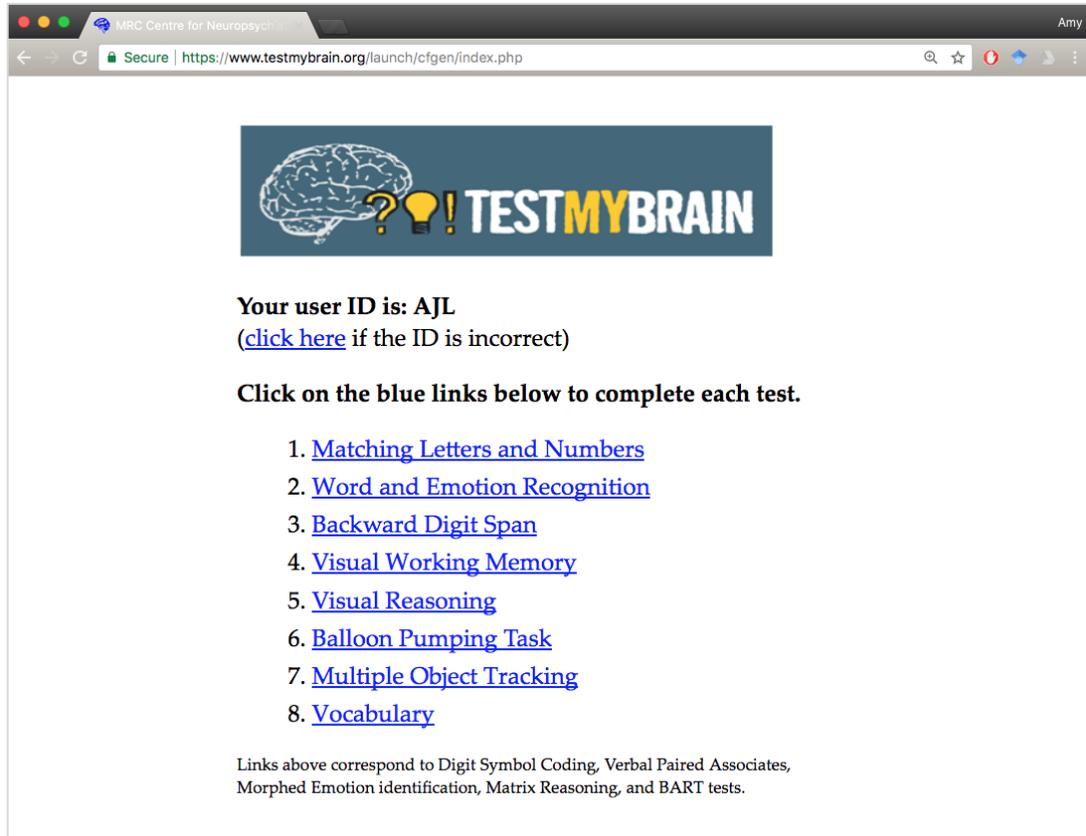
You will need to enter the following ID number if requested: TestAL

It is best to do the memory and concentration tasks in a quiet area that is free from distractions if possible. During number tasks, please use the numbers located above the letters on your keyboard.

[Please click here to complete the next stage of the study](#)

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Appendix H: TestMyBrain Online Cognitive Battery Website



MRC Centre for Neuropsychology

Secure | <https://www.testmybrain.org/launch/cfgen/index.php>

Amy



Your user ID is: AJL
([click here](#) if the ID is incorrect)

Click on the blue links below to complete each test.

1. [Matching Letters and Numbers](#)
2. [Word and Emotion Recognition](#)
3. [Backward Digit Span](#)
4. [Visual Working Memory](#)
5. [Visual Reasoning](#)
6. [Balloon Pumping Task](#)
7. [Multiple Object Tracking](#)
8. [Vocabulary](#)

Links above correspond to Digit Symbol Coding, Verbal Paired Associates, Morphed Emotion identification, Matrix Reasoning, and BART tests.

Appendix I: Feedback Questionnaire (Chapter 4)

COMPASS Web Pilot Questionnaire

Participant ID:

Part 1 - Questionnaire

	Very Clear	Clear	Unclear	Very Unclear
Was the information provided at the start of the study clear?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

How could we improve the information page?

	Very Good	Good	Fair	Poor	Very Poor
Overall, how would you rate the questionnaire:	<input type="checkbox"/>				

Were there any parts of the questionnaire that you would change?

Part 2 – Online Cognitive Tasks

	Very Clear	Clear	Unclear	Very Unclear
Were the instructions for the tasks clear?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Comments:

	Yes	No
Did you experience any technical difficulties during the tasks?	<input type="checkbox"/>	<input type="checkbox"/>

If yes, please provide details:

Overall, how would you rate the online cognitive tasks on:

	Very Good	Good	Fair	Poor	Very Poor
Enjoyability	<input type="checkbox"/>				
Interest	<input type="checkbox"/>				
Duration	<input type="checkbox"/>				
Difficulty	<input type="checkbox"/>				

Comments:

Were there any tasks that you particularly liked? Why?

Were there any tasks that you particularly disliked? Why?

How could we improve the study?

	More likely	Less likely	Don't know
After having taken part in this study, are you more or less likely to take part in further online research studies?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Thank you.

Appendix J: Comparison of counter-balanced control groups (Chapter 4)

In the validation study described in Chapter 4, the control group was counterbalanced such that ten participants completed the MCCB first and nine participants completed the online battery first. I compared scores on tasks between the two groups, adjusting for age and gender. There were no differences in performance between the groups, except that the group who completed the MCCB had better scores on the MSCEIT (see Table J-1).

Table J-1 Comparisons of counter-balanced control groups

	MCCB First	Online First	F	p
<i>MCCB Task</i>				
Digit Symbol Coding	-0.16 (0.27)	0.18 (0.28)	0.72	0.41
HVLT-R	-0.16 (0.31)	0.17 (0.33)	0.51	0.49
Letter Number Sequencing	0.07 (0.35)	-0.08 (0.37)	0.09	0.77
BVMT-R	0.06 (0.33)	-0.07 (0.35)	0.07	0.79
MSCEIT: ME	0.48 (0.31)	-0.53 (0.32)	4.9	0.04
CPT-IP	0.06 (0.35)	-0.07 (0.36)	0.07	0.8
NAB Mazes	-0.22 (0.28)	0.24 (0.30)	1.21	0.29
NART	0.26 (0.34)	-0.29 (0.36)	1.19	0.3
<i>Online Task</i>				
Digit Symbol Coding	-0.17 (0.33)	0.19 (0.35)	0.57	0.46
VPA	-0.09 (0.32)	0.1 (0.33)	0.16	0.7
Morphed Emotion Identification	-0.03 (0.27)	0.03 (0.28)	0.02	0.88
Backward Digit Span	0.24 (0.34)	-0.26 (0.36)	0.95	0.35
Hartshorne Visual Working Memory	-0.09 (0.34)	0.1 (0.36)	0.14	0.72
Matrix Reasoning	-0.3 (0.3)	0.33 (0.32)	2	0.18
BART	-0.2 (0.33)	0.22 (0.35)	0.73	0.41
Multiple Object Tracking	-0.13 (0.33)	0.14 (0.35)	0.3	0.59
Vocabulary	0.15 (0.33)	-0.15 (0.33)	0.41	0.53

Mean and standard errors shown. BART, Balloon Analogue Risk Task; BVMT-R, Brief Visuospatial Memory Test – Revised; CPT-IP, Continuous Performance Test – Identical Pairs; HVLT-R, Hopkins Verbal Learning Test – Revised; MCCB, MATRICS Consensus Cognitive Battery; MSCEIT: ME, Mayer-Salovey-Caruso Emotional Intelligence Test: Managing Emotions; NAB, Neuropsychological Assessment Battery; NART, National Adult Reading Test; VPA, Verbal Paired Associates.

Appendix K: Recruitment letters

Letters to CoMPaSS participants

Division of Psychological Medicine and Clinical Neuroscience

Hadyn Ellis Building

Maindy Road

Cardiff

CF24 4HQ

Dear [*participant's name*],

As you have previously helped us with our research at the Division of Psychological Medicine and Clinical Neuroscience, we are contacting you to let you know of an additional research opportunity that may be of interest to you.

We are looking for volunteers to complete some online memory and problem solving tasks and brief questionnaires. This is important research, which will inform our ongoing work to improve outcomes for people with psychosis and mood disorders. You will need access to the internet to participate in this study. The total study time will be no more than 1 hour and you may take breaks whenever you wish.

If you are interested in participating, would like further information or wish to contact us to let us know you do not wish to take part, please use one of the following options:

1. You can visit the study website by typing this link into your web browser: <https://cardiff.onlinesurveys.ac.uk/compass>. Here you will find the study information sheet and consent form. To enter the study, please use the following information:

Username: [*ID number*]

Password: [*password*]

(Please note: Once you have started the study, do not close the page, as you will not be able to complete the study later. If you wish to take a break and come back, scroll to the bottom of the page and click “Finish later”.)

2. You can contact the team for further information via phone 02920 688043 or email compass@cardiff.ac.uk.
3. You can return the reply slip included with this letter using the freepost envelope provided.

Please note that if you do not have access to the internet but still wish to take part, it may be possible for the team to arrange internet access for you. It is your decision whether you take part in the research and you will be able to withdraw at any stage should you wish to do so.

We like to keep our participants updated on new research and findings from our study through our newsletter. In order to do this, we need to regularly update your information to ensure the contact details we hold for you are up to date. We also plan to contact our participants via email, although this will not replace our postal newsletter. If your contact details have changed or you have not provided us with an email address, please update us with your details through the contact email or phone number above, or by returning the reply slip enclosed. We would be grateful if you could do this even if you do not wish to take part in the above study. If you would prefer us not to contact you by email, please let us know.

Thank you once again for your ongoing co-operation.

Yours sincerely,

Amy Lynham, PhD student

Dr James Walters, Clinical Reader, Honorary Consultant Psychiatrist

Cognition in Mood, Psychosis and Schizophrenia Study (CoMPaSS)

Recruitment email to NCMH participants (cases)

Dear [*participant's name*],

As you have previously helped us with our research at the National Centre for Mental Health (NCMH), we are contacting you to let you know of an additional research opportunity that may be of interest to you.

We have developed an online way of conducting a number of learning and memory tasks, which will help us in our research on mental health. Examples may include memory and problem solving tasks. These are important questions because some people who have experienced mental health problems have difficulty with concentration and memory, which we know can impact on their day-to-day life. We are looking for volunteers to complete these tasks. The total study time will be no more than 1 hour and you may take breaks whenever you wish.

If you are interested in participating or would like further information, you can visit the study website by clicking on the link below:

[*unique website link here*]

Once you have clicked on the link, do not close the page as you will not be able to complete the study later. If you wish to take a break and come back, scroll to the bottom of the page and click "Finish later".

It is your decision whether you take part in the research and you will be able to withdraw at any stage should you wish to do so.

Kind regards

Professor Ian Jones (NCMH Director)

& The NCMH Team

Recruitment email to NCMH participants (controls)

Dear [*participant's name*],

As you have previously helped us with our research at the National Centre for Mental Health (NCMH), we are contacting you to let you know of an additional research opportunity that may be of interest to you.

We have developed an online way of conducting a number of learning and memory tasks, which will help us in our research on mental health. Examples may include memory and problem solving tasks. We are looking for volunteers who have not experienced significant mental health problems to complete these tasks. Your scores will be included as part of a comparison group, which will be compared to groups of participants with mental health problems. This will help us to determine if certain mental health disorders are associated with memory and concentration problems and to what extent. These are important questions because difficulties with memory and concentration can impact on a person's day-to-day life. The total study time will be no more than 1 hour and you may take breaks whenever you wish.

If you are interested in participating or would like further information, you can visit the study website by clicking on the link below:

[*website link here*]

Once you have clicked on the link, do not close the page as you will not be able to complete the study later. If you wish to take a break and come back, scroll to the bottom of the page and click "Finish later".

It is your decision whether you take part in the research and you will be able to withdraw at any stage should you wish to do so.

Kind regards

Professor Ian Jones (NCMH Director)

& The NCMH Team

Recruitment letter to NCMH participants

Division of Psychological Medicine and Clinical Neuroscience

Hadyn Ellis Building

Maindy Road

Cardiff

CF24 4HQ

Dear [*participant's name*],

As you have previously helped us with our research at the National Centre for Mental Health (NCMH), we are contacting you to let you know of an additional research opportunity that may be of interest to you.

We have developed an online (over the internet) way of conducting a number of learning and memory tasks, which will help us in our research on mental health. Examples may include memory and problem solving tasks. These are important questions because some people who have experienced mental health problems have difficulty with concentration and memory, which we know can impact on their day-to-day life. We are looking for volunteers to complete these tasks and brief questionnaires. You will need access to the internet to participate in this study. The total study time will be no more than 1 hour and you may take breaks whenever you wish.

If you are interested in participating, would like further information or wish to contact us to let us know you do not wish to take part, please use one of the following options:

1. You can visit the study website by typing this link into your web browser: <https://cardiff.onlinesurveys.ac.uk/compass>. Here you will find the study information sheet and consent form. To enter the study, please use the following information:

Username: [*ID number*]

Password: [*password*]

(Please note: Once you have started the study, do not close the page, as you will not be able to complete the study later. If you wish to take a break and come back, scroll to the bottom of the page and click “Finish later”.)

2. You can contact the team for further information via phone 02920 688043 or email compass@cardiff.ac.uk.
3. You can return the reply slip included with this letter using the freepost envelope provided.

Please note that if you do not have access to the internet but still wish to take part, it may be possible for the team to arrange internet access for you. It is your decision whether you take part in the research and you will be able to withdraw at any stage should you wish to do so.

Many thanks for your ongoing support.

Professor Ian Jones

Director, National Centre for Mental Health (NCMH)

Appendix L: Completeness of Data (Chapter 6)

The number of scores available for each domain of the online battery is shown in Table L-1.

Table L-1 Total number of scores available for each domain

Domain	Healthy Controls	Bipolar Disorder	Major Depressive Disorder	Schizophrenia	Complete Data
Speed of Processing	61	86	106	33	286
Verbal Learning	54	76	94	31	255
Social Cognition	56	78	94	33	261
Working Memory	54	75	91	33	253
Visual Learning	53	73	88	31	245
Reasoning & Problem Solving	54	72	86	32	244
Strategic Risk Taking	53	70	88	32	243
Attention	53	63	82	31	229
Vocabulary	55	65	83	31	234
'g'	52	71	87	33	243

Appendix M: Additional analyses – Chapter 6

Comparison of cognition between validation study and main study participants

In order to maximise the sample numbers, I examined the validity of combining the study samples from Chapters 4 and 5. Within each diagnostic group, cognitive performance ('g') was compared between participants from the validation study and participants from the main study. There were no differences between the studies for healthy controls ($t=0.35$, $p=0.73$), participants with major depressive disorder ($t=-0.06$, $p=0.96$) and bipolar disorder ($t=0.28$, $p=0.78$). There was a significant difference between studies for participants with schizophrenia ($t=2.34$, $p=0.03$).

Measures of 'g'

Three measures of general cognitive performance (g) were derived using the approaches described in Chapter 5. Measures of 'g' were derived for participants who had completed at least 5 tasks ($N=321$). Principal component analysis (PCA) was conducted on complete data ($N=292$) and repeated in a dataset where missing scores had been imputed ($N=321$). The first component of the PCA was taken as a measure of 'g'. Classical multidimensional scaling (MDS) was conducted on a Euclidean distance matrix to derive a third measure of 'g'. MDS is an analogous approach to PCA but an advantage to this approach is that it can accommodate missing data. The 'g' derived using MDS was highly correlated with the 'g' derived using complete data ($r=0.997$) and the 'g' derived including imputed data ($r=0.987$). Therefore, the results for analyses using 'g' derived using MDS are presented in Chapter 6. The results for analyses using 'g' derived by conducting PCA on imputed scores and complete data are presented below.

Comparisons of cognitive function between diagnostic groups (Chapter 6)

There was a significant main effect of diagnosis for overall cognitive function ‘g’ (complete data $g: F(3, 216) = 8.97, p=1.3 \times 10^{-5}$; imputed data $g: F(3, 241) = 10.78, p=1.1 \times 10^{-6}$). Pairwise comparisons are presented in Table M-1.

Table M-1 Comparisons of g between diagnostic groups

	Imputed data g		Complete data g	
	Hedge’s g	p	Hedge’s g	p
HC vs. MDD	0.22	0.59	0.25	0.48
HC vs. BD	0.49	0.03	0.43	0.1
HC vs. SZ	1.18	<0.001	1.21	<0.001
MDD vs. BD	0.28	0.3	0.19	0.69
MDD vs. SZ	0.97	<0.001	0.97	<0.001
BD vs. SZ	0.69	0.006	0.78	0.006

Cross disorder clinical variables and cognitive performance

Across the whole sample (cases only), higher HADS depression scores and higher HADS anxiety scores were associated with lower cognitive performance ('g', see Table M-2). Age of onset was not associated with cognitive performance. The analyses were then repeated and restricted to the three main diagnoses of interest: major depressive disorder, bipolar disorder and schizophrenia. Across these three disorders, higher HADS depression scores and higher HADS anxiety scores were associated with lower cognitive performance. Age of onset was not associated with cognitive performance.

Table M-2 Associations between clinical variables and 'g' derived using PCA

	Whole Sample			Three Diagnoses Only		
	B	SE	p	B	SE	p
Imputed data 'g'						
HADS depression	-0.04	0.01	1.6 x 10 ⁻⁴	-0.04	0.01	9.1 x 10 ⁻⁴
HADS anxiety	-0.05	0.01	2.2 x 10 ⁻⁵	-0.05	0.01	1.1 x 10 ⁻⁴
Age of onset	-0.004	0.01	0.43	0.001	0.01	0.89
Complete data 'g'						
HADS depression	-0.03	0.01	0.003	-0.03	0.01	0.01
HADS anxiety	-0.04	0.01	1.2 x 10 ⁻⁴	-0.04	0.01	9.4 x 10 ⁻⁴
Age of onset	-0.006	0.01	0.28	0.001	0.01	0.89

The associations between the clinical variables and cognitive performance within each diagnostic group are shown in Table M-3. In the bipolar disorder group, higher HADS depression and anxiety scores were associated with lower cognitive performance in the imputed data set but not in the sample of participants with complete data only. Higher HADS anxiety scores were also associated with lower cognitive performance in the major depressive disorder group. In the schizophrenia group, higher scores on the HADS anxiety subscale were associated with lower cognitive performance. However, none of the results were significant after correction for multiple testing.

Table M-3 Associations between clinical variables and ‘g’ within diagnostic groups

	Imputed data ‘g’			Complete data ‘g’		
	B	SE	p	B	SE	p
Bipolar Disorder						
HADS depression	-0.04	0.02	0.049	-0.03	0.02	0.21
HADS anxiety	-0.04	0.02	0.04	-0.03	0.02	0.14
Age of onset	-0.0005	0.01	0.97	-0.002	0.01	0.85
Major Depressive Disorder						
HADS depression	-0.03	0.02	0.08	-0.04	0.02	0.04
HADS anxiety	-0.04	0.02	0.03	-0.06	0.02	0.005
Age of onset	-0.002	0.01	0.77	-0.004	0.01	0.63
Schizophrenia						
HADS depression	-0.05	0.03	0.08	-0.05	0.03	0.09
HADS anxiety	-0.05	0.02	0.04	-0.05	0.02	0.04
Age of onset	0.02	0.02	0.41	0.03	0.02	0.19

Cognitive performance and functional outcome

Linear regression across the whole sample indicated that lower cognitive performance was associated with more severe disability (*complete data* ‘g’: B=-3.08, SE=0.91, p=8.7 x 10⁻⁴; *imputed data* ‘g’: B=-3.10, SE=0.84, p=3 x 10⁻⁴). The analyses were then repeated and restricted to the three main diagnoses of interest: major depressive disorder, bipolar disorder and schizophrenia. Across these three disorders, lower cognitive performance (as measured by ‘g’ derived from PCA of complete data) was associated with higher WHODAS scores but this did not survive correction for multiple testing (see Table M-4). In analyses of individual diagnostic groups, lower cognitive performance was associated with greater disability in the depression group only.

Table M-4 Associations between cognitive performance (‘g’) and functional outcome within diagnostic groups

	Imputed ‘g’			Complete data ‘g’		
	B	SE	p	B	SE	p
Across Three Groups	-2.17	1.11	0.05	-2.79	1.23	0.03
Bipolar Disorder	0.90	1.73	0.52	0.18	2.15	0.93
Major Depressive Disorder	-4.97	1.40	7.5 x 10 ⁻⁴	-5.67	1.38	1.3 x 10 ⁻⁴
Schizophrenia	-4.79	3.41	0.19	-6.04	3.46	0.12

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