The Relationship Between Maintenance and Manipulation Components of Working Memory and Prefrontal and Parietal Brain Regions in Bipolar Disorder

by

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Abstract

Working memory has been found to be impaired across mood states in bipolar disorder. Working memory is delineated into separate components, maintenance and manipulation, where manipulation is involved in higher-order cognitive processes. No study to date has used a task differentiating the components of working memory and associated them with underlying structural brain regions in bipolar disorder. Therefore, this study aimed to examine behavioral visuospatial working memory performance and structural brain indexes in prefrontal and parietal regions in 26 bipolar patients and 24 controls. Bipolar patients were less accurate on the working memory task, without a greater deficit in the manipulation condition. Moreover, bipolar patients had thinner cortices in the prefrontal and parietal regions, areas associated with working memory. Thicker cortices in the prefrontal regions were associated with greater maintenance accuracy in bipolar patients and a thicker parietal cortex was associated with faster manipulation response times in controls.

Keywords: bipolar disorder, visuospatial working memory, maintenance, manipulation, structural neuroimaging

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Introduction

1 Introduction

Working memory involves the ability to maintain and manipulate information. This cognitive process not only has implications in simple tasks such as memorizing numbers, but also in the ability to coordinate more complex goal-directed behaviours (e.g., problem solving). Hence, working memory is a key foundational component in the ability to perform a range of cognitive tasks. This thesis aimed to fill a current gap in the literature by better understanding visuospatial working memory in bipolar disorder through the use of a task that differentiated between maintenance and manipulation. Conceptualizing working memory through the multi-component model proposed by Alan Baddeley and Graham Hitch (Baddeley & Hitch, 1974), the following was investigated: (a) differences in maintenance and manipulation components of working memory between patients with bipolar disorder and controls, (b) structural brain differences (i.e., gray matter volumes, cortical thickness, and surface area) in the prefrontal cortex (specifically the middle frontal, superior frontal, and inferior frontal regions) and the parietal cortex (specifically the inferior and superior regions), and (c) the association between maintenance and manipulation accuracy and reaction time, with gray matter volumes, cortical thickness, surface area, symptomatology, and functioning. Overall, this thesis aimed to provide greater insight into both the behavioural and structural correlates of visuospatial working memory in patients with bipolar disorder.

1.1 Bipolar Disorder

Bipolar disorder affects 1–3% of the population and is a psychological disorder characterized by grandiosity, impulsivity and risk-taking behaviour, and increased distractibility (Soraggi-Frez, Santos, Albuquerque, & Malloy-Diniz, 2017). The Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), categorizes bipolar disorder into the following different subtypes: bipolar I disorder, bipolar II disorder, cyclothymic disorder, and other specified or unspecified bipolar and related disorder (American Psychiatric Association, 2013). Specifically, bipolar I disorder is characterized by the occurrence of a manic episode(s), which can be preceded or followed by a hypomanic or major depressive episode. A manic episode is defined as a period of at least one week where the patient experiences abnormally elevated or irritable

mood and heightened levels of energy for most of the day, nearly every day. Moreover, within this time span, patients in a manic episode can present with the decreased need for sleep, increased distractibility, and engagement in high-risk behaviours which causes significant disruptions in functioning. Bipolar II disorder is characterized by the occurrence of a hypomanic episode(s), in addition to a current or past major depressive episode. A hypomanic episode is defined as a period of at least four consecutive days where the patient experiences elevated or irritable mood, and elevated levels of energy for most of the day, nearly every day. In addition, during a hypomanic episode, patients can also present with the decreased need for sleep, racing thoughts, and engagement in high-risk behaviours. However, compared to a manic episode, a hypomanic episode does not result in significant disruptions to overall functioning (American Psychiatric Association, 2013). Individuals with bipolar disorder often also present with co-occurring psychiatric illnesses. Research supports that 50–66% of bipolar patients often present with a comorbid diagnosis, including anxiety and substance-related disorders (Spoorthy, Chakrabarti, & Grover, 2019). Bipolar disorder presents as a significant disease burden, where research supports that those with bipolar disorder present with greater difficulties in psychosocial functioning (i.e., the ability to form and maintain personal relationships and partake in activities of daily living) and occupational functioning (e.g., schooling, employment; Duarte, Becerra, & Cruise, 2016).

Although not part of the diagnostic criteria for either bipolar I disorder or bipolar II disorder, difficulties in executive functioning (i.e., the effortful top-down process required to perform cognitive tasks such as inhibition, working memory, and problem solving) are often commonly seen in bipolar patients (Dell'Osso et al., 2015). Interestingly, poor performance on cognitive tasks is associated with the clinical presentation and symptomatology of bipolar disorder. For example, studies have reported that longer illness duration, hospitalization time, and a greater number of manic episodes were associated with lower scores on tests of verbal memory and executive functioning (e.g., California Verbal Learning Test and Self-Ordered Pointing Task; Martinez-Aran et al., 2004; Thompson et al., 2005). In addition, previous literature has highlighted the association between symptoms and cognitive functioning in distinguishing the clinical presentation between bipolar patients. Specifically, bipolar patients with a history of psychosis performed less accurately than patients without a history of psychosis on a variety of working memory tasks including the *n*-back (Frydecka et al., 2014). Moreover, difficulties in

cognitive functioning (e.g., verbal memory, attention, and working memory) have also been found to contribute to poor functional outcomes (i.e., psychosocial and occupational functioning; Sanchez-Moreno et al., 2018). Together this highlights the importance of measuring neurocognitive factors to better understand the clinical presentation and functional outcomes in those with bipolar disorder (Baune, Li, & Beblo, 2013; Duarte et al., 2016).

Interestingly, difficulties in executive functioning are not restricted to symptomatic periods, but can also persist into euthymic periods (i.e., asymptomatic periods) in remitted patients (Latalova, Prasko, Diveky, & Velartova, 2011). A domain of executive functioning that has been found to be impaired across mood states is working memory (Barrett, Kelly, Bell, & King, 2008; Soraggi-Frez et al., 2017).

1.2 Working Memory

Prior to the use of the term working memory, an influential model describing a unitary short-term memory store was introduced by Richard Atkinson and Richard Shiffrin (Atkinson & Shiffrin, 1968)**.** The model proposed a three-store memory model, where a unitary short-term memory store existed and processed perceptual information from the environment. This short-term memory store would then relay this information to a long-term memory store. However, many limitations existed with this model. This model supported that information placed into short-term memory would also transfer to long-term memory – a finding that has since been contradicted (Baddeley, 2003). Instead, it has been supported that the ability to store memories into long-term storage is dependent on the type of stimulus coded and how this stimulus is processed (e.g., phonemic or semantic features; Craik & Lockhart, 1972). Another limitation of this model was highlighted from findings in patients who had short-term memory difficulties, but did not present with severe learning difficulties, and were still able to complete activities of daily living. Based on the model proposed by Atkinson and Shiffrin, those with short-term memory difficulties would not be able to learn and would also have extreme cognitive difficulties – opposing what has been found in real life patients (Baddeley, 2010). Therefore, based on the limitations of this model, this model has been disregarded and alternative memory models have been proposed.

A contrast from the unitary short-term memory model described by Atkinson and Shiffrin, a multi-component model proposed by Alan Baddeley and Graham Hitch adopted the term

working memory and delineated the concept of working memory into the following: central executive, phonological loop, and a visuospatial sketchpad (Baddeley & Hitch, 1974). Since then, the model has been modified to include an episodic buffer (Baddeley, 2000). The central executive is a cognitive construct involved in the attentional shift, control, and manipulation (e.g., reordering, updating, and transformation) of information in the phonological loop and visuospatial sketchpad. Both the phonological loop and visuospatial sketchpad are temporary memory stores, where the phonological loop stores/maintains verbal information and the visuospatial sketchpad stores/maintains visual and spatial information. The phonological loop can be further separated into two components: the passive phonological store (for storage) and an active rehearsal process (Bruyer & Scailquin, 1998)**.** The visuospatial sketchpad can similarly be separated into two components: the passive visual cache (for storage) and an active inner spatial scribe (Logie, 1995). In summary, the central executive controls the manipulation of information while the phonological loop and visuospatial sketchpad are both involved in the maintenance of information. Lastly, the integration of information from a variety of senses is controlled by a temporary storage space called the episodic buffer. Although inter-individual differences can exist, literature supports that working memory capacity is allocated to three to five items (of which items can be chunked) – highlighting the limited capacity of working memory (Cowan, 2010; Engle, 2002).

Alternative to Baddeley's model, Nelson Cowan's Embedded-Processes model proposes the integration of attention to bring stimuli into working memory (Cowan, 1999). Specifically, working memory involves two components: an activated subset of the long-term memory store (the sole memory system in this model) and the focus of attention. Stimuli are brought into working memory when a subset of information in the long-term memory system is temporarily activated. Furthermore, a smaller subset of the activated information is the focus of attention. The focus of attention holds information in working memory and when attentional focus shifts to another set of information, the information held in the focus of attention moves to the activated long-term memory store. Once activated, the stimuli are attentively held and the central controller processes and manipulates the information held within the focus of attention. This model also highlights the limited capacity of working memory, where the capacity of working memory is associated with attention and its interaction with the activated long-term memory store (Cowan, 2008, 2010).

Despite multiple models of working memory, overall, working memory can be defined as the ability to not only temporarily hold/store information, but also the ability to update and manipulate the information stored (Moser et al., 2017). The higher-order cognitive processes (i.e., manipulation) is key to working memory and separates it from the function of short-term memory. The ability to both maintain and manipulate information has important implications in not only holding information over brief periods of time, but in higher-order cognitive functions such as arithmetic and reasoning (Diamond, 2013). Working memory has been found to be connected to more complex cognitive constructs such as fluid intelligence (i.e., the ability to problem solve without applying already gained knowledge) and has great implications in being understood in psychiatric populations like bipolar disorder, as patients often present with difficulties in working memory, particularly visuospatial working memory.

1.3 Tasks of Visuospatial Working Memory and Visuospatial Working Memory in Bipolar Disorder

Visuospatial working memory is of particular interest in patients with bipolar disorder, as previous studies have shown that poor performance on a task of visuospatial working memory differentiated bipolar patients from controls. Specifically, this differentiation was not seen on other memory tests (e.g., tests of auditory working memory and tests integrating short-term and long-term memory), suggesting that visuospatial working memory may be a general marker in bipolar patients (Allen et al., 2010). Moreover, specific to Baddeley's working memory model, previous studies have also found that the phonological loop may be intact in those with bipolar disorder, but when completing tasks requiring the use of both the central executive and visuospatial sketchpad bipolar patients performed less accurately (Ferrier, Stanton, Kelly, & Scott, 1999; Thompson et al., 2006).

Despite the well-defined multi-component framework of working memory using Baddeley's model, commonly used experimental tasks developed to measure working memory have often failed to differentiate maintenance and manipulation in visuospatial working memory. For example, visuospatial Sternberg working memory tasks focus heavily on the maintenance/storage component of working memory. This task requires the participant to maintain a list of items (e.g., numbers or shapes). Following a delay, participants are presented with a target item and respond whether this target item was part of the item list previously presented (Sternberg, 1966; White, Schmidt, & Karatekin, 2010). Another commonly used

experimental working memory paradigm in the field is the *n*-back task (Frydecka et al., 2014; Owen, McMillan, Laird, & Bullmore, 2005). In this task, participants respond to a specific stimulus (e.g., a letter) only if it is the same stimulus previously presented an *n* number ago. Working memory demands increase as the *n* value increases and therefore this results in increases to both maintenance (i.e., increasing the number of letters that need to be remembered) and to the central executive (i.e., increase in the number of letters that need to be updated) – without differentiating maintenance and manipulation. The lack of focus on differentiating maintenance and manipulation components is also seen in self-ordered pointing tasks, another common experimental working memory paradigm. During a self-ordered pointing task, participants are shown a block of different designs and asked to point to one of the designs presented (Petrides & Milner, 1982). After pointing, participants are then shown a different block of designs and asked to point to a design that has not been previously selected/pointed to. However, similar to the *n*-back task, the self-ordered pointing task does not differentiate maintenance and manipulation components. Therefore, poor working memory accuracy can only be understood within the general context of working memory (i.e., amalgamating maintenance and manipulation) rather than differentiating each component.

Consistent with the paradigms commonly used to understand working memory, the *n*-back test has also been extensively used to understand working memory in bipolar disorder. However, findings from behavioural studies are mixed. While certain studies reported that bipolar patients performed less accurately than controls (Adler, Holland, Schmithorst, Tuchfarber, & Strakowski, 2004; Drapier et al., 2008) other studies have reported no differences in accuracy between groups (Frangou, Kington, Raymont, & Shergill, 2008; Jogia, Dima, Kumari, & Frangou, 2012). These inconsistent findings may be attributable to methodological heterogeneity, in that previous studies have not used tasks that have differentiated maintenance and manipulation. Moreover, as manipulation involves the active role of the central executive, and tasks such as the *n*-back are better characterized as serial updating, these tasks also do not measure the active manipulation (e.g., mental rotation) of visuospatial information. The limited number of studies that have looked at the components of working memory separately, support that bipolar patients present with difficulties on tasks that involve the central executive, which is important for goal-directed behavior, but not on tasks focusing on the use of the slave systems, such as the phonological loop (Ferrier et al., 1999; Martínez-Arán et al., 2004). As this suggests the possibility that working

memory difficulties may be arising through deficits in the central executive rather than the phonological loop or visuospatial sketchpad, it is crucial that a paradigm that differentiates maintenance and manipulation is used.

Certain working memory tasks have been developed to differentiate maintenance and manipulation. A study focusing on the development of working memory in typically developing children, adolescents, and adults, used a delayed match-to-sample task where participants were presented with three objects. With these three objects, participants had two different conditions: maintenance, and maintenance and manipulation. In the maintenance condition, participants were required to rehearse the order of the objects and following a delay match the object presented. In the maintenance and manipulation condition, participants were required to reorder the three objects and following a 6000ms delay match the object presented (Crone, Wendelken, Donohue, van Leijenhorst, & Bunge, 2006). However, despite the use of a task that differentiated between maintenance and manipulation, this visuospatial working memory task lacked a mental rotation component – a cognitive manipulation that has been supported to be better associated with visuospatial working memory compared to other manipulation processes such as reordering (Hyun & Luck, 2007). Other delayed match-to-sample tasks have been used to differentiate between maintenance and manipulation in visuospatial working memory using rotations. However, these tasks have required the use of relatively complex Chinese letters or matrices, thereby increasing demands through stimulus complexity (Quee, Eling, van der Heijden, & Hildebrandt, 2011; Suchan, Botko, Gizewski, Forsting, & Daum, 2006). Hence, it is key that visuospatial working memory tasks not only involve a mental rotation component, but also use stimuli that are not confounded by the complexity of the stimulus (which may involve other higher-order manipulation processes when required to maintain information). Lastly, it is important that tasks that have been developed for use in healthy populations can be adapted for use in psychiatric populations. This is critical in determining that the complexity of the task is appropriately adapted for use in psychiatric populations.

A visuospatial working memory task has been developed to measure maintenance, and maintenance and manipulation components in both healthy and psychiatric populations (Cannon et al., 2005; Glahn et al., 2002). This experimental paradigm allows for the focus on both conditions through the use of a mental rotation. Differentiating these two components is particularly useful in the context of psychiatric disorders such as bipolar disorder as the disorder

is associated with deficits in goal-directed behaviour. Although it is difficult to separate maintenance from manipulation, as manipulation requires the maintenance of information, maintenance in isolation can be compared with maintenance and manipulation together. In this task, the maintenance condition requires the participant to hold the location of spatial stimulus within their maintenance buffer over a short delay. Following, the maintenance and manipulation condition requires the participant to not only hold the spatial location of the stimulus presented within their maintenance buffer, but also manipulate the spatial stimulus and perform a mental flip along the horizontal axis of the stimulus.

1.4 Neural Correlates of Working Memory

1.4.1 Brain Regions Associated with Working Memory in the General Population

Congruent with the multicomponent model of working memory, a stable and consistent network of brain regions has been supported to be involved in working memory, often segregated by function. A review investigating the role of training programs to enhance working memory reported the consistent activation of the dorsolateral prefrontal cortex (DLPFC) and the parietal cortex on working memory tasks (Klingberg, 2010). The results of this study are further supported by findings from a meta-analysis where the regions surrounding the prefrontal cortex (specifically Brodmann's area (BA) 44 and 45) and the parietal cortex (specifically the left intraparietal cortex and right intraparietal sulcus) were found to be activated regardless of the type of working memory task conducted (Rottschy et al., 2012). These results can be corroborated with another previous meta-analysis which also found the intraparietal sulcus to be consistently activated in response to tasks of spatial working memory (Wager & Smith, 2003). Overall, these studies suggest the involvement of two main brain areas: the prefrontal cortex and the parietal cortex.

Specific to tasks of maintenance and manipulation, functional magnetic resonance imaging (fMRI) has shown increased activation of the DLPFC in response to working memory tasks in healthy controls. Using the maintenance and manipulation task developed by Glahn and colleagues (2002), the right DLPFC (BA 9 and 46) was specifically shown to be more activated in response to tasks involving both maintenance and manipulation compared to maintenance alone, and the left ventrolateral prefrontal cortex (VLPFC; BA 47) was associated with the

maintenance of information (Glahn et al., 2002). These results are similar to a meta-analysis which found that tasks requiring the manipulation of information involved increased activation of both the ventral and anterior prefrontal cortex (specifically BA 10, 46, and 47; Wager & Smith, 2003).

The parietal cortex, with its diverse connections to the frontal cortex, has also been supported to play a role in processing spatial information (Colby & Goldberg, 1999). With the role of the parietal cortex in attending to spatial information, human lesion studies using fMRI have supported the role of the superior parietal lobule (a region of the parietal cortex) in the manipulation component of working memory. Moreover, lesions to the superior parietal lobule were found to be associated with difficulties in manipulating both acoustic and visuospatial information, but not associated with impairments in long-term memory (Koenigs, Barbey, Postle, & Grafman, 2009). This is line with a meta-analysis which found the posterior region of the parietal cortex to play a consistent role in the manipulation component of working memory (Wager & Smith, 2003). In addition, a meta-analysis looking at studies specific to *n*-back tasks, found that there was greater activation in the parietal cortex, in addition to the right DLPFC, for maintaining the location of non-verbal information (e.g., shapes) – consistent with the role of the parietal cortex in processing spatial information (Owen et al., 2005). Moreover, another study investigating the fronto-parietal network reported increased activation of the inferior parietal lobule in response to working memory tasks involving the update of information (Borst & Anderson, 2013). Together, these studies highlight the role of the parietal cortex in working memory.

1.4.2 Brain Regions Associated with Working Memory in Bipolar Disorder

Previous literature on visuospatial working memory in bipolar patients has also supported the activation of the DLPFC and parietal cortex in relation to working memory. Interestingly, previous research has focused on the activity of these brain regions involved in working memory across mood states in patients. Specifically, in response to the *n*-back, a decrease in activation of the DLPFC was seen for patients across all mood states (i.e., in euthymic, depressed, and manic states; Pomarol-Clotet et al., 2015). However, other studies have also found increased activation of the prefrontal cortex in bipolar disorder patients (Drapier et al., 2008) and increased activation specifically in the DLPFC in bipolar patients in a depressed state (Deckersbach et al., 2008). Although the inconsistency in results may be reflective of different methodological procedures

(e.g., the *n*-back test does not differentiate between manipulation and maintenance components), the literature suggests a relationship between working memory and prefrontal and parietal brain regions across mood states.

In addition to fMRI studies denoting the functional differences in patients with bipolar disorder, structural differences in bipolar patients have also been found in relation to these brain regions involved in working memory. Structural changes related to cognitive constructs, including working memory, may be important as previous studies implementing learning and training tasks have found that increased gray matter was associated with better cognitive performance in controls (Engvig et al., 2010; Schmidt-Wilcke, Rosengarth, Luerding, Bogdahn, & Greenlee, 2010). Specifically, smaller gray matter volumes in the DLPFC have been found in bipolar patients (López-Larson, DelBello, Zimmerman, Schwiers, & Strakowski, 2002). In addition, structural integrity has also been found to be associated with symptomatology in bipolar patients. Differences in gray matter volumes have highlighted the presence of manic episodes in patients with bipolar disorder, where a decrease in gray matter volume was associated with the presence of a manic episode within a six-year time period in bipolar patients compared to bipolar patients who did not have an episode (Abé et al., 2015). Suggesting the possible link between the severity of the disorder with alterations in brain morphology, this further highlights the importance of understanding the structural underpinnings involved.

1.5 Measuring the Structural Integrity of the Brain

With the importance of understanding the structural underpinnings of working memory, it is key that that the structural integrity of the brain be explored by measuring a variety of different indexes. Certain structural indexes that can be analyzed are the following: gray matter volume, cortical thickness, and surface area. Gray matter volume, calculated as the function of cortical thickness and surface area, is often explored as the sole measure of structural integrity. However, as cortical thickness and surface area measure different constructs, all three indexes should be investigated separately to provide a sensitive measure of structural integrity. Specifically, cortical thickness represents the number and size of neuronal cells in each cortical column while surface area represents the organization and number of cortical columns (Koelkebeck et al., 2014). These indexes have been found to be related to cognitive functioning and intelligence, thereby acting as important markers connecting behavior and brain structure (Brito & Noble,

2014; Yuan, Voelkle, & Raz, 2018). Moreover, a previous study has shown differences in gray matter volume, cortical thickness, and surface area in bipolar patients in the frontal cortex; therefore, measuring the structural integrity using these indexes will provide further insight into the brain structure in patients with bipolar disorder (Abé et al., 2015).

1.6 Maintenance and Manipulation Components of Working Memory in Other Psychiatric Disorders

To our knowledge, no study to date has investigated working memory in bipolar disorder using the task developed by Glahn and colleagues (2002), differentiating maintenance and manipulation components. However, this paradigm has been used to investigate visuospatial working memory in patients with schizophrenia.

To measure the maintenance and manipulation components of working memory in schizophrenia, a study conducted by Kim and colleagues (Kim, Glahn, Nuechterlein, & Cannon, 2004) investigated visuospatial working memory using the task developed by Glahn and colleagues (2002). Results from this study indicated that patients had lower accuracy on both conditions compared to controls; however, significantly lower accuracy was seen in the manipulation condition. Moreover, another study examined the relationship between performance on this task and the neural correlates of working memory in schizophrenia (Cannon et al., 2005). Supporting the results from Glahn and colleagues (2002), this study found that schizophrenia patients were less accurate in the manipulation condition. In addition, during the manipulation condition, controls had greater activity within the DLPFC compared to schizophrenia patients. Poorer performance on the manipulation condition, involving the role of the central executive, may be reflective of the difficulties in higher-order cognitive processes such as planning and inhibitory behavior often seen in schizophrenia patients.

Although not studied in bipolar disorder, a previous study by our laboratory (Goghari, MacDonald, & Sponheim, 2014) has investigated the relationship between prefrontal gray matter volumes and working memory in schizophrenia using the visuospatial working memory task developed by Glahn and colleagues (2002). This study found that schizophrenia patients had lower accuracy on both maintenance and manipulation components, without a greater deficit seen in the manipulation condition. Moreover, poor performance on the task was correlated with reduced volumes in the superior and inferior regions of the prefrontal cortex.

Both studies are especially interesting within the context of bipolar disorder. Given the overlap in symptomatology between patients with bipolar disorder and schizophrenia, similar findings may be present in bipolar patients and working memory, and affiliated correlates may represent a transdiagnostic marker for related psychiatric disorders.

1.7 Objectives and Hypotheses of Present Study

There were three aims to this study. First, we aimed to investigate differences in performance on a visuospatial working memory task measuring maintenance and manipulation. We hypothesized that patients with bipolar disorder would show lower accuracy and longer response times when manipulation was required, as it involves the central executive, rather than just maintaining information during working memory. Second, we investigated structural brain differences (i.e., gray matter volumes, surface area, and cortical thickness) in the prefrontal (middle, superior, inferior) and parietal cortex (inferior and superior) using Freesurfer, an automated processing pipeline. We hypothesized that bipolar patients would have reduced structural integrity in these brain regions. Lastly, to investigate the relationship between behavioural performance and the underlying structural underpinnings, correlations between maintenance and manipulation conditions, and structural integrity indexes were conducted. We hypothesized that poor performance on the working memory task would be correlated with reduced structural integrity, with significantly stronger associations between reduced structural integrity and the manipulation condition. As previously mentioned, manipulation is important in higher-order cognitive processes such as cognitive flexibility and problem solving (processes associated with functional outcomes). Therefore, poorer performance when manipulation is required (as it involves the central executive) may provide further insight into the functional difficulties patients with bipolar disorder often struggle with.

Chapter 2
Methodology

2 Methodology

2.1 Participants and Recruitment

Twenty-six individuals with bipolar disorder (24 bipolar I patients and 2 bipolar II patients) and 25 community controls were recruited through both online and community advertisements placed in Calgary, Alberta. Bipolar patients were recruited through an outpatient clinic, as well as a community-based organization, The Organization for Bipolar Affective Disorder Society. Although, 26 bipolar patients and 25 controls participated in the study, only 24 controls participated in both the interview and neuroimaging components of the study. Nine bipolar patients met current criteria for bipolar I (5 met criteria for a depressive episode and 4 met criteria for a manic episode) and one bipolar patient met current criteria for bipolar II (hypomanic episode).

Exclusion criteria for both bipolar patients and controls were as follows: an age less than 18 or greater than 60, a substance-related disorder in the last three months (excluding nicotine, caffeine, and cannabis), the use of inhalants three or more times, history of head injury with a loss of consciousness for more than 20 minutes and/or overnight observation, a history of electroconvulsive therapy, epilepsy, seizures, history of stroke, any neurological conditions, diabetes, and legal blindness. Given, the focus of this study on mood disorders, controls were further excluded for both a history of or a current depressive episode, a history of or current use of anti-psychotic or anti-depressant medication, and for a personal or family history of a psychotic or bipolar-related disorder.

2.2 Procedure

The study was approved by the University of Calgary's Conjoint Health Research Ethics Board and all participants provided written informed consent prior to participating in the research study.

Participants completed the study in two visits. During the first visit, the Structured Clinical Interview for DSM-5 Disorders and Functioning Assessment Short Test (both described below) were administered to each participant by a trained research assistant or doctoral level

psychologist. The second visit, scheduled within approximately two weeks after the first visit, consisted of completing the neuroimaging scan, visuospatial working memory task, intelligence test, and symptomatology measures (described below). As this study was part of a larger study investigating biomarkers of bipolar disorder, participants also completed other clinical assessments and cognitive tests as part of the visits that are not reported here. All participants were reimbursed for their time.

2.3 Diagnosis and Assessment

2.3.1 Clinical Measures

2.3.1.1 Structured Clinical Interview for DSM-5 Disorders (SCID-5)

The Structured Clinical Interview for DSM-5 Disorders (SCID-5) was completed for each participant**.** The SCID-5 is a semi-structured instrument to assess for a DSM-5 diagnosis (First, Williams, Karg, & Spitzer, 2015). Modules A (Mood Episodes), B (Psychotic and Associated Symptoms), C (Differential Diagnosis of Psychotic Disorders), D (Mood Disorders), E (Substance Use Disorders), and F (Anxiety Disorders) were completed.

2.3.1.2 Young Mania Rating Scale (YMRS)

Manic symptoms were measured using the Young Mania Rating Scale (YMRS; Young, Biggs, Ziegler, & Meyer, 1978). The YMRS is a clinician-rated scale measuring manic symptomatology based on both the symptoms reported by the patient over the previous 48 hours and behaviors observed by the clinician during the interview. The following behaviors are evaluated: mood, motor activity-energy, sexual interest, sleep, irritation, speech, coherence of language and thought, thought content (e.g., delusions, grandiose ideas), disorderly and hostile behavior, appearance, and insight. A higher score indicates greater manic symptomatology, and a score of less than or equal to 12 denotes the absence of clinically significant manic symptoms.

2.3.1.3 Hamilton Depression Scale (HAM-D)

Depressive symptomatology was measured using the Hamilton Depression Scale (HAM-D; Williams, 1988). The HAM-D is a 17-item interviewer-administered instrument that measures depressive symptoms within the past week. The interview measures the following symptoms: depressed mood, feelings of guilt, suicide, three stages of insomnia (early, middle, late),

functioning at work and with hobbies, motor functioning, agitation, anxiety (psychic and somatic), somatic symptoms (gastrointestinal and general), genital symptoms, hypochondriasis, weight loss, and insight. The HAM-D is rated out of 52, with a higher score representing the presence of greater depressive symptomatology.

2.3.1.4 Functioning Assessment Short Test (FAST)

Functioning was measured using the Functioning Assessment Short Test (FAST; Rosa et al., 2007). The FAST is an interviewer-administered test, developed to measure functioning in patients with mental disorders, that measures the following functional domains: autonomy, occupational functioning, cognitive functioning, interpersonal relationships, and leisure/hobbies. The test measures functioning in the 15 days prior to the assessment. Difficulties in these domains are rated on a scale of zero to three, where three represents "severe difficulty" and zero represents "no difficulty." The FAST is rated out 72, with a higher score representing greater difficulties in functioning.

2.3.1.5 Wechsler Test of Adult Reading (WTAR)

Participants also completed the Wechsler Test of Adult Reading (WTAR) to obtain an estimate of intelligence (Wechsler, 2001). The WTAR tests the ability of the participant to pronounce irregularly spelled words (e.g., knead or liaison). Participants are allowed to provide one pronunciation of the word and can receive a maximum raw score of 50 (which is then scaled for age). Compared to other tests of reading, the WTAR is an advantageous instrument to administer as it has been co-normed with the Wechsler Adult Intelligence Scale, Third Edition (WAIS-III) and Wechsler Memory Scale, Third Edition (WMS-III), allowing for a comparison between general intelligence and memory.

2.3.2 Visuospatial Working Memory Task

A visuospatial working memory paradigm that has successfully separated maintenance from maintenance and manipulation previously in schizophrenia was used (Cannon et al., 2005). Participants completed a visuospatial working memory task comprised of two conditions: maintenance (referred to as the "hold" condition during the task), and maintenance and manipulation (referred to as the "flip" condition during the task). This working memory task was

a block design paradigm, set up in the following order: five practice hold trials, 20 experimental hold trials, five practice flip trials, and 20 experimental flip trials.

The maintenance condition examined the ability of participants to measure the position of objects in space. Specifically, participants were asked to remember the location of an initial set of three circles (presented for 1500ms). Following a 6000ms delay, participants were shown a new set of three circles and asked if the new set of circles were in the same spatial location as the previous set. If participants believed that the new set of circles were in the same spatial location as the previous set, the left arrow key was pressed. If participants believed that the new set of circles were not in the same spatial location as the previous set, the right arrow key was pressed.

The maintenance and manipulation condition (hereafter manipulation condition) asked participants to view a set of three circles for 1500ms and after a delay (6000ms), were asked whether the second set was a mirror flip of the initial set of circles. If participants believed that the new set of circles were a horizontal mirror flip image of the previous set, the left arrow key was pressed. If participants believed that the new set of circles were not a mirror flip of the initial set of the previous set, the right arrow key was pressed.

2.3.3 Structural Neuroimaging

Structural images were collected on a General Electrics 3-telsa MRI scanner employing a standard magnetization-prepared rapid acquisition with gradient echo (MP-RAGE) sequence at the Seaman Family MR Research Centre, University of Calgary. The scanning parameters of the MP-RAGE were: flip angle = 11 degrees; inversion time (TI) = 650 ms; field of view (FOV) = 256 mm; slice thickness = 1.0 mm.

Analyses of gray matter volume, cortical thickness, and surface area were conducted using the Freesurfer image analysis suite (Version 6.0). As structural indexes are sensitive to motion artifact, qualitative quality control measures were taken to reduce bias and variance (Reuter et al., 2015). Specifically, all images were examined for the following: clarity/sharpness of overall image, Gibbs artifact(s), clear differentiation between cortical/sub-cortical regions and between gray/white matter. Following, T1 weighted images were pre-processed. Pre-processing through the automated pipeline involved skull stripping, surface smoothing, segmentation of subcortical brain structures, and parcellation of cortical structures using the Deskian-Killiany atlas (Dale,

Fischl, & Sereno, 1999; Fischl et al., 2002). From this, volumetric estimates of total gray and white matter, and subcortical gray matter were obtained. Gray matter volumes, cortical thickness, and surface area within the prefrontal and parietal cortex were obtained by extracting anatomical regions of interest (ROIs) from FreeSurfer. ROIs from the prefrontal cortex included the following: middle frontal (comprised of the caudal middle frontal and rostral middle frontal), inferior frontal (comprised of the pars opercularis, pars triangularis, and pars orbitalis), and superior frontal. ROIs from the parietal cortex included the inferior parietal and superior parietal regions.

2.4 Statistical Analyses

All statistical analyses were conducted using IBM's SPSS software (IBM SPSS Statistics for Macintosh, Version 25.0, Armonk, NY).

2.4.1 Demographic Information

Independent samples *t*-tests, Fisher's exact test, and chi-square analyses were conducted to compare differences in age, sex, education, estimated intelligence, comorbidities, depressive and manic symptoms, and functional outcome.

2.4.2 Visuospatial Working Memory Task

Accuracy and reaction time (measured in milliseconds) was analyzed. To mitigate issues of distraction, trials longer than 3000ms were treated as outliers and removed.

A 2 x 2 (Group [bipolar patient, control] x Condition [maintenance, manipulation]) analysis of variance (ANOVA) was conducted for both accuracy and reaction time. Follow-up ANOVAs comparing differences within each specific working memory condition were conducted only if an overall significant effect was found in the repeated measures ANOVA.

2.4.3 Structural Neuroimaging

2.4.3.1 Prefrontal Cortex

Gray matter volume, cortical thickness, and surface area was analyzed individually. For each indicator**,** group differences in the middle frontal region was analyzed using a 2 x 2 x 2 (Group [bipolar patient, control] x Region [caudal middle frontal, rostral middle frontal] x Hemisphere [left, right]) mixed model analysis of covariance (ANCOVA). Group differences in the superior

frontal region was analyzed using a 2 x 2 (Group x Hemisphere) ANCOVA. Lastly, group differences in the inferior frontal region was analyzed using a 2 x 3 x 2 (Group x Region [pars opercularis, pars triangularis, pars orbitalis] x Hemisphere) ANCOVA. All analyses included intracranial volume as a covariate.

Follow-up 2 x 2 (Group [patient, control] x Hemisphere [left, right]) ANCOVAs from the middle frontal and inferior frontal regions were conducted if an overall significant effect was found in the main ANCOVA (with intracranial volume included as a covariate).

2.4.3.2 Parietal Cortex

Gray matter volume, cortical thickness, and surface area was analyzed individually. For each indicator, group differences in the parietal cortex was analyzed using a 2 x 2 x 2 (Group [bipolar patient, control] x Region [inferior, superior] x Hemisphere [left, right]) ANCOVA. Intracranial volume was included as a covariate for all analyses.

Follow-up 2 x 2 (Group x Hemisphere) ANCOVAs from the superior posterior and inferior posterior regions were conducted if an overall significant effect was found in the main ANCOVA (with intracranial volume included as a covariate).

2.4.4 Effect Size

To augment tests of statistical significance, Cohen's *d* was calculated, to give an alternative indicator of magnitude. This was conducted for both the visuospatial working memory task and the structural neuroimaging data.

2.4.5 Correlation Analyses

To examine the relationship between all structural integrity indexes and working memory performance, correlational analyses using Pearson's *r* (two-tailed) were conducted. In addition, the relationship between structural integrity indexes and the working memory conditions, estimated intelligence, symptoms, and functional outcome measures were also analyzed. As correlations were conducted to better document the relationship between the variables, analyses were not corrected for multiple comparisons and the *r* value was used as an indicator of effect size of the relationships.

Chapter 3
Results

3 Results

3.1 Participant Characteristics

Demographic information and test statistics are presented in Table 1. Overall, the two groups did not differ for age, sex, handedness, or estimated intelligence. However, the two groups did differ on years of education, with controls having completed a greater a number of years. In addition, a greater number of bipolar patients had a lifetime history of alcohol use disorder. As expected bipolar patients had greater symptom severity and worse functional outcome.

3.2 Performance on the Visuospatial Working Memory Task

3.2.1 Accuracy

The means and standard deviations for each group are presented in Table 2. A 2 group x 2 working memory condition ANOVA was conducted to determine if there was a significant difference between accuracy on the maintenance and manipulation conditions and if this interacted with group. The ANOVA showed a significant main effect of working memory condition with participants having lower accuracy on the manipulation condition, $F(1, 48) = 16.32$, $p < 0.001$, partial $\eta^2 = 0.25$. There was a significant effect of group ($F(1, 48) = 4.21$, $p = 0.046$, partial $\eta^2 = 0.08$), where controls were more accurate than bipolar patients. However, there was no significant interaction between group and condition ($F(1,48) = 0.84$, $p = 0.36$, partial $\eta^2 = 0.02$). A small effect size (Cohen, 1988) was seen comparing the difference between manipulation and maintenance accuracy between groups ($d = 0.26$).

3.2.2 Reaction Time

The means and standard deviations for each group are presented in Table 2. A 2 group x 2 working memory condition showed a significant main effect of working memory condition with participants having slower responses on the manipulation condition, $F(1, 48) = 67.63$, $p < 0.001$, partial $\eta^2 = 0.59$. There was no main effect of group ($F(1, 48) = 0.24$, $p = 0.63$, partial $\eta^2 = 0.005$) or significant interaction between group and condition ($F(1,48) = 2.04$, $p = 0.16$, partial $\eta^2 = 0.04$). A small effect size was seen (Cohen, 1988) comparing the difference between manipulation and maintenance reaction time between groups ($d = 0.40$).

3.3 Structural Neuroimaging

Means and standard deviations for gray matter volume, surface area, and cortical thickness are presented in Tables 3–6.

3.3.1 Inferior Frontal Region

A 2 group x 3 region x 2 hemisphere (left, right) ANCOVA was conducted to determine whether group differences existed and interacted with inferior frontal region and hemisphere, with intracranial volume as a covariate. For cortical thickness, there was a significant main effect of group ($F(1,47) = 5.11$, $p = 0.028$, partial $\eta^2 = 0.10$), where the inferior frontal region was thicker in controls compared to patients. There were no significant interactions between group and region ($F(1.59, 74.80) = 1.70$, $p = 0.20$, partial $\eta^2 = 0.04$), group and hemisphere ($F(1, 47) = 0.04$, $p = 0.85$, partial $\eta^2 = 0.001$) or group, region and hemisphere ($F(1.71, 80.45) = 1.55$, $p = 0.22$, partial $\eta^2 = 0.03$). A medium effect size (Cohen, 1988) was found for cortical thickness between groups ($d = 0.64$). As there was no interaction between group and inferior frontal region, specific regions were not investigated. For gray matter volume and surface area, no significant group, region, hemisphere, or interaction effects were found (Fs = 0.04 – 1.53; ps = 0.22 – 0.85).

3.3.2 Middle Frontal Region

A 2 group x 2 region x 2 hemisphere ANCOVA was conducted. There was a significant main effect of group ($F(1, 47) = 7.85$, $p = 0.007$, partial $\eta^2 = 0.14$) and intracranial volume covariate ($F(1,47) = 11.09$, $p = 0.002$, partial $\eta^2 = 0.19$), with the middle frontal region being thicker in controls compared to patients. There was a trend towards a significant interaction between group and region ($F(1,47) = 3.92$, $p = 0.054$, partial $\eta^2 = 0.08$), where inspection of group means showed that controls had a thicker cortex for the caudal middle frontal region compared to bipolar patients, and the groups were more comparable for the rostral middle frontal region. There was no significant interaction between group and hemisphere ($F(1,47) = 0.03$, $p = 0.87$, partial $\eta^2 = 0.001$) or group, region and hemisphere ($F(1,47) < 0.001$, $p = 0.99$, partial $\eta^2 < 0.000$). A medium effect size (Cohen, 1988) was found when comparing the cortical thickness of the caudal middle frontal region ($d = 0.75$) and the rostral middle frontal region ($d = 0.60$) between groups. For gray matter volumes and surface area, no significant group, region, hemisphere, or interaction effects were seen (Fs = 0.004 – 1.22; ps = 0.28– 0.92).

3.3.3 Superior Frontal Region

A 2 group x 2 hemisphere ANCOVA was conducted. There was a significant main effect of group ($F(1,47) = 7.82$, $p = 0.007$, partial $\eta^2=0.14$) and intracranial volume covariate ($F(1,47) = 4.52$, $p = 0.039$, partial $\eta^2=0.09$), where the superior frontal region was thicker in controls compared to patients. There was no significant interaction between group and hemisphere ($F(1, 47) = 0.09$, $p = 0.76$, partial $\eta^2 = 0.002$). A medium effect size (Cohen, 1988) was found when comparing the cortical thickness of the superior frontal region between groups ($d = 0.78$). For gray matter volumes and surface area, no significant group, hemisphere, or interaction effects were seen (Fs = 0.07 – 0.63; ps = 0.43 – 0.79).

3.3.4 Parietal Cortex

A 2 group x 2 region x 2 hemisphere ANCOVA was conducted. There was a significant main effect of group ($F(1,47) = 5.99$, $p = 0.018$, partial $\eta^2=0.11$), where the parietal region was thicker in controls compared to patients. There were no significant interactions between group and region ($F(1,47) = 2.97$, $p = 0.091$, partial $\eta^2= 0.06$), group and hemisphere ($F(1,47) = 0.25$, $p = 0.62$, partial $\eta^2= 0.005$), or group, region and hemisphere ($F(1,47) = 1.65$, $p = 0.21$, partial $\eta^2 = 0.03$). A medium effect size (Cohen, 1988) was seen when comparing the cortical thickness of the parietal cortex between groups ($d = 0.69$). For gray matter volumes and surface area, no significant group, region, hemisphere, or interaction effects were seen (Fs = 0.009 – 1.76; ps = 0.19 – 0.92).

3.4 Correlations between Working Memory Task Performance, Cortical Thickness, Symptoms, and Functioning

The inferior frontal and parietal regions were collapsed across regions and hemispheres, given the lack of a significant interaction between group, region, and hemisphere when examining the association between cortical thickness and symptomatology, functioning, and working memory performance. Moreover, as no hemisphere specific effects were found in the middle frontal and superior frontal regions, cortical thickness values were collapsed across hemispheres. Specifically, in bipolar patients, a thicker cortex in the rostral middle frontal region ($r = 0.41$, $p = 0.04$) was associated with higher depression scores on the HAM-D. Moreover, a thicker cortex in the parietal region ($r = -0.41$, $p = 0.048$) was associated with faster response times on the manipulation condition in controls. Lastly, thicker cortices in the rostral middle frontal region (r

= 0.53, p = 0.005), caudal middle frontal region (r = 0.53, p = 0.006), and superior frontal region (r = 0.54, p = 0.004) were associated with greater accuracy on the maintenance condition in bipolar patients.

Chapter 4
Discussion

4 Discussion

This thesis investigated maintenance and manipulation components of visuospatial working memory, structural brain integrity, and the relationship between them in bipolar patients and community controls. To the best of our knowledge, this is the first study that has used the visuospatial working memory task developed by Cannon and colleagues (2002) to compare bipolar patients and controls, where the use of this task allowed us to differentiate maintenance and manipulation components. Behaviorally, bipolar patients did demonstrate lower visuospatial working memory accuracy when compared to community controls. However, contrary to our hypothesis, bipolar patients did not show a greater deficit on the manipulation condition. In addition, as hypothesized, bipolar patients demonstrated reduced structural integrity compared to controls in brain regions known to play an important role in working memory. We also found associations between structural integrity and maintenance accuracy in bipolar patients.

4.1 Behavioural Components of Visuospatial Working Memory

Although we did find poorer accuracy overall on the visuospatial working memory task in bipolar patients compared to controls, we did not find a greater deficit for the manipulation condition compared to maintenance as hypothesized. Moreover, the small effect size seen for the difference between maintenance and manipulation further supported that the two groups did not differ greatly in performance accuracy between the two conditions. These results suggest poor working memory performance may not be driven by greater deficits in the manipulation component of working memory in all samples with bipolar disorder. These findings are in contrast to studies that have investigated visuospatial working memory in euthymic bipolar patients, where deficits were attributable to the higher order executive processes of working memory (Thompson et al., 2006). However, these differences in findings may potentially be explained by the particular working memory task employed. In the study conducted by Thompson and colleagues (2006), a number of different working memory tasks were used to separately target the phonological loop, visuospatial sketchpad, and central executive. Therefore, given the use of multiple different tasks, each component of the working memory model may have been measured through different constructs.

In addition to methodological differences, performance on the visuospatial working memory task may have been dependent on symptomatology. Our bipolar group included patients from all three states, and the differences in mood state may further explain the differences in findings. The role of mood in working memory performance has been highlighted in previous literature, where comparing patients in all three mood states (mania, depression, and euthymia) on the *n*-back task, manic and depressed patients both performed worse than controls; however, this same pattern was not seen in euthymic patients (Pomarol-Clotet et al., 2015). Therefore, the presence of mood symptoms across bipolar patients may be a possible explanation of these results. We chose to include all patients with bipolar disorder regardless of mood state to increase our sample size.

4.2 Structural Integrity of Visuospatial Working Memory

In addition to the behavioral deficits in visuospatial working memory, we also found differences in brain regions important to working memory performance, suggesting that disruptions to structural brain markers are present in bipolar patients. Specifically, we found thinner cortices in the bilateral inferior frontal, middle frontal, superior frontal regions, and in the parietal cortex in bipolar patients compared to controls. These findings are consistent with previous literature supporting reduced cortical thickness in the prefrontal and parietal regions, specifically the rostral area of the middle frontal region in bipolar patients (Abé et al., 2016; Elvsåshagen et al., 2013; Hanford, Nazarov, Hall, & Sassi, 2016; Hibar et al., 2018). We also found that accuracy on the maintenance condition was associated with thicker cortices in the prefrontal cortex. Interestingly, regions previously found to be associated with manipulation in controls (e.g., rostral middle frontal) were associated with better maintenance accuracy in bipolar patients as part of our study. This suggests that prefrontal brain regions are probably associated with both processes, though related more to one process than another. Alternatively, the brain may have undergone neuroplasticity and the brain-behavior associations may be different for bipolar disorder than controls. Altered brain-behavior associations in bipolar disorder have been previously supported in functional neuroimaging studies, where bipolar patients recruited additional temporal brain regions while performing a working memory task, regions that were not recruited by controls when completing the same working memory task (Lagopoulos, Ivanovski, & Malhi, 2007; Townsend, Bookheimer, Foland–Ross, Sugar, & Altshuler, 2010). Alternatively, this could be a sample specific finding. Regardless, this finding should be

replicated in larger samples. In addition to associations with cognition, structural integrity was also associated with symptomatology. Interestingly, more severe depressive symptomatology was associated with a thicker cortex in the middle frontal region (i.e., the DLPFC) in bipolar patients. This suggests the possible role of the DLPFC in depressive symptomatology in bipolar patients, additionally supported by previous fMRI findings associated with increased activity in the DLPFC in the regulation of sad emotions (Rive et al., 2015). This finding should also be replicated in independent samples and in samples with greater depression symptomatology.

Of note, our findings of reduced structural integrity in bipolar patients were limited to cortical thickness measurements alone, suggesting that cortical thickness may be more sensitive to changes in the brain in psychological disorders. Findings specific to differences in cortical thickness, but not surface area, in bipolar patients are also supported in the literature. Specifically, thinning of cortices were seen in the left pars opercularis (inferior frontal gyrus), left fusiform gyrus, and left rostral middle frontal cortex, but not surface area in bipolar patients (Hibar et al., 2018). The thinning of the brain may reflect cortical changes including a reduction in the number of neurons and nerve fibers, or neurodegeneration including degradation of the myelin sheath – overall highlighting a specific underlying neuropathological change in bipolar disorder (Hibar et al., 2018; Koelkebeck et al., 2014).

4.3 Limitations and Future Directions

This study has its limitations. First, it would have been beneficial to have a larger sample size; however, an alternative indicator of significance, effect sizes, demonstrated medium-to-large effect sizes for many of our markers. Second, our bipolar group was mixed, including participants across all bipolar disorder diagnoses and mood states. However, as our sample size was small, we were unable to separate findings based on mood states or bipolar diagnosis. Given the heterogeneity across the bipolar patient group, future studies could focus on testing this paradigm and underlying structural brain differences in specific mood states or specific bipolar diagnosis. Lastly, another limitation is the potential effect of medication. As most studies of bipolar disorder, many of our bipolar patients were medicated, namely on lithium. Previous studies have shown that lithium is associated with increased gray matter volumes in bipolar patients (Bearden et al., 2007; Sassi et al., 2002). Therefore, the absence of group differences in gray matter volume may have been a reflection of medication.

With the important role of symptomatology and cognitive functioning in functional outcomes in bipolar patients, future studies should focus on further understanding the relationship between symptomatology, like psychosis, and working memory. Better understanding psychosis has important implications in the functional outcomes of bipolar patients, including occupational functioning (Levy & Manove, 2012). As previous studies have highlighted, working memory has been found to be a potential candidate in differentiating between bipolar patients with or without a history of psychosis. Although we did not separate bipolar patients based on psychosis, future studies could focus on using this specific task as to further investigate the relationship between psychosis, and maintenance and manipulation in bipolar patients. This could also highlight possible transdiagnostic markers with schizophrenia and bipolar disorder. In addition, further highlighting the neurobiological correlates of working memory found within this study, future studies should also focus on understanding working memory as a potential endophenotype for bipolar disorder. With the literature supporting the genetic risk associated with bipolar disorder, it is of potential interest to further examine visuospatial working memory as an endophenotype for bipolar disorder (McCormack et al., 2016; Thermenos et al., 2009). Specifically, studies could focus on investigating bipolar patients across all mood states, their first-degree relatives (both affected and unaffected), and controls to compare both brain and behavioral markers in order to understand the influence of genetics in the presentation of bipolar disorder.

Lastly, these findings also have potential therapeutic implications in improving functional outcome in bipolar patients. Although therapeutic interventions focused on improving cognition are not currently available for bipolar disorder, cognitive remediation therapy is an approved psychological treatment for improving cognition in schizophrenia. Given the overlap in cognitive difficulties between schizophrenia and bipolar disorder, cognitive remediation therapy has been investigated as a potential psychological treatment for bipolar disorder (Deckersbach et al., 2010; Veeh, Kopf, Kittel-Schneider, Deckert, & Reif, 2017). Specifically, cognitive remediation therapy can be divided into different types: simple drill and practice exercises or higher-order exercises focused on extending and generalizing more basic cognition to functional behaviours (important for occupational outcomes and interpersonal functioning). Hence, future studies should continue to investigate cognition in bipolar disorder using tasks that target and differentiate specific underlying cognitive processes.

4.4 Conclusion

The present study provides insight into visuospatial working memory in bipolar patients through the use of a working memory task differentiating maintenance and manipulation and structural neuroimaging. This study suggests that bipolar patients behaviorally perform less accurately than community controls on the visuospatial working memory task and this is supported by underlying thinner cortices in brain regions focal to visuospatial working memory. Moreover, structural integrity was associated with not only cognitive functioning, but also symptomatology in bipolar patients. Together, this suggests that poor behavioral working memory performance and symptomatology may potentially be supported by underlying differences in structural brain integrity. Future research should focus on multiple indicators that involve different levels of investigation and include brain and behavioral markers, to fully understand the nature of cognitive abnormalities in bipolar disorder.

References

Abé, C., Ekman, C.J., Sellgren, C., Petrovic, P., Ingvar, M., & Landén, M. (2015). Manic episodes are related to changes in frontal cortex: a longitudinal neuroimaging study of bipolar disorder 1. *Brain*, *138*(11), 3440–3448. doi:10.1093/brain/awv266

Abé, C., Ekman, C.J., Sellgren, C., Petrovic, P., Ingvar, M., & Landén, M. (2016). Cortical thickness, volume and surface area in patients with bipolar disorder types I and II. *Journal of Psychiatry & Neuroscience*, *41*(4), 240–250. doi:10.1503/jpn.150093

Adler, C. M., Holland, S. K., Schmithorst, V., Tuchfarber, M. J., & M Strakowski, S. (2004). Changes in neuronal activation in patients with bipolar disorder during performance of a working memory task. *Bipolar Disorders*, *6*(6), 540–549. doi:10.1111/j.1399-5618.2004.00117.x

Allen, D. N., Randall, C., Bello, D., Armstrong, C., Frantom, L., Cross, C., & Kinney, J. (2010). Are working memory deficits in bipolar disorder markers for psychosis? *Neuropsychology*, *24*(2), 244–254. doi:10.1037/a0018159

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Arlington, VA: American Psychiatric Publishing.

Atkinson, R. C., & Shiffrin, R. M. (1968). Human memory: A proposed system and its control processes. In K.W. Spence & J.T. Spence (Eds.), *The psychology of learning and motivation: II* (pp. 89–195). Oxford, England: Academic Press. doi:10.1016/S0079-7421(08)60422-3

Baddeley, A. (2000). The episodic buffer: a new component of working memory? *Trends in Cognitive Sciences*, *4*(11), 417–423. doi:10.1016/S1364-6613(00)01538-2

Baddeley, A. (2003). Working memory: looking back and looking forward. *Nature Reviews Neuroscience*, *4*(10), 829–839. doi:10.1038/nrn1201

Baddeley, A. (2010). Working memory. *Current Biology*, *20*(4), R136-140. doi:10.1016/j.cub.2009.12.014

Baddeley, A., & Hitch, G. (1974). Working memory. *Psychology of Learning and Motivation, 8*, 47–89. doi:10.1016/S0079-7421(08)60452-1

Barrett, S. L., Kelly, C., Bell, R., & King, D. J. (2008). Gender influences the detection of spatial working memory deficits in bipolar disorder. *Bipolar Disorders*, *10*(5), 647–654. doi:10.1111/j.1399-5618.2008.00592.x

Baune, B. T., Li, X., & Beblo, T. (2013). Short- and long-term relationships between neurocognitive performance and general function in bipolar disorder. *Journal of Clinical and Experimental Neuropsychology*, *35*(7), 759–774. doi:10.1080/13803395.2013.824071

Bearden, C. E., Thompson, P. M., Dalwani, M., Hayashi, K. M., Lee, A. D., Nicoletti, M., … Soares, J. C. (2007). Greater cortical gray matter density in lithium-treated patients with bipolar disorder. *Biological Psychiatry*, *62*(1), 7–16. doi:10.1016/j.biopsych.2006.10.027

Borst, J. P., & Anderson, J. R. (2013). Using model-based functional MRI to locate working memory updates and declarative memory retrievals in the fronto-parietal network.

Proceedings of the National Academy of Sciences, *110*(5), 1628–1633. doi:10.1073/pnas.1221572110

Brito, N. H., & Noble, K. G. (2014). Socioeconomic status and structural brain development. *Frontiers in Neuroscience*, *8,*1-12. doi:10.3389/fnins.2014.00276

Bruyer, R., & Scailquin, J.C. (1998). The visuospatial sketchpad for mental images: Testing the multicomponent model of working memory. *Acta Psychologica*, *98*(1), 17–36. doi:10.1016/S0001-6918(97)00053-X

Cannon, T. D., Glahn, D. C., Kim, J., Van Erp, T. G. M., Karlsgodt, K., Cohen, M. S., … Shirinyan, D. (2005). Dorsolateral prefrontal cortex activity during maintenance and manipulation of information in working memory in patients with schizophrenia. *Archives of General Psychiatry*, *62*(10), 1071–1080. doi:10.1001/archpsyc.62.10.1071

Cohen, J. (1988). *Statistical Power Analysis for the Behavioral Sciences* (2nd ed.). New York, NY: Academic Press.

Colby, C. L., & Goldberg, M. E. (1999). Space and attention in parietal cortex. *Annual Review of Neuroscience*, *22*(1), 319–349. doi:10.1146/annurev.neuro.22.1.319

Cowan, N. (1999). An embedded-processes model of working memory. In A. Miyake & P. Shah (Eds.), *Models of working memory: Mechanisms of active maintenance and executive control* (pp. 62–101). New York, NY: Cambridge University Press. doi:10.1017/CBO9781139174909.006

Cowan, N. (2008). What are the differences between long-term, short-term, and working memory? *Progress in Brain Research*, *169*, 323–338. doi:10.1016/S0079-6123(07)00020-9

Cowan, N. (2010). The magical mystery four: How is working memory capacity limited, and why? *Current Directions in Psychological Science*, *19*(1), 51–57. doi:10.1177/0963721409359277

Craik, F. I. M., & Lockhart, R. S. (1972). Levels of processing: A framework for memory research. *Journal of Verbal Learning and Verbal Behavior*, *11*(6), 671–684. doi:10.1016/S0022-5371(72)80001-X

Crone, E. A., Wendelken, C., Donohue, S., van Leijenhorst, L., & Bunge, S. A. (2006). Neurocognitive development of the ability to manipulate information in working memory. *Proceedings of the National Academy of Sciences of the United States of America*, *103*(24), 9315–9320. doi:10.1073/pnas.0510088103

Dale, A. M., Fischl, B., & Sereno, M. I. (1999). Cortical surface-based analysis: I. Segmentation and surface reconstruction. *NeuroImage*, *9*(2), 179–194. doi:10.1006/nimg.1998.0395

Deckersbach, T., Nierenberg, A. A., Kessler, R., Lund, H. G., Ametrano, R. M., Sachs, G., … Dougherty, D. (2010). Cognitive rehabilitation for bipolar disorder: An open trial for employed patients with residual depressive symptoms. *CNS Neuroscience & Therapeutics*, *16*(5), 298–307. doi:10.1111/j.1755-5949.2009.00110.x

Deckersbach, T., Rauch, S. L., Buhlmann, U., Ostacher, M. J., Beucke, J.C., Nierenberg, A. A., … Dougherty, D. D. (2008). An fMRI investigation of working memory and sadness in

females with bipolar disorder: a brief report. *Bipolar Disorders*, *10*(8), 928–942. doi:10.1111/j.1399-5618.2008.00633.x

Dell'Osso, B., Cinnante, C., Di Giorgio, A., Cremaschi, L., Palazzo, M. C., Cristoffanini, M., … Altamura, A. C. (2015). Altered prefrontal cortex activity during working memory task in bipolar disorder: A functional magnetic resonance imaging study in euthymic bipolar I and II patients. *Journal of Affective Disorders*, *184*, 116–122. doi:10.1016/j.jad.2015.05.026

Diamond, A. (2013). Executive functions. *Annual Review of Psychology*, *64*(1), 135–168. doi:10.1146/annurev-psych-113011-143750

Drapier, D., Surguladze, S., Marshall, N., Schulze, K., Fern, A., Hall, M.H., … McDonald, C. (2008). Genetic liability for bipolar disorder is characterized by excess frontal activation in response to a working memory task. *Biological Psychiatry*, *64*(6), 513–520. doi:10.1016/j.biopsych.2008.04.038

Duarte, W., Becerra, R., & Cruise, K. (2016). The relationship between neurocognitive functioning and occupational functioning in bipolar disorder: A literature review. *Europe's Journal of Psychology*, *12*(4), 659–678. doi:10.5964/ejop.v12i4.909

Elvsåshagen, T., Westlye, L. T., Bøen, E., Hol, P. K., Andreassen, O. A., Boye, B., & Malt, U. F. (2013). Bipolar II disorder is associated with thinning of prefrontal and temporal cortices involved in affect regulation. *Bipolar Disorders*, *15*(8), 855–864. doi:10.1111/bdi.12117

Engle, R. W. (2002). Working memory capacity as executive attention. *Current Directions in Psychological Science*, *11*(1), 19–23. doi:10.1111/1467-8721.00160

Engvig, A., Fjell, A. M., Westlye, L. T., Moberget, T., Sundseth, Ø., Larsen, V. A., & Walhovd, K. B. (2010). Effects of memory training on cortical thickness in the elderly. *NeuroImage*, *52*(4), 1667–1676. doi:10.1016/j.neuroimage.2010.05.041

Ferrier, I. N., Stanton, B. R., Kelly, T. P., & Scott, J. (1999). Neuropsychological function in euthymic patients with bipolar disorder. *The British Journal of Psychiatry: The Journal of Mental Science*, *175*, 246–251. doi:10.1192/bjp.175.3.246

Fischl, B., Salat, D. H., Busa, E., Albert, M., Dieterich, M., Haselgrove, C., … Dale, A. M. (2002). Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron*, *33*(3), 341–355. doi:10.1016/S0896-6273(02)00569-X

Frangou, S., Kington, J., Raymont, V., & Shergill, S. S. (2008). Examining ventral and dorsal prefrontal function in bipolar disorder: A functional magnetic resonance imaging study. *European Psychiatry*, *23*(4), 300–308. doi:10.1016/j.eurpsy.2007.05.002

Frydecka, D., Eissa, A. M., Hewedi, D. H., Ali, M., Drapała, J., Misiak, B., … Moustafa, A. A. (2014). Impairments of working memory in schizophrenia and bipolar disorder: The effect of history of psychotic symptoms and different aspects of cognitive task demands. *Frontiers in Behavioral Neuroscience*, *8*. doi:10.3389/fnbeh.2014.00416

Glahn, D. C., Kim, J., Cohen, M. S., Poutanen, V. P., Therman, S., Bava, S., … Cannon, T. D. (2002). Maintenance and manipulation in spatial working memory: Dissociations in the prefrontal cortex. *NeuroImage*, *17*(1), 201–213. doi:10.1006/nimg.2002.1161

Goghari, V. M., MacDonald, A. W., & Sponheim, S. R. (2014). Relationship between prefrontal gray matter volumes and working memory performance in schizophrenia: A family study. *Schizophrenia Research*, *153*(1–3), 113–121. doi:10.1016/j.schres.2014.01.032

Hanford, L. C., Nazarov, A., Hall, G. B., & Sassi, R. B. (2016). Cortical thickness in bipolar disorder: A systematic review. *Bipolar Disorders*, *18*(1), 4–18. doi:10.1111/bdi.12362

Hibar, D. P., Westlye, L. T., Doan, N. T., Jahanshad, N., Cheung, J. W., Ching, C. R. K., … Andreassen, O. A. (2018). Cortical abnormalities in bipolar disorder: An MRI analysis of 6503 individuals from the ENIGMA bipolar disorder working group. *Molecular Psychiatry*, *23*(4), 932–942. doi:10.1038/mp.2017.73

Hyun, J.S., & Luck, S. J. (2007). Visual working memory as the substrate for mental rotation. *Psychonomic Bulletin & Review*, *14*(1), 154–158. doi:10.3758/BF03194043

Jogia, J., Dima, D., Kumari, V., & Frangou, S. (2012). Frontopolar cortical inefficiency may underpin reward and working memory dysfunction in bipolar disorder. *The World Journal of Biological Psychiatry*, *13*(8), 605–615. doi:10.3109/15622975.2011.585662

Kim, J., Glahn, D. C., Nuechterlein, K. H., & Cannon, T. D. (2004). Maintenance and manipulation of information in schizophrenia: Further evidence for impairment in the central executive component of working memory. *Schizophrenia Research*, *68*(2–3), 173–187. doi:10.1016/S0920-9964(03)00150-6

Klingberg, T. (2010). Training and plasticity of working memory. *Trends in Cognitive Sciences*, *14*(7), 317–324. doi:10.1016/j.tics.2010.05.002

Koelkebeck, K., Miyata, J., Kubota, M., Kohl, W., Son, S., Fukuyama, H., … Murai, T. (2014). The contribution of cortical thickness and surface area to gray matter asymmetries in the healthy human brain: Gray matter asymmetries in the human brain. *Human Brain Mapping*, *35*(12), 6011–6022. doi:10.1002/hbm.22601

Koenigs, M., Barbey, A. K., Postle, B. R., & Grafman, J. (2009). Superior parietal cortex is critical for the manipulation of information in working memory. *Journal of Neuroscience*, *29*(47), 14980–14986. doi:10.1523/JNEUROSCI.3706-09.2009

Lagopoulos, J., Ivanovski, B., & Malhi, G. S. (2007). An event-related functional MRI study of working memory in euthymic bipolar disorder. *Journal of Psychiatry & Neuroscience*, *32*(3), 174–184. Retrieved from http://jpn.ca/vol32-issue3/32-3-174

Latalova, K., Prasko, J., Diveky, T., & Velartova, H. (2011). Cognitive impairment in bipolar disorder. *Biomedical Papers*, *155*(1), 19–26. doi:10.5507/bp.155.2011.003

Levy, B., & Manove, E. (2012). Functional outcome in bipolar disorder: The big picture. *Depression Research and Treatment*, *2012,* 1–12. doi:10.1155/2012/949248.

Logie, R. H. (1995). *Essays in cognitive psychology. Visuo-spatial working memory.* Hillsdale, NJ: Lawrence Erlbaum Associates, Inc.

López-Larson, M. P., DelBello, M. P., Zimmerman, M. E., Schwiers, M. L., & Strakowski, S. M. (2002). Regional prefrontal gray and white matter abnormalities in bipolar disorder. *Biological Psychiatry*, *52*(2), 93–100. doi:10.1016/S0006-3223(02)01350-1

Martinez-Aran, A., Vieta, E., Colom, F., Torrent, C., Sanchez-Moreno, J., Reinares, M., … Salamero, M. (2004). Cognitive impairment in euthymic bipolar patients: Implications

for clinical and functional outcome. *Bipolar Disorders*, *6*(3), 224–232. doi:10.1111/j.1399-5618.2004.00111.x

Martínez-Arán, A., Vieta, E., Reinares, M., Colom, F., Torrent, C., Sánchez-Moreno, J., … Salamero, M. (2004). Cognitive function across manic or hypomanic, depressed, and euthymic states in bipolar disorder. *American Journal of Psychiatry*, *161*(2), 262–270. doi:10.1176/appi.ajp.161.2.262

McCormack, C., Green, M. J., Rowland, J. E., Roberts, G., Frankland, A., Hadzi-Pavlovic, D., … Mitchell, P. B. (2016). Neuropsychological and social cognitive function in young people at genetic risk of bipolar disorder. *Psychological Medicine*, *46*(4), 745–758. doi:10.1017/S0033291715002147

Moser, D. A., Doucet, G. E., Ing, A., Dima, D., Schumann, G., Bilder, R. M., & Frangou, S. (2017). An integrated brain–behavior model for working memory. *Molecular Psychiatry*. doi:10.1038/mp.2017.247

Owen, A. M., McMillan, K. M., Laird, A. R., & Bullmore, E. (2005). N-back working memory paradigm: A meta-analysis of normative functional neuroimaging studies. *Human Brain Mapping*, *25*(1), 46–59. doi:10.1002/hbm.20131

Petrides, M., & Milner, B. (1982). Deficits on subject-ordered tasks after frontal- and temporal-lobe lesions in man. *Neuropsychologia*, *20*(3), 249–262. doi:10.1016/0028-3932(82)90100-2

Pomarol-Clotet, E., Alonso-Lana, S., Moro, N., Sarró, S., Bonnin, M. C., Goikolea, J. M., … Salvador, R. (2015). Brain functional changes across the different phases of bipolar

disorder. *British Journal of Psychiatry*, *206*(02), 136–144. doi:10.1192/bjp.bp.114.152033

Quee, P.J., Eling, P.M., van der Heijen, F.A., & Hildebrandt, H. (2011). Working memory in schizophrenia: A systematic study of specific modalities and processes. *Psychiatry Research*, 185(1–2), 54–59. doi:10.1016/j.psychres.2009.08.012.

Reuter, M., Tisdall, M. D., Qureshi, A., Buckner, R. L., van der Kouwe, A. J. W., & Fischl, B. (2015). Head motion during MRI acquisition reduces gray matter volume and thickness estimates. *NeuroImage*, *107*, 107–115. doi:10.1016/j.neuroimage.2014.12.006

Rive, M. M., Mocking, R. J. T., Koeter, M. W. J., van Wingen, G., de Wit, S. J., van den Heuvel, O. A., … Schene, A. H. (2015). State-dependent differences in emotion regulation between unmedicated bipolar disorder and major depressive disorder. *JAMA Psychiatry*, *72*(7), 687. doi:10.1001/jamapsychiatry.2015.0161

Rosa, A. R., Sánchez-Moreno, J., Martínez-Aran, A., Salamero, M., Torrent, C., Reinares, M., … Vieta, E. (2007). Validity and reliability of the Functioning Assessment Short Test (FAST) in bipolar disorder. *Clinical Practice and Epidemiology in Mental Health*, *3*(1), 5. doi:10.1186/1745-0179-3-5

Rottschy, C., Langner, R., Dogan, I., Reetz, K., Laird, A. R., Schulz, J. B., … Eickhoff, S. B. (2012). Modelling neural correlates of working memory: A coordinate-based meta-analysis. *NeuroImage*, *60*(1), 830–846. doi:10.1016/j.neuroimage.2011.11.050

Sanchez-Moreno, J., Bonnin, C. M., González-Pinto, A., Amann, B. L., Solé, B., Balanzá-Martinez, V., … CIBERSAM Functional Remediation Group. (2018). Factors associated

with poor functional outcome in bipolar disorder: Sociodemographic, clinical, and neurocognitive variables. *Acta Psychiatrica Scandinavica*, *138*(2), 145–154. doi:10.1111/acps.12894

Sassi, R. B., Nicoletti, M., Brambilla, P., Mallinger, A. G., Frank, E., Kupfer, D. J., … Soares, J. C. (2002). Increased gray matter volume in lithium-treated bipolar disorder patients. *Neuroscience Letters*, *329*(2), 243–245. doi:10.1016/S0304-3940(02)00615-8

Schmidt-Wilcke, T., Rosengarth, K., Luerding, R., Bogdahn, U., & Greenlee, M. W. (2010). Distinct patterns of functional and structural neuroplasticity associated with learning morse code. *NeuroImage*, *51*(3), 1234–1241. doi:10.1016/j.neuroimage.2010.03.042

Soraggi-Frez, C., Santos, F. H., Albuquerque, P. B., & Malloy-Diniz, L. F. (2017). Disentangling working memory functioning in mood states of bipolar disorder: A systematic review. *Frontiers in Psychology*, *8*. doi:10.3389/fpsyg.2017.00574

Spoorthy, M. S., Chakrabarti, S., & Grover, S. (2019). Comorbidity of bipolar and anxiety disorders: An overview of trends in research. *World Journal of Psychiatry*, *9*(1), 7–29. doi:10.5498/wjp.v9.i1.7

Sternberg, S. (1966). High-speed scanning in human memory. *Science, 153*(3736), 652–654. doi:10.1126/science.153.3736.652

Suchan, B., Botko, R., Gizewski, E., Forsting, M., & Daum, I. (2006). Neural substrates of manipulation in visuospatial working memory. *Neuroscience,* 139(1), 351–257. doi:10.1016/j.neuroscience.2005.08.020.

Thermenos, H. W., Goldstein, J. M., Milanovic, S. M., Whitfield-Gabrieli, S., Makris, N., LaViolette, P., … Seidman, L. J. (2009). An fMRI study of working memory in persons with bipolar disorder or at genetic risk for bipolar disorder. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, 153B*,* 120–131. doi:10.1002/ajmg.b.30964

Thompson, J. M., Gallagher, P., Hughes, J. H., Watson, S., Gray, J. M., Ferrier, I. N., & Young, A. H. (2005). Neurocognitive impairment in euthymic patients with bipolar affective disorder. *British Journal of Psychiatry*, *186*(1), 32–40. doi:10.1192/bjp.186.1.32

Thompson, J. M., Hamilton, C. J., Gray, J. M., Quinn, J. G., Mackin, P., Young, A. H., & Nicol Ferrier, I. (2006). Executive and visuospatial sketchpad resources in euthymic bipolar disorder: Implications for visuospatial working memory architecture. *Memory*, *14*(4), 437–451. doi:10.1080/09658210500464293

Townsend, J., Bookheimer, S. Y., Foland–Ross, L. C., Sugar, C. A., & Altshuler, L. L. (2010). fMRI abnormalities in dorsolateral prefrontal cortex during a working memory task in manic, euthymic and depressed bipolar subjects. *Psychiatry Research: Neuroimaging*, *182*(1), 22–29. doi:10.1016/j.pscychresns.2009.11.010

Veeh, J., Kopf, J., Kittel-Schneider, S., Deckert, J., & Reif, A. (2017). Cognitive remediation for bipolar patients with objective cognitive impairment: A naturalistic study. *International Journal of Bipolar Disorders*, *5*(1). doi:10.1186/s40345-017-0079-3

Wager, T. D., & Smith, E. E. (2003). Neuroimaging studies of working memory: A meta-analysis. *Cognitive, Affective, & Behavioral Neuroscience*, *3*(4), 255–274. doi:10.3758/CABN.3.4.255

Wechsler, D. (2001). *Wechsler Test of Adult Reading: WTAR*. San Antonio, TX: Psychological Corporation.

White, T., Schmidt, M., & Karatekin, C. (2010). Verbal and visuospatial working memory development and deficits in children and adolescents with schizophrenia: Working memory in early-onset schizophrenia. *Early Intervention in Psychiatry*, *4*(4), 305–313. doi:10.1111/j.1751-7893.2010.00204.x

Williams, J. B. (1988). A structured interview guide for the Hamilton Depression Rating Scale. *Archives of General Psychiatry*, *45*(8), 742–747. doi:10.1001/archpsyc.1988.01800320058007

Young, R. C., Biggs, J. T., Ziegler, V. E., & Meyer, D. A. (1978). A rating scale for mania: reliability, validity and sensitivity. *The British Journal of Psychiatry: The Journal of Mental Science*, *133*, 429–435. doi:10.1192/bjp.133.5.429

Yuan, P., Voelkle, M. C., & Raz, N. (2018). Fluid intelligence and gross structural properties of the cerebral cortex in middle-aged and older adults: A multi-occasion longitudinal study. *NeuroImage*, *172*, 21–30. doi:10.1016/j.neuroimage.2018.01.032

Table 1

Demographic Characteristics for Bipolar Patients and Community Controls

	Bipolar (n = 26)	Control (n = 24)	Test Statistics t, χ^2, Fisher's exact (df)
Age (years), mean (SD)	38.88 (11.50)	37.42 (9.98)	t(48) = 0.48, $p = 0.63$
Sex, % female	69.23	66.67	$\chi^2(1) = 0.038$, $p = 0.85$
Education (years completed), mean (SD)	14.42 (2.69)	16.13 (1.78)	t(39.90) = -2.60, $p = 0.013$
Handedness, % right handed	96.15	91.67	$\chi^2(2) = 1.11$, $p = 0.57$
WTAR standard score, mean (SD)	111.77 (11.34)	108.54 (10.49)	t(48) = 1.04, $p = 0.30$
YMRS, mean (SD)	3.73 (3.72)	0.75 (1.15)	t(30.12) = 3.89, $p = 0.001$
Range	0–16	0–4	
HAM-D, mean (SD)	7.50 (6.56)	0.63 (1.28)	t(27.05) = 5.24, $p < 0.001$
Range	0–23	0–6	
FAST, mean (SD)	11.42 (9.40)	1.43 (2.27)	t(28.27) = 5.25, $p < 0.001$
Range	0–37	0–8	
History of psychosis, % yes	42.3	0	-

Substance Use Disorder (Alcohol), % lifetime	38.5	12.5	$\chi^2(1) = 4.37$, $p = 0.037$
Substance Use Disorder (Cannabis), % lifetime	19.2	4.2	$p = 0.19$
Substance Use Disorder (Stimulants), % lifetime	11.5	0	-
Substance Use Disorder (Hallucinogens), % lifetime	7.7	0	-
Panic Disorder, % lifetime	11.54	0	-
Social Anxiety Disorder, % lifetime	7.69	0	-
Generalized Anxiety Disorder, % lifetime	19.23	0	-
Atypical antipsychotics, % on	65.38	0	-
Typical antipsychotics, % on	3.85	0	-
Anticonvulsants, % on	53.85	0	-
Antidepressants, % on	34.62	0	-
Mood stabilizers, % on	26.92	0	-
Anxiolytic, % on	3.85	0	-
Sedative-hypnotics, % on	11.54	0	-
Other psychiatric medications, % on	0	0	-

Note. SD., standard deviation; WTAR., Wechsler Test of Adult Reading; YMRS., Young Mania Rating Scale; HAM-D., Hamilton Depression Scale; FAST., Functioning Assessment Short Test

Table 2

Performance on the Visuospatial Working Memory Task in Bipolar Patients and Community Controls

	Bipolar (n = 26)	Control (n = 24)
Maintenance accuracy %, mean (SD)	83.46 (10.37)	89.58 (7.79)
Manipulation accuracy %, mean (SD)	78.08 (11.58)	81.04 (9.32)
Maintenance reaction time[a], mean (SD)	1142.00 (266.23)	1058.88 (321.39)
Manipulation reaction time[a], mean (SD)	1344.31 (330.10)	1346.25 (327.56)

Note. SD., standard deviation

[a]., milliseconds

Table 3

Gray Matter Volume, Surface Area, and Cortical Thickness of the Inferior Frontal Region in Bipolar Patients and Community Controls

	Structural Integrity Index					
	Gray matter volume[a]		Surface area[b]		Cortical thickness[c]	
Region of Interest	Bipolar (n = 26)	Control (n = 24)	Bipolar (n = 26)	Control (n = 24)	Bipolar (n = 26)	Control (n = 24)
Pars opercularis, mean (SD)						
Left hemisphere	5083.88 (796.32)	5017.04 (1159.10)	1673.58 (246.63)	1630.00 (342.69)	2.66 (0.14)	2.72 (0.09)
Right hemisphere	4088.35 (719.29)	4170.83 (774.28)	1406.69 (232.10)	1396.00 (244.31)	2.64 (0.13)	2.69 (0.13)
Pars orbitalis, mean (SD)						
Left hemisphere	2480.50 (286.98)	2602.21 (393.72)	669.12 (72.12)	812.15 (67.21)	2.80 (0.17)	2.86 (0.15)
Right hemisphere	2825.85 (336.21)	2925.33 (377.12)	693.50 (85.81)	826.63 (110.34)	2.79 (0.14)	2.80 (0.12)
Pars triangularis, mean (SD)						
Left hemisphere	3958.04 (516.19)	4059.58 (667.62)	1353.92 (150.34)	1359.38 (211.66)	2.56 (0.13)	2.62 (0.08)
Right hemisphere	4483.65 (840.40)	4851.58 (914.05)	1548.85 (251.79)	1615.46 (285.73)	2.54 (0.11)	2.64 (0.09)

Note. [a]., mm^3

[b]., mm^2

[c]., mm

Table 4

Gray Matter Volume, Surface Area, and Cortical Thickness of the Middle Frontal Region in Bipolar Patients and Community Controls

	Structural Integrity Index					
	Gray matter volume[a]		Surface area[b]		Cortical thickness[c]	
Region of Interest	Bipolar (n = 26)	Control (n = 24)	Bipolar (n = 26)	Control (n = 24)	Bipolar (n = 26)	Control (n = 24)
Caudal middle frontal, mean (SD)						
Left hemisphere	6429.42 (1297.76)	6633.25 (1111.70)	2235.38 (384.17)	2239.21 (343.17)	2.62 (0.14)	2.57 (0.12)
Right hemisphere	6098.27 (1183.04)	6163.08 (1099.20)	2123.31 (316.48)	2073.83 (323.89)	2.71 (0.14)	2.67 (0.12)
Rostral middle frontal, mean (SD)						
Left hemisphere	15964.46 (2248.16)	16504.63 (2112.65)	5513.04 (656.48)	5606.63 (740.18)	2.51 (0.10)	2.55 (0.08)
Right hemisphere	16123.58 (2183.00)	16389.96 (2006.85)	5687.04 (674.35)	5702.58 (711.34)	2.44 (0.09)	2.49 (0.75)

Note. SD., standard deviation

[a]., mm^3

[b]., mm^2

[c]., mm

Table 5

Gray Matter Volume, Surface Area, and Cortical Thickness of the Superior Frontal Region in Bipolar Patients and Community Controls

	Structural Integrity Index					
	Gray matter volume[a]		Surface area[b]		Cortical thickness[c]	
Region of Interest	Bipolar (n = 26)	Control (n = 24)	Bipolar (n = 26)	Control (n = 24)	Bipolar (n = 26)	Control (n = 24)
Superior frontal, mean (SD)						
Left hemisphere	23190.23 (2890.22)	23549.83 (2534.38)	7234.19 (801.89)	7168.88 (716.72)	2.70 (0.13)	2.87 (0.09)
Right hemisphere	22338.81 (2433.24)	22925.13 (2571.85)	7010.92 (570.75)	7030.71 (744.28)	2.77 (0.12)	2.84 (0.09)

Note. SD., standard deviation

[a]., mm^3

[b]., mm^2

[c]., mm

Table 6

Gray Matter Volume, Surface Area, and Cortical Thickness of the Parietal Cortex in Bipolar Patients and Community Controls

	Structural Integrity Index					
	Gray matter volume[a]		Surface area[b]		Cortical thickness[c]	
Region of Interest	Bipolar (n = 26)	Control (n = 24)	Bipolar (n = 26)	Control (n = 24)	Bipolar (n = 26)	Control (n = 24)
Superior parietal mean (SD)						
Left hemisphere	13408.85 (1592.39)	13831.88 (1552.39)	5230.74 (566.92)	5292.38 (488.27)	2.30 (0.09)	2.34 (0.08)
Right hemisphere	13595.04 (1758.17)	13748.83 (1432.08)	5287.04 (598.82)	5308.96 (459.63)	2.29 (0.09)	2.33 (0.08)
Inferior parietal, mean (SD)						
Left hemisphere	12184.31 (1328.89)	12564.33 (1671.31)	4389.08 (509.77)	4441.58 (510.72)	2.50 (0.10)	2.55 (0.07)
Right hemisphere	14231.85 (1703.77)	14941.96 (1836.50)	4965.77 (535.61)	5122.58 (601.38)	2.51 (0.10)	2.58 (0.08)

Note. SD., standard deviation

[a]., mm^3

[b]., mm^2

[c]., mm

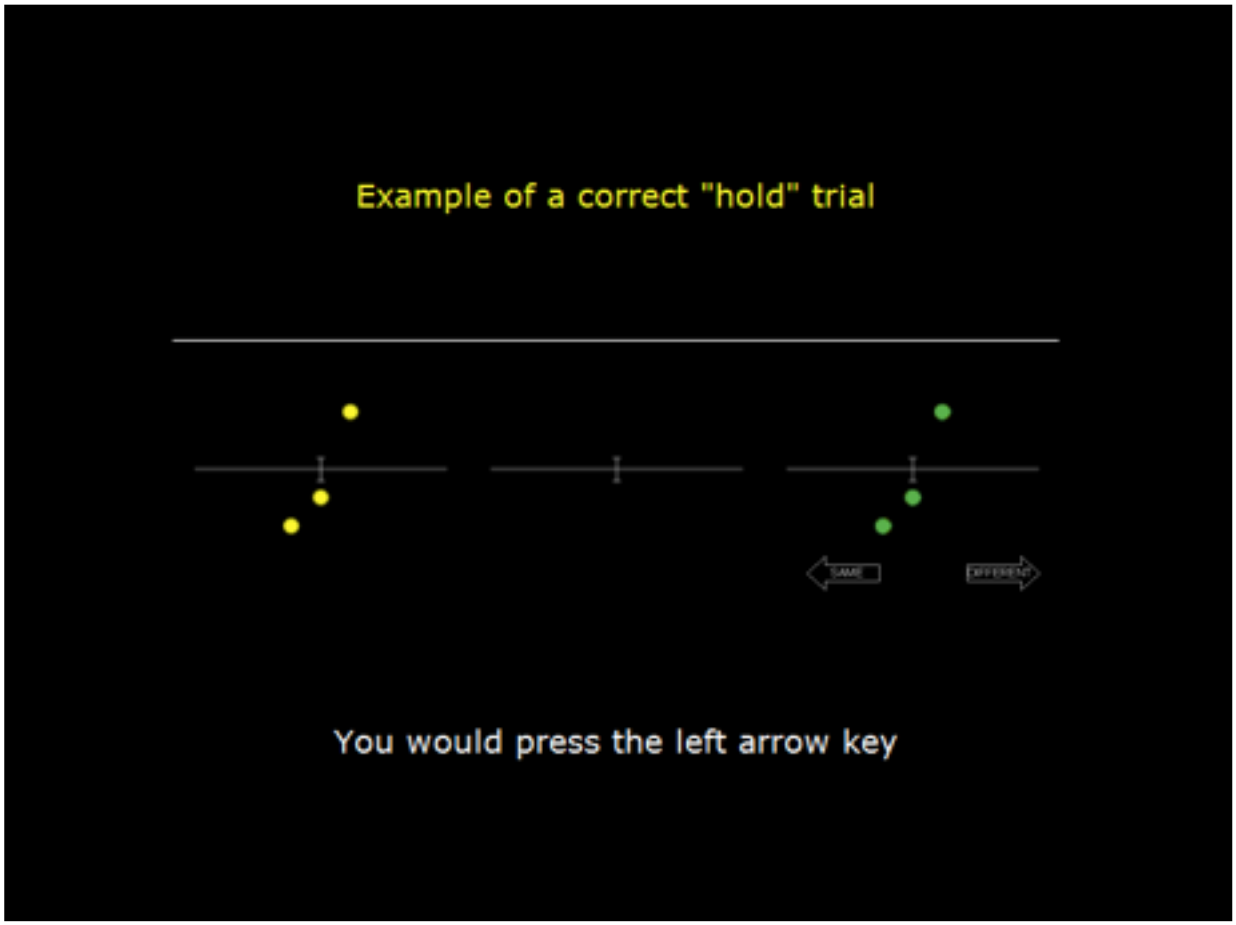

Figure 1. Instruction screen for correct trial. Participants are instructed to press the left arrow key if the stimuli are the same (the same instructions apply to the “flip” trials).

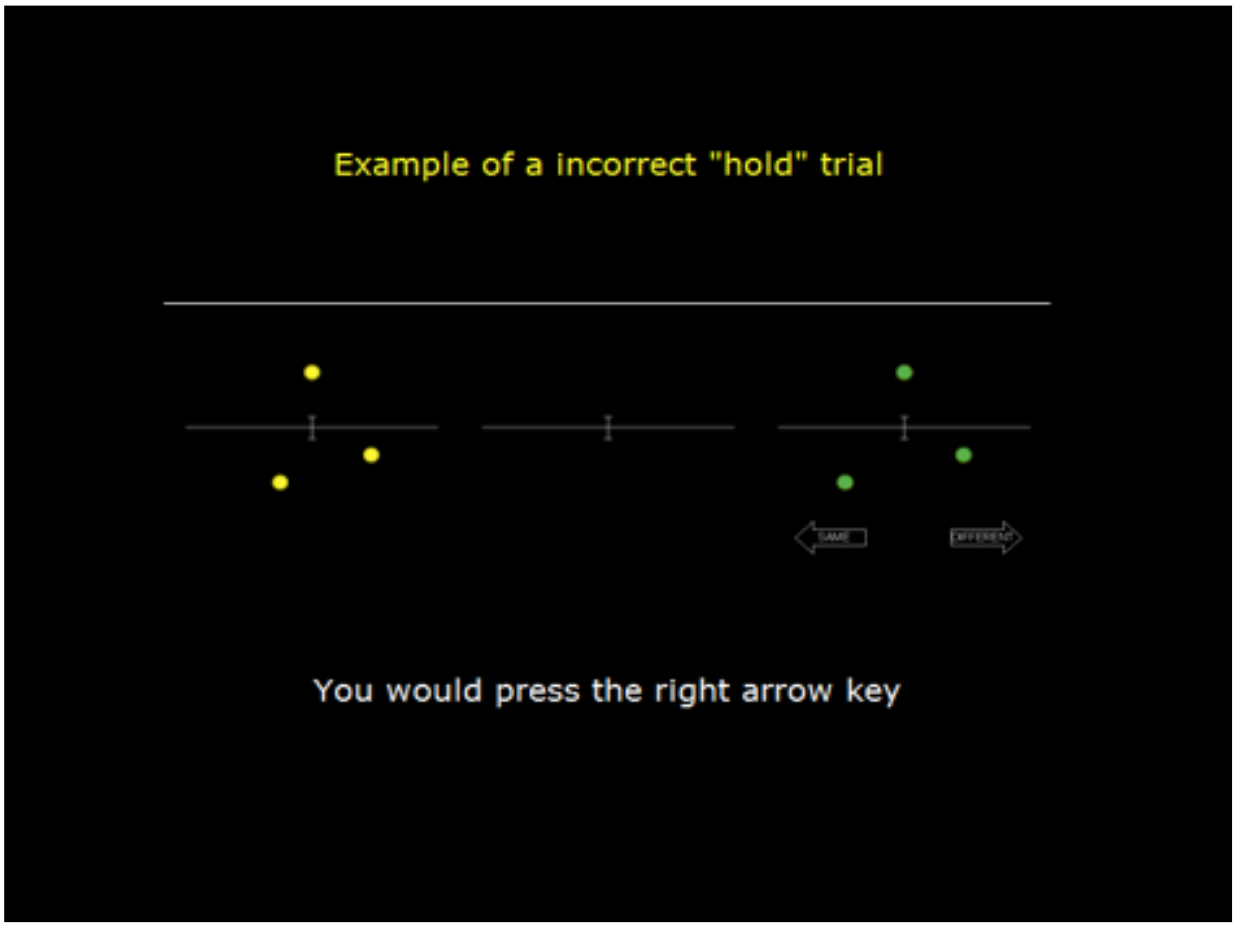

Figure 2. Instruction screen for incorrect trial. Participants are instructed to press the right arrow key if the stimuli are different (the same instructions apply to the “flip” trials).

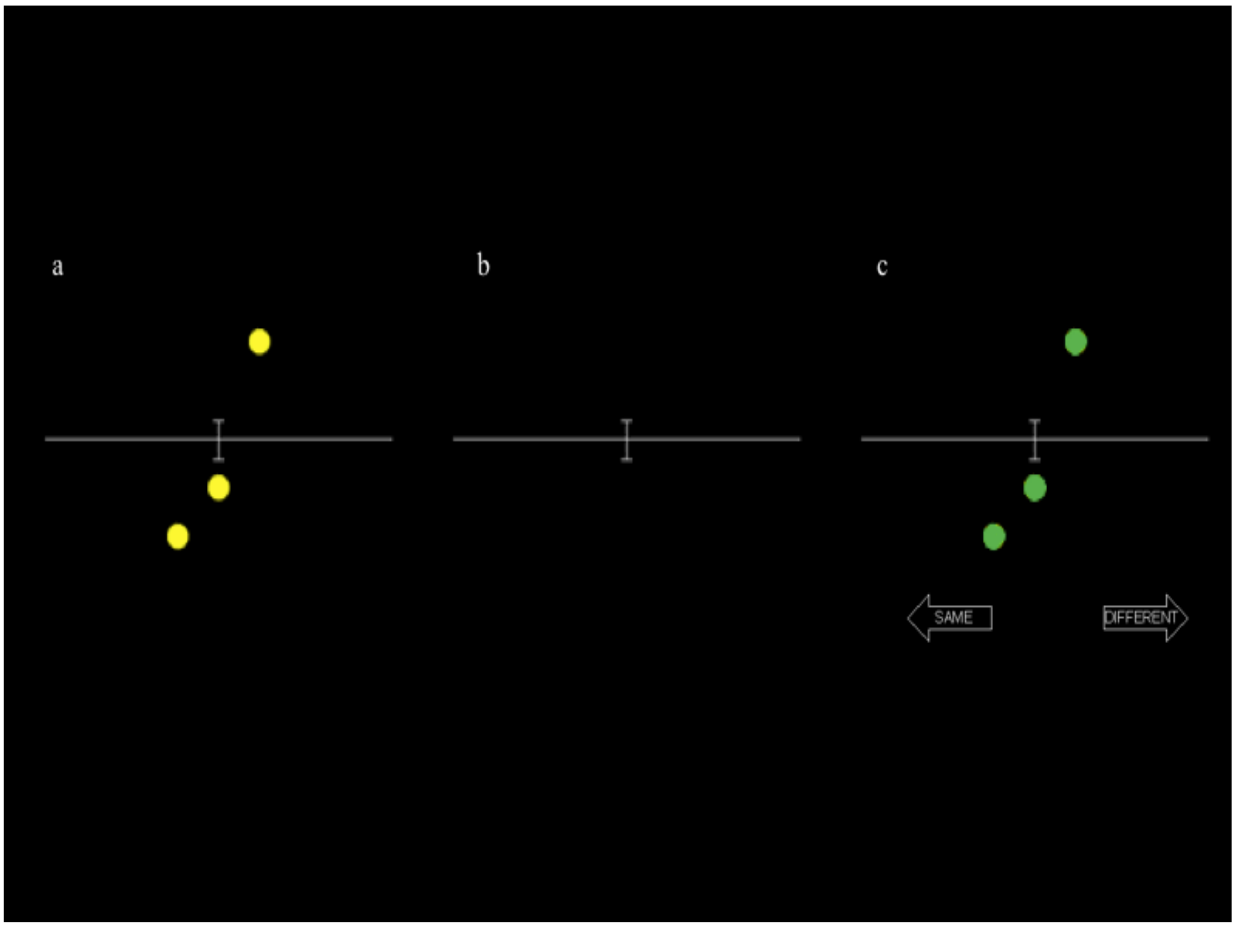

Figure 3. Example of correct "hold" trial. The original stimulus is presented first for 1500ms (a). Following, a 6000ms break is presented (b). Participants are then asked to respond (using the left or right key buttom as practiced during the instructional set) if the newly presented stimulus (green; c) is in the same position as the original stimulus (yellow).

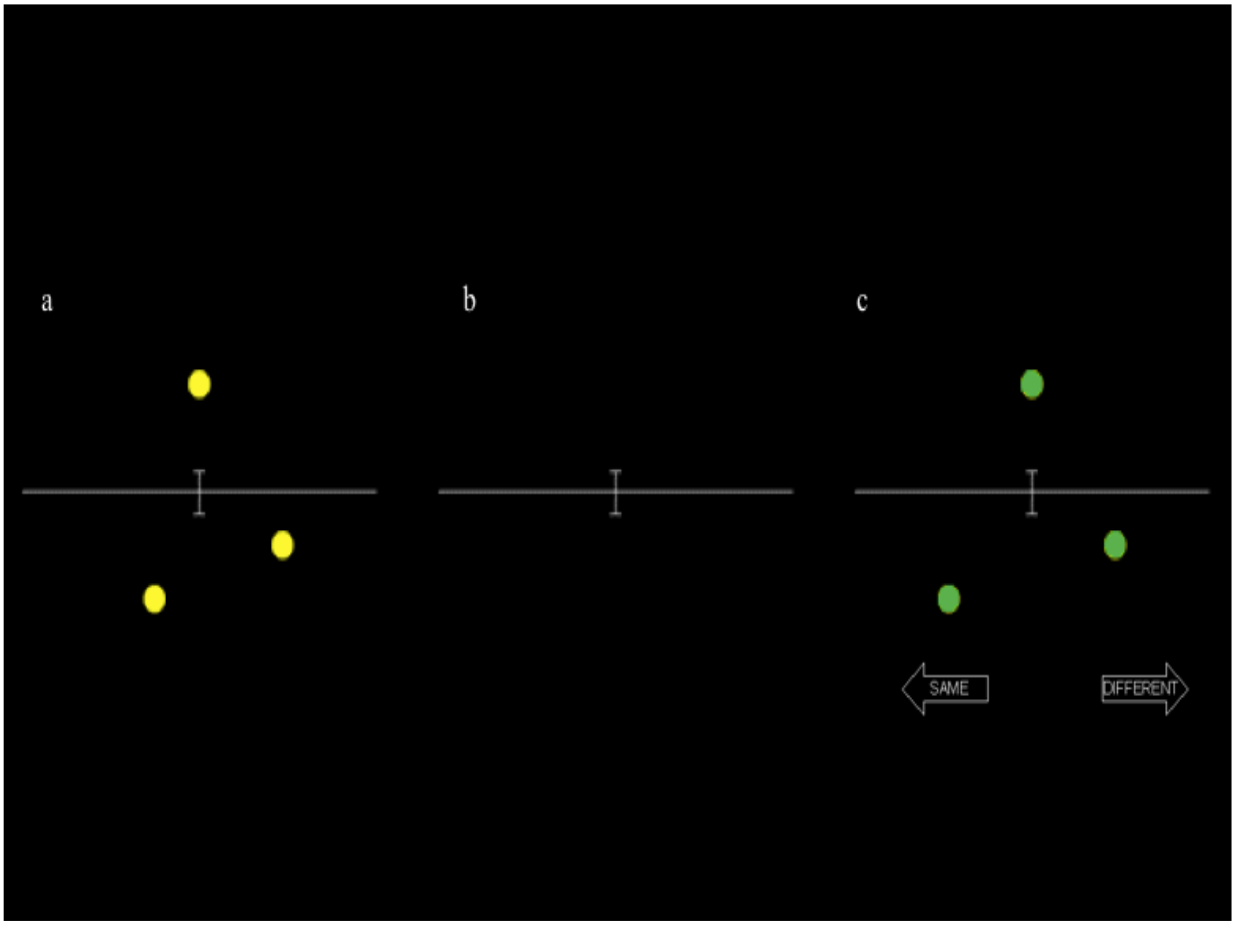

Figure 4. Example of incorrect "hold" trial. The original stimulus is presented first for 1500ms (a). Following, a 6000ms break is presented (b). Participants are then asked to respond (using the left or right key buttom as practiced during the instructional set) if the newly presented stimulus (green; c) is in the same position as the original stimulus (yellow).

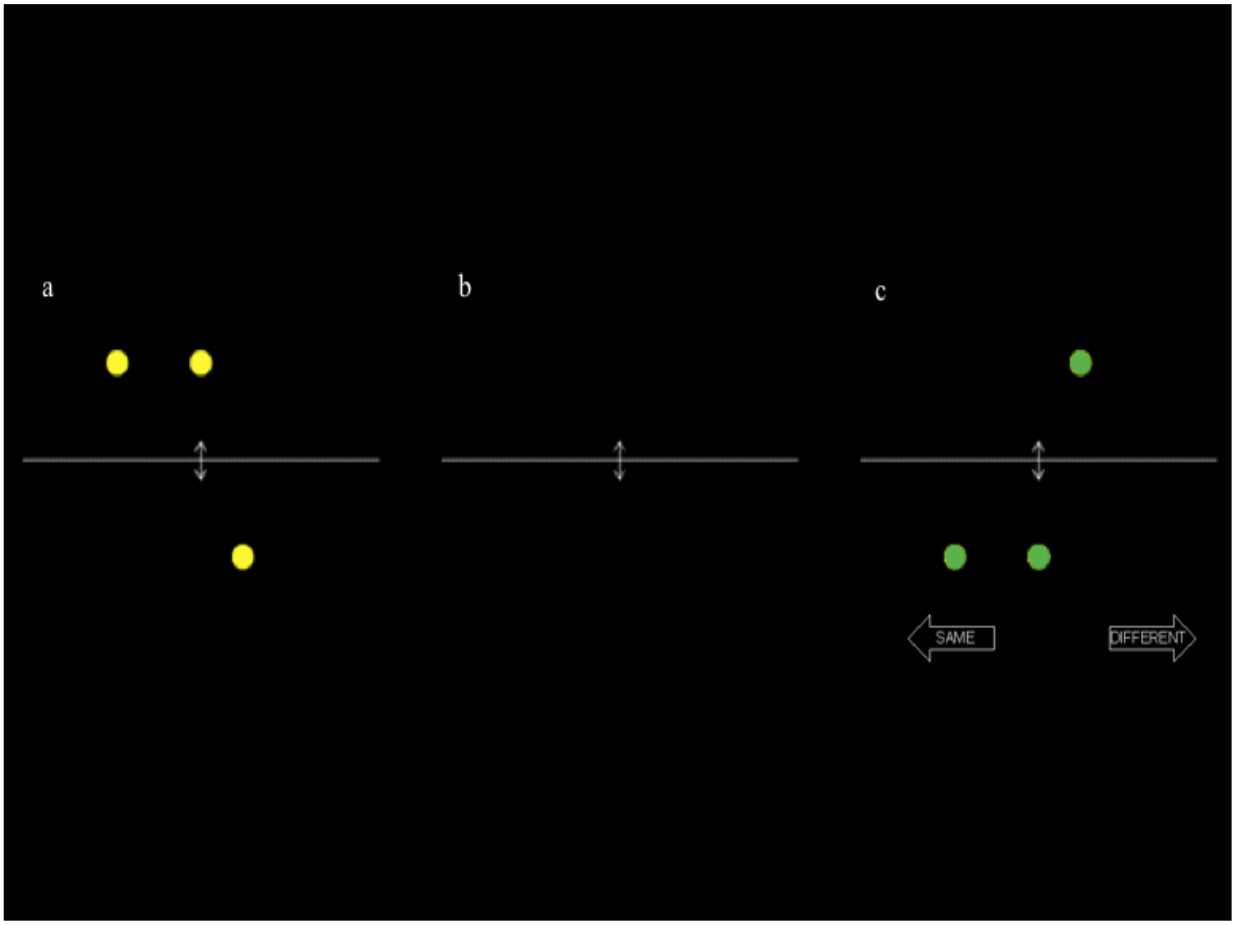

Figure 5. Example of correct "flip" trial. The original stimulus is presented first for 1500ms (a). Following, a 6000ms break is presented (b). Participants are then asked to respond (using the left or right key button as practiced during the instructional set) if the newly presented stimulus (green; c) has been flipped on the horizontal axis in relation to the original stimulus (yellow).

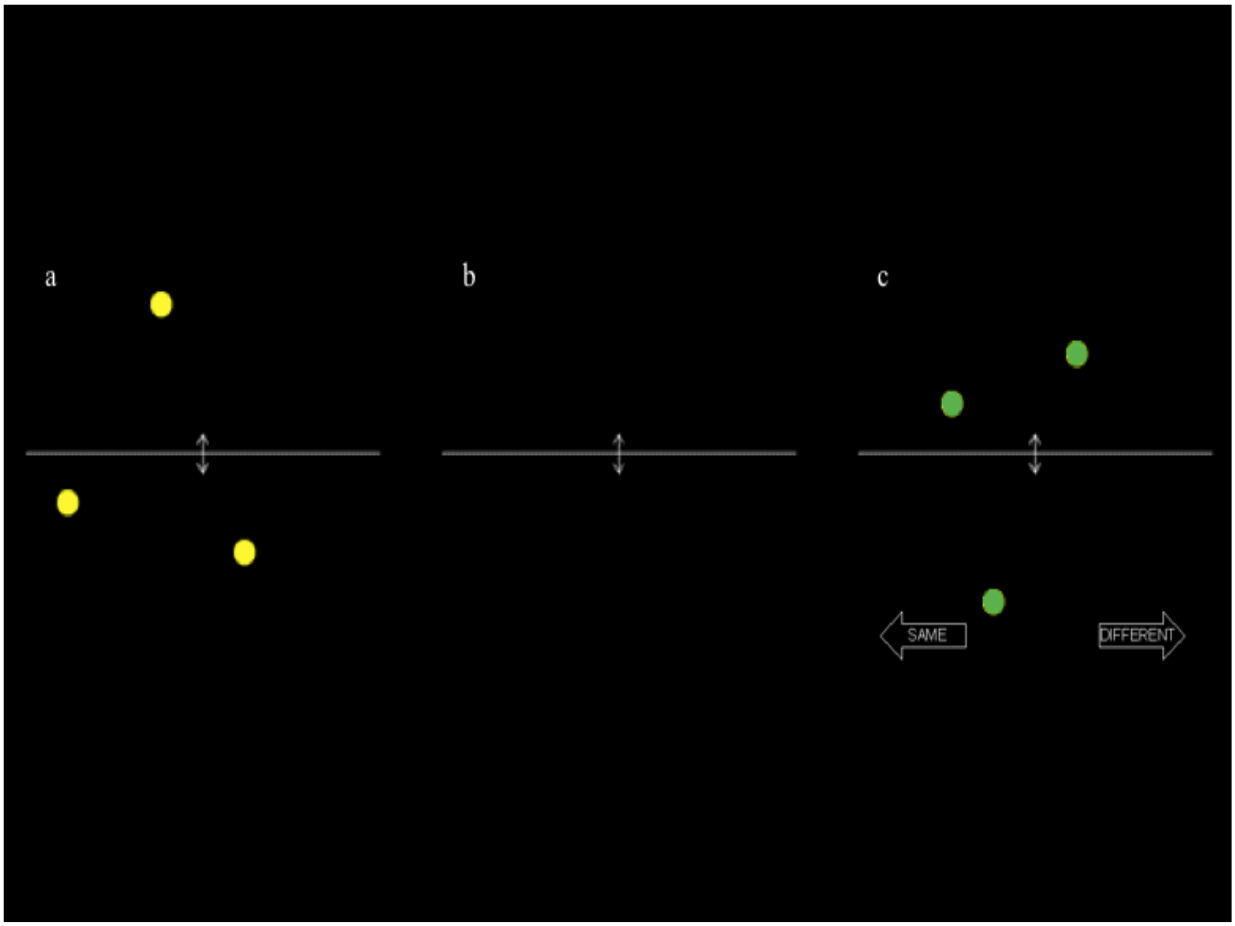

Figure 6. Example of incorrect "flip" trial. The original stimulus is presented first for 1500ms (a). Following, a 6000ms break is presented (b). Participants are then asked to respond (using the left or right key button as practiced during the instructional set) if the newly presented stimulus (green; c) has been flipped on the horizontal axis in relation to the original stimulus (yellow).