

UCLA

UCLA Electronic Theses and Dissertations

Title

Spatial Working Memory in Twins Discordant for Schizophrenia and Bipolar Disorder

Permalink

<https://escholarship.org/uc/item/3xb4m2m4>

Author

Higier, Rachel Gloria

Publication Date

2014

Peer reviewed|Thesis/dissertation

UNIVERSITY OF CALIFORNIA

Los Angeles

Spatial Working Memory in Twins Discordant for Schizophrenia and Bipolar Disorder

A dissertation submitted in partial satisfaction of the
requirements for the degree Doctor of Philosophy
in Psychology

by

Rachel Gloria Higier

2014

ABSTRACT OF THE DISSERTATION

Spatial Working Memory in Twins Discordant for Schizophrenia and Bipolar Disorder

by

Rachel Gloria Higier

Doctor of Philosophy in Psychology

University of California, Los Angeles, 2014

Professors Tyrone D. Cannon and Jesse A. Rissman, Co-Chairs

Emerging evidence indicates substantial genetic overlap between schizophrenia and bipolar disorder, but the neurobiological mechanisms underlying these shared susceptibility factors remain unclear. Examining the specific neural disruptions associated with susceptibility to these illnesses, and clarifying the nature of overlap between them, is critical to understanding the etiological bases of these disorders. In view of prior reports supporting working memory dysfunction as a candidate endophenotype of schizophrenia and bipolar disorder, we examined the neural mechanisms subserving working memory function in individuals carrying liability for both syndromes. To our knowledge, no prior neuroimaging study has simultaneously examined twin pairs discordant for schizophrenia and bipolar disorder to determine whether liability-related disruptions of working memory in the disorders overlap. We employed a trial-based spatial working memory task paradigm designed to separate activation in encoding and retrieval phases. As predicted, schizophrenia and bipolar probands as well as their non-affected co-twins

exhibited hypoactivation as well as hypoconnectivity in fronto-parietal working memory circuitry compared with controls, indicating significant endophenotypic overlap in aberrant task-related functional and network activation. These cortical alterations were significantly more pronounced during encoding phases of working memory compared with retrieval phases. Additionally, both proband groups showed hyperactivation in key nodes of the default network during retrieval phases of working memory, suggesting that failure to disengage this network during memory-guided response may represent an area of phenotypic overlap. These findings are consistent with previous evidence indicating overlapping functional alterations in schizophrenia and bipolar disorder and may inform models of mechanisms underpinning the apparent biological overlap between disorders, particularly in regards to encoding processes. Findings from this study help to characterize the nature of overlap and are consistent with a model of shared inheritance of working memory dysfunction in schizophrenia and bipolar disorder.

The dissertation of Rachel Gloria Higier is approved.

Carrie E. Bearden

Michael F. Green

Lara A. Ray

Tyrone D. Cannon, Committee Co-Chair

Jesse A. Rissman, Committee Co-Chair

University of California, Los Angeles

2014

TABLE OF CONTENTS

Abstract	ii
List of Tables	vi
List of Figures	vii
Acknowledgments	viii
Vita	ix
Background	1
The Current Study	27
Methods	30
Results	41
Discussion	53
Tables	68
Figures	73
References	81

LIST OF TABLES

Table 1. Social Demographic Characteristics by Group 68

Table 2. Single-Trial Spatial Capacity Working Memory Task Performance by Group 69

Table 3. Task-Specific Within-Group Activation Coordinate Locations of Local z-Maxima ...70

Table 4. Results of Discriminant Function Analysis 71

Table 5. Peak Coordinates of Clusters and Local Maxima from Whole-Brain Functional
Connectivity Analyses with Four Seed Regions 72

LIST OF FIGURES

Figure 1. Single-Trial Spatial Capacity Working Memory Task Paradigm	73
Figure 2. Functional Regions-of-Interest	74
Figure 3. Working Memory Task Phase Effects	75
Figure 4. Regional Activation of Controls > Bipolar Probands > Schizophrenia Probands During Encoding Trials	76
Figure 5. Regional Activation Associated with Liability to Illness during Encoding Trials	77
Figure 6. Relationship between Behavioral Performance and Activation in the Right Dorsolateral Prefrontal Cortex during Encoding Trials	78
Figure 7. Reduced Fronto-Parietal Connectivity among Non-Affected Co-Twins Relative to Control Subjects	79
Figure 8. Overlapping Encoding-Based Deviations from Control Subjects among Individuals Carrying Liability for Schizophrenia and Bipolar Disorder	80

ACKNOWLEDGMENTS

This work represents a research collaboration between The University of California, Los Angeles and The Karolinska Institutet in Stockholm, Sweden. The manuscript based on this work is currently in preparation for publication with the following co-authors: Katherine H. Karlsgodt (experimental design), Anna Xu (data analysis), Martin Ingvar (experimental design), Christina M. Hultman (co-principal investigator), Henrik Larson (data analysis), and Tyrone D. Cannon (co-principal investigator). Primary funding was provided by The National Institutes of Health ROIMH052857 Grant to Tyrone D. Cannon with additional support from The National Science Foundation Graduate Research Fellowship to Rachel Gloria Higier.

VITA

Education

2009 MA Clinical Psychology (Minor: Behavioral Neuroscience), UCLA
2006 BA Psychology (Minor: Spanish), *summa cum laude*, Emory University

Grants/Awards

National Science Foundation Graduate Research Fellowship, 2010-2013
Student Research Award, International Society for Improvement and Teaching of DBT, 2011
NIMH-Funded Advanced Neuroimaging Training Program Fellowship, 2009-2010
UCLA Graduate Research Mentorship Award, 2009-2010
NIMH-Funded Pre-doctoral Training Grant in Psychoses, 2008-2009
NIMH Intramural Research Training Award, 2006-2008

Employment

2013-2014 Pre-doctoral Intern, Weill Cornell Medical Center/New York-Presbyterian Hospital
2012-2013 Pre-doctoral Extern, Resnick Neuropsychiatric Adult Partial Hospital Program
2011-2012 Clinical Interviewer, VA Greater Los Angeles Healthcare System
2010-2012 Pre-doctoral Extern, Harbor-UCLA Medical Center
2009-2010 Clinical Assessor, Center for the Assessment and Prevention of Prodromal States
2008-2013 Therapist and Supervisor, UCLA Psychology Clinic
2006-2008 Research Fellow, NIMH Clinical Brain Disorders Branch

Publications

Higier RG, Jimenez AM, Hultman C, Borg J, Roman C, Kizling I, & Cannon TD. (In Press). Enhanced neurocognitive functioning and positive temperament in twins discordant for bipolar disorder. *Am J Psychiatry*.

Higier RG, Benson LA, Mallam S, Testerman L, Glenn D, Baucom KW, Bedics JD, & McFarr LM. (2011). Predictors of therapist burnout in DBT: The role of secondary treatment targets. *Psychomed* 3, 41.

Nicodemus KK, Callicott JH, **Higier RG**, Luna A, Nixon DC, Lipska BK, Vakkalanka R, Giegling I, Rujescu D, Shugart YY, & Weinberger DR. (2010). Evidence of statistical epistasis between DISC1, CIT, and NDEL1 impacting risk for schizophrenia: biological validation with functional neuroimaging. *Human Genetics* 127(4), 441-452.

Sabb FW, Burggren AC, **Higier RG**, Fox J, He J, Parker DS, Poldrack RA, Chu W, Cannon TD, Freimer NB, & Bilder RM. (2009). Challenges in phenotype definition in the whole-genome era: multivariate models of memory and intelligence. *Neuroscience* 164(1), 88-107.

Callicott JH, Nixon DC, Tan HY, **Higier RG**, Sust S, Prust MJ, Zolnick B, Brooke JK, Mattay VS, & Rypma B. (2009). Impact of COMT Val158Met polymorphism on processing speed activation in healthy volunteers. *Schizophr Res* 102(1), 183-184.

Presentations

Higier RG. (2014). Neural Endophenotypes for Schizophrenia and Bipolar Disorder. Talk presented at Weill Cornell Medical Center/New York-Presbyterian Hospital Department of Psychiatry Grand Rounds, New York, NY.

- Higier RG**, McFarr LM, Ansell E, & Axelrod S. (2012). Development and Validation of the Dialectical Dilemmas Scale. Talk presented at The Dialectical Behavior Therapy Strategic Planning Meeting (DBT-SPM), Seattle, WA.
- Higier RG**, Jimenez A, Hultman C, Borg J, Roman C, Kizling I, & Cannon TD. (2012). Neurocognitive functioning in twins discordant for schizophrenia and bipolar disorder. Talk presented at symposium entitled Do Schizophrenia and Bipolar Disorder Have Opposite Associations with Intelligence? JH MacCabe and A Reichenberg, Co-Chairs, The 4th Biennial Schizophrenia International Research Society (SIRS) Conference, Florence, Italy.
- Higier RG**, Benson LA, Testerman L, Glenn D, Jackson LL, Mallam S, Baucom KJW, Bedics J, & McFarr LM. (2011). Predictors of therapist burnout in DBT: Dialectical dilemmas and therapy-interfering behaviors. Poster presented at the International Society for the Improvement and Teaching of Dialectical Behavior Therapy (ISITDBT) Annual Convention, Toronto, Canada. ***Student Research Award**
- Higier RG**, Hultman C, Roman C, Borg J, Kizling I, & Cannon TD. (2011). Neurocognitive functioning in twins discordant for schizophrenia and bipolar disorder. Poster presented at the Biennial International Congress on Schizophrenia Research (ICOSR) Conference, Colorado Springs, CO.
- Higier RG**, Benson LA, Testerman L, Glenn D, Mallam S, Baucom KJW, & McFarr LM. (2011). Predictors of therapist burnout in DBT: The association between secondary targets and therapy-interfering behaviors of borderline individuals. Talk presented at symposium entitled Factors Influencing Effectiveness of Dialectical Behavior Therapy across Clinical Settings, **RG Higier**, Chair, The 7th Biennial International Congress of Cognitive Psychotherapy (ICCP), Istanbul, Turkey.
- Higier RG**, Karlsgodt KH, Xu, A, Jimenez A, Gee DG, Ingvar M, Hultman C, Larson H, & Cannon TD. (2010). Temporal jittering isolates differential brain activation and functional connectivity during encoding and retrieval phases of working memory. Poster presented at the Organization for Human Brain Mapping (HBM), Barcelona, Spain.
- Higier RG**, Nuechterlein K, Asarnow R, Shirinyan D, Kim J, Kuppinger H, & Cannon TD. (2010). Impairment of executive and storage aspects of spatial working memory in patients with schizophrenia and their first-degree relatives. Poster presented at the Society for Biological Psychiatry (SOBP), New Orleans, LA.
- Callicott JH, Nicodemus KK, **Higier RG**, Tan HY, Buckholtz JW, Kolachana B, Straub RE, & Weinberger DR. (2007). Allelic variation in NOS1AP (CAPON) is associated with altered prefrontal cortex function. Talk presented at the Annual Meeting of the Society for Neuroscience (SFN), San Diego, CA.
- Higier RG**, Brooke JK, Buckholtz JW, Tan HY, Mattay VS, Weinberger DR, & Callicott JH. (2007). Working memory in depression and the impact of 5-HTTLPR genotype. Poster presented at the Annual Meeting of the Society for Neuroscience (SFN), San Diego, CA.
- Higier RG**, Nicodemus KK, Tan HY, Buckholtz JW, Kolachana B, Straub RE, Weinberger DR, & Callicott JH. (2007). Allelic variation in CAPON (NOS1AP) impacts dorsolateral prefrontal cortex function. Poster presented at the Organization for Human Brain Mapping (HBM), Chicago, IL.

Spatial Working Memory in Twins Discordant for Schizophrenia and Bipolar Disorder

Beginning with Emil Kraepelin's (1919) proposal that dementia praecox (schizophrenia) be differentiated from manic depression (bipolar disorder), this nosological dichotomy has greatly influenced the diagnosis, treatment, and research of these two disorders. However, this concept has recently been challenged by rapidly growing evidence showing biological overlap between schizophrenia (SZ) and bipolar disorder (BP) (e.g., Berrettini, 2004; Lichtenstein et al., 2009; Purcell et al., 2009), thus leading researchers to question the validity of the Kraepelinian dichotomy at the etiological level and to search for common biological determinants. Towards this end, the current study aimed first to investigate whether SZ and BP share a common pathophysiology in terms of brain physiology measured with functional magnetic resonance imaging (fMRI); secondly, this study sought to examine whether genetic liability to SZ and genetic liability to BP are associated with shared pathophysiological alterations.

Evidence Supporting a Shared Etiology

SZ and BP show complex patterns of inheritance, involving hundreds to thousands of small effect genetic variants (Purcell et al., 2009) and a non-trivial environmental component (Kendler & Diehl, 1993; Cannon et al., 1998a), with heritability estimated at about 80% for both disorders (Sullivan, Kendler, & Neale, 2003; McGuffin et al., 2003). There are striking similarities in prevalence rates and risk factors between SZ and BP. Lifetime prevalence rates are similar (~ 1%) across disorders and stable across countries and cultures; male-to-female ratios of affected patients are comparable; and age at onset reveals a broad overlap in the range of 18-30 years (Maier et al., 2005). However, there is also evidence for differences in risk factors (see Mortensen et al., 2003). For example, lower premorbid IQ score appears to be a risk factor for SZ but not for BP (Zammit et al., 2004).

Evidence for a shared liability between SZ and BP comes from phenomenological (Lin & Mitchell, 2008), epidemiological (Berretini, 2004), and clinical genetic studies (Lichtenstein et al., 2009; Purcell et al., 2009). From a phenomenological viewpoint, perhaps the most distinctive clinical feature shared by patients with SZ and BP is psychosis. Previous studies have estimated that at least 50% of BP individuals have experienced at least one psychotic episode during their lifetime (Coryell et al., 2001; Keck et al., 2003). Likewise, while the distinctive element of BP is manic episodes, SZ patients may also exhibit affective disturbances. One study estimated that the lifetime prevalence for depressed mood (lasting at least two weeks) at first admission for SZ is 83%; additionally, during the first psychotic episode 71% of SZ patients presented with clinically relevant depression (Häfner et al., 2005). That many individuals with severe psychiatric illness have both psychotic and prominent mood symptoms raises the possibility that there may not be a clear biological distinction between these clinical phenotypes.

In addition, evidence for the co-aggregation of SZ and BP in families has been reported. An early hallmark study by Tsuang and colleagues (1980) reported increased base rates of BP in families of SZ probands, a finding that has been replicated in more recent reports showing a marked overrepresentation of bipolar disorders in families of SZ patients and vice versa (Gershon et al., 1998; Valles et al., 2000; Maier et al., 2002). Specifically, Valles and colleagues (2000) determined that first-degree relatives of BP patients had a four-fold higher risk of SZ compared with relatives of healthy individuals. Notably, the results of these studies have been questioned due to their employment of hospital registrar diagnoses, which may have introduced the possibility of misdiagnoses given the clinical resemblances of these two syndromes and thereby inflated results. However, equivalent findings were obtained using well-validated diagnostic measures, such as structured clinical interviews (Maier et al., 2002). Moreover, a

psychotic dimension (delusional proneness) was found to aggregate in families of both BP and SZ probands (Schurhoff et al., 2003), suggesting that there may be an inherited predisposition to both disorders.

A limitation of this approach is that family studies do not permit specific conclusions to be drawn about the putative roles of genetic and environmental factors, as relatives who share genes are also more likely to share environmental risk factors. Twin studies represent a special type of family analysis that can be used to differentiate genetic and environmental contributions by comparing disease prevalence in monozygotic (MZ) twin siblings of affected probands to disease prevalence in dizygotic (DZ) twin siblings of affected probands (assuming that environmental risk factors are shared equally among MZ and DZ twin pair types). Cardno and colleagues (2002) examined genetic correlations in same-sex twin pairs of SZ, schizoaffective disorder, and BP probands using non-hierarchical diagnostic criteria and found that the overlap of familial vulnerabilities is due to genetic factors shared between SZ and BP. More specifically, the authors demonstrated both common and disorder-specific genetic contributions to the variance in liability to SZ and BP, whereas the genetic liability to schizoaffective disorder was entirely shared in common with the other two disorders.

Perhaps the most compelling support for a common biological pathogenesis shared by SZ and BP is provided by genetic studies indicating that some of the same genes influence risk for both disorders. In a recent population-based genetic epidemiological study of 2 million nuclear families in Sweden, about one-half of the genetic component of SZ was found to overlap with BP, and about two-thirds of the genetic component of BP was found to overlap with SZ (Lichtenstein et al., 2009). Moreover, linkage and association studies demonstrate shared genetic susceptibility in SZ and BP. This has been shown through systematic whole-genome linkage

analyses that have identified linkage to at least five common chromosomal regions (Bramon & Sham, 2001; Berrettini, 2004) as well as candidate gene association studies whose variants were shown to be associated with both SZ and BP (Craddock, O'Donovan, & Owen, 2006; Owen, Craddock, & Jablensky, 2007; O'Donovan et al., 2008; Purcell et al., 2009; Williams et al., 2011). In fact, six out of the eight genome-wide significant susceptibility loci for SZ and BP reported to date span traditional diagnostic boundaries and show evidence for trans-disorder effects in independent datasets (Williams et al., 2011). For example, the gene demonstrating the strongest association with SZ in genome-wide association studies (*ZNF804A*) shows strengthened association when the diagnosis phenotype is broadened to include BP (O'Donovan et al., 2008; Williams et al., 2011). Taken together, molecular genetic evidence seems to support a model in which a psychosis-bipolar spectrum of clinical phenotypes is modulated by clusters of susceptibility genes that likely overlap with each other (see Craddock & Owen, 2005).

While evidence indicates substantial genetic overlap between SZ and BP, the downstream neurobiological mechanisms of shared genetic determinants remain unclear. Given the clinical heterogeneity of these disorders and the apparent imprecision of the categorical distinctions between them, it may be worthwhile to examine potential neurocognitive markers shared between SZ and BP. In particular, working memory (WMem) deficits are a core feature of SZ (Cannon et al., 2000; Green, 2006) and persist throughout the course of illness (Manoach, 2003). Likewise, emerging evidence documents deficits of WMem in BP patients that appear to persist during euthymic periods when affective symptoms are not present (Bearden et al., 2001; Green, 2006; Robinson et al., 2006). However, despite observations of WMem deficits in patients with both SZ and BP, it remains unclear whether impairments involve similar or disorder-specific pathophysiological processes.

Working Memory as a Neural Phenotype

WMem is a highly complex cognitive process known to rely on the coordination of multiple brain regions (Baddeley, 2003). Briefly, WMem can be described as the ability to store and maintain mental representations of stimuli for a short period of time, in the absence of the original stimuli. The system of WMem enables us to hold information in an active state and to work with stored information in order to perform tasks. In this way, WMem supports thought processes and may be a key component of a number of higher-order cognitive functions, including planning, problem-solving, reasoning, and language, such that disturbance of WMem may have severe consequences for more general cognitive abilities.

It has been proposed that WMem is not a unitary process but instead is composed of three independent components that operate dynamically (see Baddeley, 2003). According to this model, WMem comprises a visuospatial sketchpad and phonological loop that store and manipulate visuospatial and verbal information, respectively, together with a central executive that regulates attentional processes and controls the flow of information. While the precise neurobiological substrates of WMem have not yet been fully elucidated, results of neuroimaging studies lend tentative support for this three-component model with the implication of such regions as the prefrontal cortex (D'Esposito et al., 1999), parietal cortex (Jonides et al., 1998), and anterior cingulate (Carter, Botvinick, & Cohen, 1999). However, to accurately elucidate the brain regions involved in WMem task performance, it is necessary to disentangle the contributions of various WMem subcomponents, such as encoding, maintenance, and retrieval processes; such differentiation is needed because each of these may preferentially engage separate brain regions and networks.

Basic research examining the subprocesses of WMem indicates possible regional specialization, bearing in mind the dynamic interplays between neural systems involved in WMem. For example, the prefrontal cortex (PFC) is thought to play a preferential role in higher-order cognitive functions (Rypma & D'Esposito, 1999; Petrides, 2000; Glahn et al., 2002), whereas posterior parietal regions appear to be involved in storage processes (Curtis & D'Esposito, 2006). Within the lateral PFC, evidence suggests a relative distinction between dorsal and ventral regions, whereby ventral regions may mediate simpler maintenance processes, and dorsal regions more complex tasks requiring additional processing demands, such as manipulation or monitoring (Petrides, 2000), although alternative theories suggest that ventral and dorsal PFC might be differentially specialized for maintaining object and spatial information, respectively (Goldman-Rakic, 1995; Courtney et al., 1998; see Ranganath & D'Esposito, 2005 for a synthesis of these views). Rypma and D'Esposito (1999) showed that, while both dorsal and ventral PFC were involved in the encoding, maintenance, and retrieval of verbal information in WMem, dorsal PFC played a greater role in the encoding of information with high memory loads, consistent with other reports (e.g., Cairo et al., 2004). Further, Manoach and colleagues (2003b) demonstrated that encoding, maintenance, and retrieval functions of WMem were associated with distinct but overlapping patterns of regional activation in a Sternberg item-recognition task. In particular, engagement of the dorsolateral PFC, thalamus, and basal ganglia were associated with probe conditions, thus suggesting that fronto-striatal circuitry may play a unique role in retrieval processes. Taken together, these results highlight the importance of parsing the cognitive subcomponents of WMem in order to better characterize WMem dysfunction in patients with SZ and BP.

Additionally, neurophysiological studies of monkeys (e.g., Chafee & Goldman-Rakic, 1998; Takeda & Funahashi, 2002) and event-related fMRI studies of humans (Cohen et al., 1997; Courtney et al., 1997; Postle et al., 2000; Curtis & D'Esposito, 2003; Curtis & D'Esposito, 2006; Srimal & Curtis, 2008) have recorded persistent activity during delay periods in frontal and parietal regions, activity which is thought to reflect the stored representation of the remembered stimuli. Experimental lesions in the dorsolateral PFC appear to cause delay-dependent impairments in monkeys, such that performance decreases not only when a delay is imposed but also as the delay period increases (Funahashi, Bruce, & Goldman-Rakic, 1993), thus suggesting that this region plays a key role in the ability to draw on information stored in spatial WMem. Additionally, in a visuospatial delayed-response oculomotor task, Curtis and D'Esposito (2006) found persistent activity throughout a memory delay period in the frontal eye fields (FEF) but not in the intraparietal sulcus (IPS), despite robust activation in both of these regions during response selection (i.e., retrieval). These results suggest that the FEF and IPS make distinct contributions to spatial WMem, whereby the FEF supports the selection and prospective coding of spatial cues used to guide a response, and the IPS supports the retrospective storage of spatial representations. Consistent with this report, Rowe and colleagues (2000) showed that activation of the dorsal PFC (Brodmann's area 46) was associated with the selection of an item from spatial WMem, whereas the FEF and intraparietal cortex were associated with the maintenance of an item within WMem. Although the exact mechanisms of sustained regional activation are unclear (e.g., the rehearsal of encoding strategies versus the selection of attention towards goal-directed behavior), the evidence suggests that prefrontal regions play a role in preparing a response based on information stored in WMem, whereas parietal regions function to store spatial cues of retrospective stimuli.

Working Memory Dysfunction in Schizophrenia

Several lines of evidence suggest WMem and particularly the dorsolateral prefrontal cortex (DLPFC) as a potential locus of dysfunction in the pathophysiology of SZ (Callicott et al., 2003a; Cannon et al., 2005; reviewed in Reichenberg & Harvey, 2007). SZ patients appear to have a basic deficit in WMem (Lee & Park, 2005), which could be conceived as, for example, inadequate filtering of irrelevant information or difficulties in the maintenance of goal-directed thought process. In neuropsychological studies, while patients with SZ have been found to show performance deficits on nearly all measures of cognitive functioning, WMem appears to be more severely affected against the background of a more generalized deficit (Saykin et al., 1991; Saykin et al., 1994). In fact, covarying performance on WMem tasks tends to eliminate patient-control differences on other neurocognitive measures, such as abstraction, attention, and language (Condray et al., 1996; Gold et al., 1997; Stone et al., 1998; Silver et al., 2003), thus suggesting that WMem deficits might underlie performance decrements in other domains. In addition, deficits in WMem might account for a substantial proportion of the symptomatology associated with SZ, such as delusions, disorganization, and thought disorder (Goldman-Rakic, 1994; Perlstein et al., 2001) and appear to represent large impediments to functional outcome in schizophrenic patients (Green, Kern, Braff, & Mintz, 2000).

Impairments on spatial WMem tasks in particular are thought to be a marker of cognitive dysfunction in SZ (Park et al., 1995; Cannon et al., 2000). A number of studies have shown that patients perform worse than healthy control subjects on spatial WMem tasks (Park & Holzman, 1992; Park & Holzman, 1993; Fleming et al., 1997; Keefe et al., 1995; Keefe, Lees-Roitman, & Dupre, 1997; Cannon et al., 2000; Gooding & Tallent, 2001; McGrath, Chapple, & Wright, 2001; Glahn et al., 2003; Kim et al., 2004; Cannon et al., 2005; Karlsgodt et al., 2007), deficits

that are independent of exposure to antipsychotic drugs (Carter et al., 1996). Moreover, Park and Holzman (1992) found that SZ patients manifested a deficit in spatial WMem but were intact or less severely compromised on simple tests of verbal WMem (e.g., digit span). Within the spatial domain, patients are deficient in identifying spatial locations held in WMem after a very brief (1 second) or no delay and are marginally to significantly more vulnerable to disruption compared with controls after a longer delay (5 to 30 seconds), indicating deficits in encoding as well as maintenance processes (Park & Holzman, 1992; Park & Holzman, 1993; Carter et al., 1996; Fleming et al., 1997). Additionally, Hartman and colleagues (2003) showed that increasing the duration of the stimulus presentation improved performance on a visuospatial WMem task in patients with SZ, suggesting that inefficient encoding processes in patients with SZ may be amenable to ameliorative interventions.

More direct evidence of involvement of the prefrontal cortex in the pathophysiology of SZ comes from structural and functional neuroimaging studies. Evidence from human in-vivo and post-mortem studies converge on findings of neuropathological abnormalities in frontal lobe structure (Benes et al., 1991; Daviss & Lewis, 1995; Selemon et al., 1995; Goldman-Rakic & Selemon, 1997; Selemon et al., 1998; Cannon et al., 2002) and function (Andreasen et al., 1997; Ragland et al., 1998; Cannon et al., 2005; Karlsgodt et al., 2007) in patients with SZ. A voxel-based analysis revealed significant gray matter density reductions in schizophrenic patients compared with controls in the DLPFC and superior parietal lobule (Cannon et al., 2002), two regions that have been consistently implicated in the mediation of WMem functions. Further, global and DLPFC volumetric deficits in schizophrenic patients have been found to correlate with performance deficits on tests sensitive to WMem processes (i.e., executive-attention measures) (Seidman et al., 1994; Maher et al., 1995).

Several functional neuroimaging studies have demonstrated anomalous activation of the dorsal PFC during WMem challenge in SZ patients compared with control subjects (Ragland et al., 1998; Manoach et al., 1999; Callicott et al., 2000; Manoach et al., 2000; Perlstein et al., 2001; Barch et al., 2003; Cannon et al., 2005; Karlsgodt et al., 2007; Driesen et al., 2008; Scheuerecker et al., 2008; Karlsgodt et al., 2009; Potkin et al., 2009), although the regional specificity, magnitude, and direction of activation appears to depend on task demands and performance levels (Callicott et al., 2003b; Manoach, 2003a; Karlsgodt et al., 2007; Karlsgodt et al., 2009). Although studies more typically report hypoactivation of prefrontal regions in patients with SZ compared with controls (Ragland et al., 1998; Barch et al., 2003; Cannon et al., 2005; Driesen et al., 2008; Scheuerecker et al., 2008), hyperactivation has also been reported (Manoach et al., 1999; Callicott et al., 2000; Manoach et al., 2000). Of note, a model has been proposed suggesting that DLPFC activation relates to WMem performance in an inverted-U shaped curve, with hypoactivation occurring when WMem load has exceeded capacity (Callicott et al., 1999; Karlsgodt et al., 2007). While most studies to date scanned medicated patients, observations of dorsal prefrontal hypoactivation in medication-free schizophrenic patients (Scheuerecker et al., 2008) suggest that these differences are not likely attributable to the use of antipsychotics. Of particular interest, one study to date attempted to contrast DLPFC activation during encoding versus retrieval phases of WMem in patients with SZ compared with controls using a Sternberg item recognition paradigm and found that patient-control differences were observed in retrieval but not encoding phases of WMem (Potkin et al., 2009).

Moreover, there is evidence that fronto-parietal regions show synchronized neural activity and are functioning as an integrated circuit (Chafee & Goldman-Rakic, 1998; Smith et al., 1998), making not only the cortical regions themselves but also the interactions of these

regions of interest. In a meta-analysis of brain activation studies using the n-back task, Glahn and colleagues (2005) found support for hypoactivation in the DLPFC in patients with SZ as well as increased activation in the anterior cingulate and left frontal pole relative to control subjects. These findings could suggest that dorsolateral disturbances may not represent focal abnormalities but instead probably demonstrate an impairment in the ability to engage functional networks (Barch, 2005), an interpretation that is consistent with studies showing pronounced disruptions of distributed WMem networks in patients with SZ compared with controls (Meyer-Lindenberg et al., 2001; Peled et al., 2001; Schlösser et al., 2003; Fornito et al., 2011).

Working Memory Dysfunction in Bipolar Disorder

The neuropsychology of BP is a relatively recent area of study, perhaps in part because patients with BP were historically thought to return to normative levels of functioning between affective episodes (Kraepelin, 1919). In the last decade, however, a number of studies have reported neuropsychological impairments in BP (Martinez-Aran et al., 2000; Bearden, Hoffman, & Cannon, 2001; Zubieta et al., 2001; Quraishi & Frangou, 2002; Altshuler et al., 2004; Green, 2006; Mur et al., 2007), although it is unclear whether these deficits are related to medication status (Goswami et al., 2009; Jamrozinski et al., 2009). Moreover, such deficits appear to endure during euthymic phases of illness in the absence of clinically significant mood symptoms (Martinez-Aran et al., 2000; Bearden, Hoffman, & Cannon, 2001; Zubieta et al., 2001; Quraishi & Frangou, 2002; Altshuler et al., 2004; Green, 2006; Mur et al., 2007), thus raising the possibility that neurocognitive impairments represent trait rather than state deficits of BP. Five meta-analytic reports have reported cognitive decrements in euthymic BP patients compared with control subjects (Krabbendam et al., 2005; Robinson et al., 2006; Torres, Boudreau, & Yatham, 2007; Arts et al., 2008; Bora, Yucel, & Pantelis, 2009), with moderate to large effect

sizes for deficits in executive function, verbal memory, and sustained attention. Moreover, cognitive impairments have also been associated with diminished functional outcomes in patients with BP (Green, 2006; Gruber, Rosso, & Yurgelun-Todd, 2008; Altshuler et al., 2008; Bearden, Woogen, & Glahn, 2010; Torres et al., 2011), thus indicating that patients might benefit substantially from ameliorative interventions.

Given that executive dysfunction is thought to represent a core deficit in BP (Mur et al., 2007), deficits in visuospatial WMem warrant further investigation. Impairments in spatial WMem have been demonstrated in both the manic (Sweeney, Kmiec, & Kupner, 2000; McGrath et al., 2001) and remitted phases of illness in BP (Adler et al., 2004; Barrett et al., 2008; Pan, Hsieh, & Liu, 2011). Three studies show significant impairments on measures of visuospatial WMem in symptomatic manic BP patients compared with healthy controls (Sweeney, Kmiec, & Kupfer, 2000; McGrath et al., 2001; Badcock, Michie, Rock, 2005), but results from studies investigating spatial WMem function in euthymic patients with BP have been inconsistent. Using a visuospatial n-back task paradigm, Pan and colleagues (2011) found increasingly pronounced performance decrements across WMem loads in euthymic BP patients compared with healthy controls, deficits which appear to be independent of general cognitive functions or clinical symptoms, consistent with some reports (Adler et al., 2004; Kieseppä et al., 2005; Barrett et al., 2008) but not others (Park & Holzman, 1992; Park & Holzman, 1993; Gooding & Tallent, 2001; Clark, Iversen, Goodwin, 2002; Pirkola et al., 2005). The discrepancies in results might be due to differences in methods used to assess WMem function and in sample characteristics.

Evidence from neuroimaging studies supports the possibility that abnormalities in frontal structure and function might be implicated in the pathophysiology of BP. While neuroanatomical findings in patients with BP appear to be relatively less consistent than those reported in patients

with SZ (Baumann & Bogerts, 1999), there is an emerging consensus regarding the key nodes of disrupted neural circuitry in BP, which appear to at least partially involve dysfunction within prefrontal-subcortical networks (Bearden, Hoffman, & Cannon, 2001; Strakowski, Delbello, & Adler, 2005; Adler, DelBello, & Strakowski, 2006). Several studies have identified neuroanatomical abnormalities including volumetric reductions in the prefrontal cortex of patients with BP (Drevets et al., 1997; Hirayasu et al., 1999; Brambilla et al., 2001; Lopez-Larson et al., 2002; reviewed in Strakowski, DelBello, & Adler, 2005). A recent meta-analysis of voxel-based morphometry studies comparing bipolar individuals with control subjects identified gray matter reductions in a single cluster encompassing the right ventral prefrontal cortex, insula, temporal cortex, and claustrum (Selvaraj et al., 2012), consistent with hypotheses of impaired prefrontal modulation of anterior limbic system networks in mood regulation in BP. Further, a study by Sax and colleagues (1999) found decreased cortical volumes in BP patients compared with healthy controls, and, in the patients, prefrontal cortical volume inversely correlated with performance on a measure of attention (Continuous Performance Test). In addition, post-mortem studies have shown decreased neuron density in dorsolateral prefrontal cortical regions (Rajkowska, 2000; Cotter, Pariate, & Everall, 2001). Taken together, these studies suggest the presence of neuropathological deficits in regions critical to WMem function in patients with BP.

Only a handful of functional neuroimaging studies have examined WMem function in BP. The findings from these studies have varied, likely based on differences in experimental paradigms, sample characteristics, and individual differences in task performance; however, altered physiological activations in the frontal and parietal cortices appear to be consistently implicated in BP (Adler et al., 2004; Monks et al., 2004; Lagopoulos et al., 2007; Frangou et al., 2008; Robinson et al., 2009; Thermenos et al., 2010; Townsend et al., 2010). While

hypoactivation of the dorsolateral prefrontal cortex is more commonly reported in euthymic BP patients compared with control subjects (Monks et al., 2004; Lagopoulos et al., 2007; Townsend et al., 2010), hyperactivation has also been reported, particularly in the frontopolar cortex (Adler et al., 2004; Robinson et al., 2010; Jogia et al., 2011). One study of particular interest examined activation during an n-back task in samples of manic, euthymic, and depressed bipolar subjects compared with controls (Townsend et al., 2010). Results revealed significantly attenuated activation in the DLPFC (BA9/46) and posterior parietal cortex (BA40) in BP patients compared with controls, independent of mood state, thus providing evidence that reductions of WMem network activation may represent a trait- rather than state-related deficit.

Similar to SZ, it has been proposed that patients with BP demonstrate a pattern of frontopolar cortical inefficiency that may underpin WMem dysfunction (Jogia et al., 2011), and several studies have shown distributed regions of increased activation in patients with BP compared with controls (Monks et al., 2004; Robinson et al., 2009; Townsend et al., 2010), possibly indicating compensatory mechanisms to support WMem function. For example, Monks and colleagues (2004) found that euthymic BP patients showed an overall reduction in activation in bilateral frontal, temporal, and parietal regions during a 2-back task but also some regions of increased activation compared with control subjects. The authors interpreted these results as the recruitment of intact compensatory system resources to support WMem performance due to a failure to engage normal frontal-executive function in patients with BP. Further, Frangou and colleagues (2008) found increased activation in the parietal cortices related to increasing memory load but no other differences in a small sample of remitted BP patients without cognitive deficits compared with controls, suggesting a pattern of neuronal inefficiency within the WMem network. Additionally, increases in activity within subcortical regions associated with emotion processing

rather than cognitive processing have also been demonstrated in euthymic individuals with BP compared with controls during various WMem task paradigms (Adler et al., 2004; Gruber et al., 2010; Jogia et al., 2011). Of note, each of the studies described thus far suffered from small sample sizes, with no BP samples exceeding twenty subjects. One larger study of 36 euthymic BP patients compared with 37 healthy control subjects found that patients with BP showed inefficient engagement within the ventral frontopolar prefrontal cortex as well as overactivation in regions involved in emotional arousal (e.g., anterior cingulate cortex and insula) during both the Iowa Gambling Task and the n-back WMem task (Jogia et al., 2011). Taken together, these neuroimaging studies implicate increased activity in regions mediating emotion processing but predominantly decreased DLPFC activity during WMem tasks in remitted individuals with BP.

Most of the studies described thus far have explored WMem function in patients with BP using traditional n-back memory tasks; however, experiments using block-design paradigms do not allow for the consideration of WMem subprocesses when entire blocks are averaged. To date, one fMRI study attempted to partition WMem subprocesses using an event-related verbal delayed-response Sternberg memory paradigm in 10 patients with BP compared to 10 healthy controls (Lagopoulos et al., 2007). Findings indicate that BP patients exhibited attenuated activity compared to controls across each WMem component in several brain regions, including the DLPFC and regions of the parietal cortex. In addition, the authors identified differential results related to components of WMem, such that patients with BP showed decreases in the right inferior frontal gyrus during encoding conditions, increases in the right and medial frontal cortex but decreases in the middle and inferior frontal cortices during delay conditions, and decreases in superior frontal and anterior cingulate cortices during response conditions,

compared with control subjects. These results highlight the potential importance of partitioning cognitive subcomponents in order to better characterize WMem dysfunction in BP.

Comparisons of Neurocognitive Dysfunctions across Disorders

Most of the studies to date have examined neurocognitive dysfunction in patients with SZ and BP separately, thus making it difficult to draw direct comparisons across the two disorders; however, a few neuropsychological studies have directly compared the two disorders. Although an early report on inpatient samples showed that SZ patients did not differ significantly from BP patients in their manic phase on neuropsychological tests (Hoff et al., 1990), it is generally thought that euthymic BP patients show attenuated neuropsychological deficits compared to patients with SZ (Seidman et al., 2002). Several reports have consistently demonstrated that patients with BP exhibit cognitive deficits relative to healthy controls that are milder but qualitatively similar to those of SZ patients (Altshuler et al., 2004; Krabbendam et al., 2005; Daban et al., 2006; Glahn et al., 2006b; Green, 2006; Schretlen et al., 2007; Barrett et al., 2009; Reichenberg et al., 2009), with two reports showing equivalent impairments across groups (Smith, Barch, & Csernansky, 2009; Ivleva et al., 2012), thus supporting the notion that SZ and BP share some phenotypic similarity in the nature of their neuropsychological deficits. Meta-analysis revealed worse performance for schizophrenia patients compared with bipolar patients in 9 of 11 neurocognitive domains, even when groups were matched for clinical and demographic characteristics (Krabbendam et al., 2005). However, a subsample of BP patients with psychotic features appears to display a neuropsychological profile more similar to the profile of SZ patients (Seidman et al., 2002; Altshuler et al., 2004; Badcock, Michie, Rock, 2005; Glahn et al., 2006b; Glahn et al., 2007). Of particular note, Glahn and colleagues (2006b) found that bipolar I patients with a history of psychosis showed differential impairments in spatial

WMem – on a version of the task employed in the current study – when compared to non-psychotic bipolar samples.

Inferences regarding selective dysfunction of the cognitive subcomponents of memory in SZ and BP in large part come from neuropsychological studies comparing patterns of behavioral performance on various types of memory tasks. For example, one study of particular relevance used different versions of a novel visual delayed non-match to sample (DNMS) task in order to examine possible dissociable mechanisms underlying memory impairments in patients with SZ and BP (Glahn et al., 2006a). The authors found evidence for disturbances in partially overlapping memory systems in SZ and BP, with support for commonalities in limited encoding abilities. Specifically, BP patients showed evidence of impairment when performance required the organization of memory representations or holistic processing, whereas SZ patients were impaired when performance required the organization of contextual information but did not show differential holistic processing impairments compared with controls, perhaps due to core deficits in the ability to encode memory representations. These findings are consistent with other reports of impaired encoding of verbal information in BP patients (Bearden et al., 2006) and encoding-related pathophysiological abnormalities as measured by electrophysiological recordings in SZ patients (Bachman et al., 2009). Taken together, evidence suggests that deficits in encoding processes contribute substantially to WMem dysfunction.

Most of the functional neuroimaging studies to date have examined WMem dysfunction in SZ and BP separately, thereby precluding direct comparisons between the groups. This is particularly problematic given that it is unknown whether the deficits observed in these disorders involve impairments in similar or disparate components of WMem function. A review of the literature revealed only two functional magnetic resonance imaging (fMRI) studies that directly

compared SZ and BP patients during WMem challenge. McIntosh and colleagues (2008) showed that reduced activation of the dorsal prefrontal cortex during a sentence completion test clearly differentiated patients with SZ from those with BP, thus suggesting that circuits involving the DLPFC are implicated in the pathophysiology of SZ but less clearly in BP. Consistent with these results, Hamilton and colleagues (2009) demonstrated that, although BP patients exhibited intermediate hypoactivation in the DLPFC with respect to SZ patients and controls, effects were significant only between schizophrenic patients and controls despite similar WMem task performance. Together, these findings suggest that hypoactivation in prefrontal cortices in patients with BP may be less pronounced than in patients with SZ.

The Search for Common Biological Determinants

The search for common biological determinants may be facilitated by the examination of the neural mechanisms by which genetic variation increases risk for SZ and BP. While it is known that common genetic factors influence susceptibility to SZ and BP (Lichtenstein et al., 2009; Purcell et al., 2009), the search for specific casual variants has remained largely elusive despite considerable enthusiasm. For example, in many cases, findings from genetic association studies have failed to be replicated in subsequent reports (e.g., Munafo et al., 2005), and risk alleles demonstrating significant associations to illness show small effect sizes and account for a relatively small proportion of the genetic variance in these psychiatric disorders.

The complexity of psychiatric disorders such as SZ and BP poses considerable challenges to the search for susceptibility genes in several ways briefly described here (see Bearden, Reus, & Freimer, 2004 for a detailed account). First, liability to these syndromes is thought to arise from numerous genes of small effect and/or de novo mutations and their interactions with the environment (Cannon & Keller, 2006). This complex underlying architecture of multiple and

interacting causative factors likely contributes substantial heterogeneity to the diagnostic categories described in the current nosological systems (Tsuang, Stone, & Faraone, 2000). Second, dichotomous traits do not accurately reflect variation in liability to the disorders given that liability functions on a continuum of severity, ranging from non-affected individuals to those with extreme forms of the disorder, rather than a truly dichotomous distribution (Cannon & Keller, 2006). Consequently, the use of diagnostic categories as phenotypes may represent not only inaccurate models of liability but also a limited statistical approach due to restricted variance caused by binary independent variables, thereby requiring very large sample sizes in order to obtain adequate statistical power (which may further exasperate issues of heterogeneity). Third, the success of gene-mapping studies depends on the delineation of genetically-homogenous phenotypes, yet the question of the etiological boundaries of diagnostic categories remains controversial. For these reasons among others, the specific putative risk genes and their mechanisms of action remain in large part unknown. The identification of susceptibility genes for complexly inherited disorders such as SZ and BP might be facilitated by the use of endophenotypes.

The Endophenotype Concept: A Tool for Uncovering Biological Bases

The endophenotype concept represents a strategy for characterizing the neural systems affected by genetic liability to illness in order to elucidate mechanistic aspects of brain function implicated in psychiatric disease. Endophenotypes are traits intermediate between the mechanisms of gene action and overt expressions of the disorder (Cannon et al., 2001; Gottesman & Gould, 2003). Such endophenotypic traits are expected to vary quantitatively among individuals at genetic risk for the disorder, regardless of whether the illness is expressed phenotypically (Cannon & Keller, 2006). That is, if neurocognitive deficits are related to genetic

risk for SZ and BP, then impairments would also be observed in non-affected relatives who carry liability factors without overt expression of the illness.

The endophenotype concept has received considerable attention in psychiatric genetics over the past decade, conferring several advantages. First, the employment of a quantitative trait that varies according to degree of genetic liability enables the use of relatively powerful statistical methods known as quantitative trait loci (QTLs; Abecasis, Cardon, & Cookson, 2000) in clinical genetic studies. Second, this approach circumvents issues of clinical and genetic heterogeneity by allowing for the examination of traits more proximal to causative genes with a putatively simpler genetic structure, making it more amenable to genetic study than downstream diseases. Third, the examination of neural endophenotypes may help to characterize the mechanisms by which putative risk genes exert their effects. Fourth, this approach is not constrained by a diagnostic hierarchy, thereby enabling the simultaneous investigation of phenotypes in SZ and BP populations, which may help resolve questions about etiological models from the bottom-up perspective of clinical genetic research.

Gottesman and Gould (2003) proposed specific criteria for the identification of endophenotypic markers in psychiatric genetics; specifically, endophenotypes should be (1) substantially heritable, (2) associated with the illness in the population, (3) primarily state-independent, (4) co-segregate with the illness, and (5) occur at higher rates in unaffected relatives compared with the general population. Neurocognitive impairments are thought to represent candidate endophenotypes for SZ and, albeit to a lesser extent, BP (Burdick et al., 2006). The current study specifically aims to investigate components of WMem dysfunction as potential candidate endophenotypes for BP and SZ.

WMem dysfunction in particular might be a promising candidate endophenotype for SZ and BP, meeting the four conditions outlined by Gottesman and Gould (2003). Briefly, (1) behavioral WMem performance and the functional engagement and structural integrity of neural correlates subserving WMem function are heritable in the healthy population (ranging from $h^2 = 0.54$ to 0.73 ; Tuulio-Henriksson et al., 2002; Blokland et al., 2008; Karlsgodt et al., 2010) and share common genetic factors (Karlsgodt et al., 2010); (2) impairments in WMem have been observed in patients with SZ (Lee & Park, 2005) and in patients with BP (Arts et al., 2008) relative to healthy controls; (3) these deficits appear to persist at least to some extent across varying phases of illness in both SZ (Rund et al., 2007) and BP (Burdick et al., 2006; Arts et al., 2008); and (4) first-degree non-affected relatives of probands show behavioral deficits of executive functions intermediate between patients and controls (Glahn et al., 2003; Arts et al., 2008).

Working Memory Dysfunction as an Endophenotype for Schizophrenia

Many of the neuropsychological deficits shown by SZ patients have also been observed, to varying degrees, in their clinically unaffected relatives. In particular, impairments in WMem function appear to be a promising candidate endophenotypic marker of SZ (Cannon et al., 2000; Snitz, MacDonald, & Carter, 2006; Gur et al., 2007), possibly over and above dysfunction in other neurocognitive domains (Cannon et al., 2000; Touloupoulou et al., 2005). Touloupoulou and colleagues (2005) demonstrated that the genetic liability to SZ was overlapping to a large extent with the genetic contribution to performance on the WMem factor of the Wechsler Intelligence Scale but did not overlap with the other three factors (processing speed, perceptual organization, and verbal comprehension). In addition, WMem deficits appear to uniquely contribute to the

prediction of the degree of genetic loading for SZ in unaffected co-twins of patients over and above other neurocognitive domains (Cannon et al., 2000).

A number of previous studies have demonstrated impairments in spatial WMem in unaffected relatives of SZ probands (Park, Holtzman, & Goldman-Rakic, 1995; Cannon et al., 2000; Keri et al., 2001; Glahn et al., 2003; Tuulio-Henricksson et al., 2003; Toulopoulou et al., 2005). The severity of these WMem impairments is related to genetic loading for SZ among singleton versus multiplex families (Tuulio-Henricksson et al., 2002; Tuulio-Henricksson et al., 2003) and in discordant dizygotic versus monozygotic twin pairs (Cannon et al., 2000; Glahn et al., 2003; Toulopoulou et al., 2005). Specifically, these studies demonstrate that performance deficits in spatial WMem scale linearly with genetic relatedness; for example, MZ non-affected co-twin siblings are significantly more impaired than DZ non-affected co-twin siblings, who in turn are significantly more impaired than healthy control twin siblings (Cannon et al., 2000; Glahn et al., 2003). Further, previous schizophrenia twin studies from our laboratory have demonstrated that spatial working memory deficits – as assessed by a version of the spatial WMem paradigm employed in the current study – may be heritable (Glahn et al., 2003), thus indicating that this task may be sensitive to genetic loading for SZ. Taken together, these studies suggest that the ability to maintain spatial representations online decreases in a dose-dependent fashion with increasing genetic liability to SZ.

Neuroimaging studies appear to converge on prefrontal regions and functions as areas of relatively greater deficit in non-affected relatives of SZ patients compared with healthy controls. At the structural-anatomical level, two early studies identified reductions in cortical tissue volumes in non-affected relatives of schizophrenic probands compared with healthy controls, deficits most pronounced in frontal as well as temporal regions (Cannon et al., 1993; Cannon et

al., 1998b). Further, our laboratory previously demonstrated that the volume of the dorsolateral prefrontal cortex correlates in a dose-dependent fashion with the degree of genetic loading for SZ in samples of twins (MZ co-twins > DZ co-twins > control twins) (Cannon et al., 2002; Cannon et al., 2006). Moreover, Karlsgodt and colleagues (2010) showed that the structural integrity of the superior longitudinal fasciculus – a primary fronto-parietal connection – and performance on a spatial delayed response task share common genetic factors. Taken together, these studies suggest substantial genetic influence on cortical regions and tracts critical to WMem function.

Functional neuroimaging studies examining WMem dysfunction have also identified anomalous prefrontal cortical activation in unaffected relatives of SZ probands compared with control subjects (Callicott et al., 2003a; Karlsgodt et al., 2007; Whitfield-Gabrieli et al., 2009). In these fMRI studies, unaffected relatives show abnormal physiological response in the DLPFC while performing WMem tasks, although evidence has been mixed in regards to the direction of the response, similar to findings in SZ patients (i.e., hypoactivation versus hyperactivation). In an attempt to resolve these differences, Karlsgodt and colleagues (2007) showed that the relationship between behavioral performance on a WMem task and brain physiology may be heritable in twins discordant for SZ, such that low performance is associated with lower activation and high performance is associated with higher activation in SZ patients compared with controls, with unaffected relatives being intermediate between the groups.

Working Memory Dysfunction as an Endophenotype for Bipolar Disorder

Compared to SZ, investigations of potential BP endophenotypes have been relatively understudied, despite substantial interest in identifying endophenotypes for BP (Merikangas et al., 2002; Hasler et al., 2006; Phillips & Vieta, 2007). As studies have begun to investigate cognitive functioning in unaffected relatives of individuals with BP (Kremen et al., 1998;

Gourovitch et al., 1999; Gilvarry et al., 2001a; Gilvarry et al., 2001b; Keri et al., 2001; Ferrier et al., 2004; Kieseppä et al., 2005; Zalla et al., 2007; Ivleva et al., 2012), neurocognitive dysfunction has emerged as a potential endophenotype for BP (Glahn et al., 2004; Savitz et al., 2005; Green, 2006). For example, one study by McDonough-Ryan and colleagues (2002) found that children at genetic risk for BP showed generalized impairments on academic achievement tests, thus suggesting that individuals who carry liability to BP may experience some level of cognitive dysfunction in the absence of clinical symptomatology.

There is some evidence for neurocognitive impairments in non-affected relatives of BP patients, although overall study findings have been mixed. Two recent meta-analyses of neuropsychological functioning in euthymic BP patients and their first-degree relatives found support for executive function, verbal memory, and sustained attention as candidate endophenotypes of BP (Arts et al., 2008; Bora, Yucel, & Pantelis, 2009). Several studies have specifically observed WMem disturbances in unaffected relatives of BP probands compared with control subjects (Gourovitch et al., 1999; Ferrier et al., 2004; Balanza-Martinez et al., 2008). For example, Ferrier and colleagues (2004) reported selective impairments in non-affected first-degree relatives of BP patients on visual and verbal span tasks, two putative assessments of WMem function, but not on a range of other neuropsychological tests, although results from other studies have been inconsistent (Kremen et al., 1998; Kieseppä et al., 2005). Similar to the patterns observed in comparisons of SZ and BP patients, evidence from early family studies comparing the relatives of SZ and BP patients indicates more pronounced deficits in unaffected relatives of SZ patients than in relatives of BP patients (Kremen et al., 1998; Keri et al., 2001; Pirkola et al., 2005). For example, Pirkola and colleagues (2005) assessed spatial WMem in a discordant twin study and found support for a pattern of genetic liability to SZ but less clearly to

BP. Additional studies have demonstrated increased slowness on the Stroop Word Color Test (Zalla et al., 2007) as well as other tasks of ventral prefrontal function (Frangou et al., 2007) as potential neurocognitive markers for familial vulnerability to BP, although other reports implicate tasks mediated by dorsal prefrontal regions (Clark et al., 2005).

Of note, most of these studies included small sample sizes, and it may be necessary to obtain additional power in order to detect subtle neurocognitive differences in the relatives of BP probands compared with control subjects. Two recent studies have examined larger samples of non-affected relatives of individuals with BP. The first study of more than 700 individuals from extended pedigrees found support for WMem as a candidate endophenotype for BP (Glahn et al., 2010). Specifically, behavioral performance on an object delayed response task was heritable, impaired in individuals with BP and their non-affected relatives, and genetically correlated with affection status, suggesting that WMem performance may indeed represent a promising candidate endophenotype of BP. Of particular interest, the second report found that unaffected relatives of bipolar patients did not differ from relatives of schizophrenia patients on four neurocognitive domains, including WMem (Ivleva et al., 2012). Although it is worth noting that this study lacked a healthy comparison group, these findings nonetheless lend tentative support for WMem dysfunction as a shared neurocognitive endophenotype of SZ and BP. Together, these studies highlight the importance of examining the neural correlates of WMem deficits in order to explore potential overlapping areas of dysfunction.

There is a limited literature on brain structure and function in relatives of BP probands (Noga et al., 2001; Kieseppa et al., 2003; McDonald et al., 2004; Drapier et al., 2008). A recent meta-analysis of fMRI studies identified increased activations in the left superior frontal gyrus, medial frontal gyrus, and left insula in unaffected individuals at genetic risk for BP compared

with controls, regardless of the cognitive task (Fusar-Poli et al., 2012), indicating possible neurobiological trait abnormalities associated with liability to BP. Moreover, in a study of Finnish twins discordant for BP, Kieseppa and colleagues (2003) observed familial aggregation for BP of decreased gray matter in the medial prefrontal cortex and decreased white matter in the left hemisphere. Consistent with this report, McDonald and colleagues (2004) found evidence in white matter volume reductions in left frontal and temporoparietal regions as common susceptibility markers for SZ and BP as well as specific susceptibility for SZ in distributed gray matter volumetric deficits and for BP in gray matter deficits exclusively in the right anterior cingulate gyrus and ventral striatum. Each of these regions showing neuroanatomical alterations has been implicated in WMem function, whether through engagement of the WMem network (e.g., frontal and temporoparietal regions; Owen et al., 2005) or through the attenuation of the default mode network (e.g., medial prefrontal regions; Raichle et al., 2001; Greicus et al., 2003). While several studies show dysregulation of WMem and default-mode networks in SZ (Pomaroli-Clotet et al., 2008; Kim et al., 2009; Whitfield-Gabrieli et al., 2009), no studies to date have explicitly examined the interactions of these networks in BP.

A review of the literature revealed only three fMRI studies that have examined WMem function in unaffected relatives of BP. Drapier and colleagues (2008) demonstrated hyperactivity in the left frontal polar cortex and ventrolateral gyrus in unaffected BP relatives compared with healthy controls during 2-back performance, thus suggesting that anomalous activation in the left prefrontal cortex might be associated with genetic liability to BP. Consistent with these results, another study demonstrated a failure to suppress activation in the left anterior insula cortex and hyperactivation in the superior parietal cortex in unaffected BP relatives compared with controls during 2-back performance (Thermenos et al., 2010). Thermenos and colleagues (2011)

compared activation during the 2-back task and during a 0-back control task and found that relatives of BP probands showed poor task-dependent modulation activity in the cerebellum and insula as well as hyperactivation in the frontopolar cortex. These results might argue that hyperactivation during WMem challenge could be driven by failure to modulate activity in the low-level baseline task, which could be conceived as a form of the default-mode network.

The Current Study

Most of the studies to date have operationalized WMem as a unitary construct, thereby preventing inferences about its cognitive subcomponents. It may be useful to parse the cognitive processes necessary for WMem function into dissociable components in order to better characterize processes that contribute to impairments observed in SZ and BP (Lee & Park, 2005; Reichenberg & Harvey, 2007). While both patients with SZ and BP appear to exhibit deficits in WMem, such deficits may occur via overlapping or different disease-specific pathophysiological processes. For example, findings from one electrophysiological study indicate that neurophysiological disturbances of WMem in SZ probands and their non-affected co-twins were specifically related to encoding aspects of WMem function (Bachman et al., 2009). Studies examining WMem function as a unitary process are ill-equipped to detect such subtle differences. Given that block designs cannot isolate brain activity associated with component WMem subprocesses, in this study we temporally jittered the delay period in a single-trial design in order to isolate differential regional brain activation during encoding and retrieval phases of WMem. The consideration of these cognitive subcomponents separately may reveal promising targets for cognitive rehabilitation of cognitive deficits in SZ and BP (Barch & Smith, 2008).

The current study investigated WMem dysfunction as a potential endophenotypic marker of SZ and BP, with the general aim of determining whether there is genetic-etiological overlap

between SZ and BP in terms of spatial WMem measured at the behavioral and physiological levels. We first sought to determine whether WMem impairments in SZ and BP are the result of similar neurophysiological processes, perhaps with more pronounced disturbances in SZ, or whether different components of WMem are affected in SZ compared with BP. Towards this end, we assessed cortical function across WMem task phase in probands and controls in order to test (1) whether SZ and BP probands show phenotypic specificity of activation in regions and networks subserving WMem function, and (2) whether encoding-phase deficits are critical to the WMem deficits observed in these populations. Consistent with a model of biological overlap between these syndromes, we expected both groups to differ from controls but not each other on behavioral performance and corresponding physiological activity, thereby implicating WMem dysfunction as a phenotypic dimension that spans SZ and BP. Specifically, based on prior research (e.g., Cannon et al., 2005; Glahn et al., 2006; Hamilton et al., 2009), we hypothesized that both SZ and BP patients would show hypofrontality and hypoconnectivity relative to controls, with quantitative differences in the degree of dysfunction. Moreover, although no prior study has probed WMem circuitry separately by task phase in a direct comparison of SZ and BP, patterns of behavioral and neurophysiological differences between each patient group and controls (e.g., Glahn et al., 2006a; Bearden et al., 2006; Bachman et al., 2009) suggest that cortical alternations will be relatively more pronounced in encoding than in retrieval phases.

Additionally, we sought to clarify whether spatial WMem dysfunction represents a specific endophenotypic marker of liability to SZ, or whether such deficits might also mark liability to BP by simultaneously comparing twin samples discordant for SZ and BP and demographically similar control twins. The discordant twin pair design serves to separate the neural features of these syndromes into their heritable and non-heritable subcomponents by way

of comparing affected probands not only to unrelated healthy controls but also to their own non-affected twin sibling. In this way, WMem function can be evaluated for dose-dependency with genetic risk for SZ and BP by comparing the non-affected MZ co-twins of probands, the non-affected DZ co-twins of patients, and healthy control twins. On average, non-affected family members carry higher degrees of liability (including the influences of predisposing genes and environmental risk exposures) to illness compared with individuals from the general population. However, because non-affected family members do not have the illness themselves, the measurement of liability-related traits is not confounded by secondary phenomena such as the effects of disease chronicity and exposure to psychotropic medications. Despite their value, twin studies that incorporate neuroimaging measures are quite rare and typically involve relatively small sample sizes.

To our knowledge, no prior study has examined the neural correlates of spatial WMem in a direct comparison of twin pairs discordant for SZ and BP. We assessed regional and network activation across the genetic liability spectrum for SZ and BP (MZ > DZ > control). If WMem dysfunction represents an endophenotypic dimension that spans SZ and BP, then individuals carrying liability to both syndromes would differ from controls but not each other. Based on the model in which WMem deficits represent an area of genetic overlap between SZ and BP, we expected non-affected individuals at genetic risk for SZ and BP to exhibit common physiological markers of WMem dysfunction in fronto-parietal circuitry. That is, we hypothesized that non-affected co-twins would show attenuated cortical alterations intermediate between probands and controls, according to their degree of genetic relatedness to probands. Like their proband counterparts, such deficits were expected to be relatively more pronounced during encoding than retrieval phases of WMem.

Methods

This work is based on a larger twin study conducted at the Karolinska Institutet in Stockholm, Sweden in collaboration with the University of California, Los Angeles. The study protocol was reviewed and approved by the institutional review board (IRB) of the University of California, Los Angeles, and the ethical review board at the Karolinska Institute in Stockholm, Sweden. All participants signed IRB-approved informed-consent forms prior to participation.

Participants. To identify a participant subject pool from which to draw eligible subjects, the Swedish Twin Registry was linked to the Swedish National Patient Registry to yield twin pairs containing at least one member with a history psychiatric diagnosis as well as healthy control subjects. The register is based on a universal healthcare system involving nation-wide coverage of all inpatient and psychiatric and somatic outpatient treatment facilities and includes full admission histories and discharge diagnoses. For more details concerning ascertainment of the sample, see (Lichtenstein et al., 2009 and Ludvigsson et al., 2011).

Briefly, we recruited same-sex twin pairs between the ages of 25 and 65 born in Sweden during 1940-1985 (inclusive). This cohort was screened to identify twin pairs containing at least one member with a hospital discharge diagnosis of schizophrenia or schizoaffective disorder or bipolar I disorder, yielding 562 potential probands: 257 male and 305 female, ranging in age from 25 to 65. The age range was selected to avoid sampling pairs in which a non-affected co-twin might develop BP or SZ after the completion of the study. Discordant monozygotic (MZ) and dizygotic (DZ) pairs were recruited randomly from this population, along with demographically balanced samples of control pairs of each zygosity. The control twins were matched to the index twins in terms of age, sex, and zygosity. Twin pairs recruited as discordant in which the co-twin was determined to have an eligible psychiatric diagnosis on direct clinical

interview, and control pairs in which either co-twin was found to meet diagnostic criteria for an eligible psychiatric diagnosis, remained eligible and were reclassified accordingly.

While larger samples were studied overall, the final sample of individuals with useable fMRI data consisted of 30 SZ probands, 40 SZ co-twins, 31 BP probands, 35 BP co-twins, and 44 healthy controls for a total of 180 subjects. Demographic and clinical characteristics of the sample are shown in Table 1. Participants did not differ significantly in terms of age, sex, handedness, or years of education. There were no statistically significant differences in lifetime medication status between co-twins and controls ($F(1,9) = 0.07, p = 0.80$). As expected, significant group differences were observed on ratings of mania, such that BP probands showed elevated scores relative to co-twins and controls, who did not differ. However, BP probands' ratings of mania were below a clinically significant threshold, indicating that individuals with BP were euthymic at the time of evaluation. Additionally, there were significant group differences on ratings of depression, whereby probands demonstrated elevated scores relative to co-twins and controls, who did not differ. Similarly, significant group differences were observed on ratings of positive and negative psychotic symptoms, such that SZ probands showed elevated scores relative to co-twins and controls, who did not differ. Finally, SZ and BP probands indicated lower role functioning compared to control subjects, who did not differ from co-twins.

Procedures

Clinical evaluation. Diagnostic status was determined using direct clinical interview in addition to register data based on diagnostic history dating back to 1973. Each participant was interviewed by a clinical psychiatrist using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I; First et al., 2002) and the Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II; First et al., 1997). All subjects were also rated using the

Hamilton Depression Rating Scale (HAM-D; Hamilton, 1960), Young Mania Rating Scale (YMRS; Young et al., 1978), Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984), Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1983), and the NAPLS Social and Role Functioning Scales (Cornblatt et al., 2005). For each subject, a detailed case report summarizing clinical, social, occupational and medical history was generated, and a consensus diagnostic status was reached after review by the clinical evaluation team at the Karolinska Institute. For BP probands, the determination of a lifetime history of psychotic features was based on information gathered from the lifetime psychosis modules of the SCID. Psychosis was defined as the occurrence of hallucinations and/or delusions during at least one affective episode.

Participation criteria. Eligibility for inclusion as a proband was a consensus diagnosis of schizophrenia/schizoaffective disorder or bipolar I disorder. Exclusion criteria for all participants were the presence of a neurological disorder, history of significant head injury with loss of consciousness, mental retardation, history of substance use disorder within 6 months of the screening interview, inability to read or comprehend spoken and written Swedish, and not between the ages of 25 and 65 years at the time of evaluation. In addition, all proband participants were clinically stable, receiving medication and/or in a period of remission. No modifications to existing medication regimes were made in relation to participation in the study. Finally, healthy control twin pairs were screened to exclude individuals with a personal or family history of schizophrenia or bipolar disorder.

Subjects were also excluded for poor or missing behavioral data, scanner artifacts, excessive motion, or co-morbid medical diagnosis thought to affect measurement of blood-

oxygen-level-dependent (BOLD) response (e.g., myocardial infarction, hypertension, insulin-dependent diabetes).

Zygosity. For all pairs, zygosity was initially determined by self-report regarding physical similarity ratings and family testimony. Subsequently, DNA analysis was conducted to confirm zygosity following the procedure described by Hannelius et al. (2007) using a highly multiplexed 47 single nucleotide polymorphism (SNP) panel, including a sex specific marker, to calculate percent of allele sharing between twins in a twin pair. Likelihood of zygosity for the genotyped twin samples was then calculated assuming a 1% prior genotyping error rate, which is expected to result in a false positive rate of less than .01.

Single-trial spatial capacity (stSCAP) task paradigm. A previously validated delayed response spatial working memory task (Glahn et al., 2003; Cannon et al., 2005; Glahn et al., 2006b) was adapted to a single-trial format in order to probe neural activation during different phases of working memory, specifically parsing encoding and retrieval components (see Figure 1). Participants were first asked to study an array of three yellow target circles, arranged in a pseudorandom pattern around a central fixation point on the screen, for about 2.5 seconds. After a jittered delay period (varying about three to six seconds), a single green probe circle appeared on the screen, either in the location of a correct target or in the location of an incorrect foil, and participants were asked to press the response key to indicate whether the green probe circle was in the same position as one of the three yellow target circles within a two second response window. The task was comprised of 26 trials; half were true positive (correct answer ‘yes’) trials and the other half were true negative (correct answer ‘no’) trials.

In order to maximize the number of trials for analysis and minimize the task duration, we decided to test only at a working memory load of three. Previous research from our laboratory

indicates that patients with SZ and BP are able to perform the task well above chance at this load (Glahn et al., 2003; Pirkola et al., 2005). This memory set size was selected not only to expose performance differences between groups but also to maximize the number of correct trials per subject in order to analyze between-group differences in physiological activation during the task. Other changes in the task design from that of Cannon et al. (2005) were that the delay period is slightly longer, as is the inter-trial interval. Although the delay period is, on average, slightly longer than in previous versions of the task, there is no evidence that this will attenuate performance differences between SZ patients and healthy controls (Lee & Park, 2005). An additional result of the jittering technique is that the delay period and inter-trial intervals have variable lengths, allowing the dissociation of encoding and retrieval phases. Additionally, we inserted a beep before the start of each trial to ensure that the participant knows the fixation is over and the task will begin again.

Prior to scanning, participants completed a brief training session via E-prime on a computer outside the scanner. First, instructions for the task were displayed and participants were allowed to ask clarifying questions until the administrator was confident the subject fully understood the task. Then, practice trials were completed with performance feedback provided (“correct,” “incorrect,” or “no response detected”). If the subject did not get any of the practice trials correct, or if he/she did not respond to most of the trials, the training session was repeated as necessary.

Neuroimaging Parameters

A 7.5 second fixation cross was presented at the beginning of each scan to account for the first three scans discarded by the scanner to allow for saturation of the T1 effects before the start of data collection. Subjects’ responses were recorded through a hand-held fiber optic

response box connected to a computer, allowing for button box responses and reaction time to be recorded. Subjects were asked to respond as quickly and accurately as possible. The total scan time for the stSCAP task was 7.83 minutes.

Scanning parameters. Data were acquired on a 1.5 Tesla GE (Milwaukee, WI) scanner equipped with a fast gradient system for echo-planar imaging with a standard radiofrequency (RF) head coil. For each subject, a high resolution structural T2-weighted image was acquired for anatomical registration [spin echo; AC-PC aligned; repetition time (TR) = 4000 ms; echo time (TE) = 82 ms; 25 axial slices; 4 mm thickness; matrix size = 128 x 128] as well as a Gradient Echo Planar Imaging (EPI) sequence (TR = 2500 ms; TE = 40 ms; flip angle = 90°; 25 interleaved slices; 3.5 mm thickness; voxel size = 3.44 x 3.44 x 4.5; matrix = 64 x 64). A total of 188 volumes were collected during the stSCAP functional scan. Prior to imaging, three dummy scans were acquired to reach equilibrium magnetization.

Image processing. Data were analyzed using FSL (FMRIB's Software Library v4.1; Analysis Group, Oxford, UK). During preprocessing, images were skull stripped and corrected for major motion artifacts (6 DoF). Individual subject analyses were performed using FEAT (FMRI Expert Analysis Tool). Data were spatially smoothed (8 mm FWHM Gaussian Kernel), high pass filtered, and referenced to individual T2 images. At the individual subject level, the data for correct trials only were modeled with four explanatory variables (EVs: target, delay, probe, and incorrect), each convolved with a canonical hemodynamic response function. The estimates of the subjects' movement during the scan were also entered as confounding covariates in order to minimize the possibility of motion artifacts. Contrasts were constructed to examine all four trial types versus baseline and pair-wise comparisons between trial types. For each contrast of interest, one contrast image per subject was entered into a second-level random effects

analysis to examine areas of activation within each of the groups and differences in activation between the groups using analysis of variance. Age and sex were entered into the model as covariates.

Given that the brains of patients may be morphologically different from those of control participants and subjects comprising standard space templates, a group-averaged template brain was created exclusively based on subjects included in the analyses, rather than using a pre-existing standard space template for group-level registration. This study-specific standard brain was created to minimize the distortion of the functional data during spatial normalization and avoid creating spurious group differences due to relatively greater distortion in patients relative to control subjects (see Karlsgodt et al., 2007). This template was accomplished via an iterative averaging process using FLIRT (FMRIB's Linear Image Registration Tool) and the `fslmaths` tool.

Regions of interest. Regions-of-interest (ROIs) were defined functionally from the all subjects, all trial types contrasts to allow each group to contribute to the definition of the ROI. The t -statistic map for this contrast was thresholded at $T_{\infty} > 1.96$ (2-tailed, $p < .05$). From this thresholded map, the peak activation voxel was identified for each ROI using Brodmann's and anatomical landmarks, and a 6mm sphere was applied. Four ROIs were selected to characterize the working memory network: (1) right DLPFC (BA 9, MNI Coordinates: [42, 34, 24]), (2) left DLPFC (BA 9, MNI Coordinates: [-34, 48, 22]), (3) right inferior parietal lobule (BA 40, MNI Coordinates: [40, -42, 42]), and (4) left inferior parietal lobule (BA 40, MNI Coordinates: [-38, -48, 44]). Two additional ROIs were selected to characterize the default-mode network given the observed patterns of activation during retrieval trials: (1) medial prefrontal cortex (BA 10, MNI Coordinates: [8, 62, 8]), and (2) precuneus/posterior cingulate cortex (BA 31, MNI Coordinates: [-8, -52, 24]). ROIs are displayed in Figure 2. These ROIs were implemented as seed regions in

PPI analysis and were used to explore differences in activation across co-twins split by zygosity and group differences in the relationship between activation and performance.

Statistical Analysis of Behavioral Data

Performance below chance level (50%) could be interpreted as reflecting problematic inattention, insufficient motivation, or lack of engagement with the task while in the scanner. Fifteen subjects were excluded from analyses due to below chance level performance (5 SZ probands, 5 BP probands, and 5 non-affected subjects).

Mixed model analyses of variance with repeated measures were conducted to compare stSCAP task performance of each group across delay periods. For completeness, simple effect analyses were performed in the absence of a group x delay interaction to examine whether overall performance varied by group. Separate analyses were conducted for accuracy (% correct), omissions (% omitted), and reaction time for correct trials (milliseconds). Age and sex were entered into the models as covariates. Interaction terms for age and sex were not significant and therefore dropped from the model unless otherwise noted, and data were collapsed across zygosity for primary analyses. To account for the clustered nature of the twin data and correlation among repeated effects, subjects were treated as individuals nested within pairs, and the data were modeled with an unstructured variance-covariance matrix form, allowing for unique variance within each group and covariance within each twin pair.

Data were analyzed using PROC mixed SAS version 9.2 (SAS Institute Inc., Cary, NC). Significant group effects were evaluated with post-hoc *t*-tests. All analyses measured significance at the .05 level (two-tailed) unless otherwise noted.

fMRI Data Analysis

Whole-brain analysis. Statistical analyses were performed using the general linear model as implemented in FSL version 4.1.9 (FMRIB's Software Library v4.1; Analysis Group, Oxford, UK). Primary hypotheses tested whole brain blood-oxygen-level-dependent (BOLD) signal analysis using cluster-thresholding to control for multiple comparisons in contrasts comparing diagnostic groups. All analyses measured significance at $Z > 2.3$, $p < .05$, cluster corrected, unless otherwise noted. Tests of linear trends on genetic loading for SZ and BP were conducted contrasting probands, co-twins, and control subjects. Since encoding trials appeared to distinctly activate the canonical WMem network, and since prior research has demonstrated deficits specific to encoding-related aspects of WMem in both proband groups (Bearden et al., 2006; Glahn et al., 2006a; Bachman et al., 2009), primary tests of hypotheses examined between-group differences in activation during encoding trials. All coordinates are reported according to the standard Montreal Neurological Institute (MNI) brain template.

Discriminant function analysis on region-of-interest activation. Percent signal change in a priori regions of interest (ROIs) were extracted for analysis using Featquery. BOLD signal in these ROIs were then entered into a discriminant function analysis in order to assess whether differences in regional activation separated groups with potentially clinically useful precision.

Functional connectivity analysis. Functional connectivity in putative fronto-parietal WMem networks was examined using psycho-physiological interaction (PPI) analysis (Friston et al., 1997). A PPI analysis was conducted to examine whether task-dependent fronto-parietal connectivity differed between groups. That is, the PPI analysis tested whether probands, non-affected co-twins, and control subjects differed on the extent to which a selected seed region

covaried with other brain regions within the WMem network during the task. Seed regions for PPI analysis were based on the four functional ROIs selected to characterize the WMem network.

The GLM analysis was performed in FSL with regressors for task, seed region timeseries, and the interaction of task and timeseries. The psychological (task condition) regressor was collapsed across trial type (encoding, delay, and retrieval) in order to increase power given the limited power of single-trial task designs in PPI analysis. The physiological (seed region timeseries) regressor comprised the timeseries for the seed region of interest. A third regressor modeled the interaction of the psychological regressor and the physiological regressor, such that it identified regions that covaried in a task-dependent manner with the seed ROI (i.e., regions that significantly correlated more with the seed ROI during the task).

As in the prior analyses of functional activation, a first level analysis was conducted for each individual participant to identify regions that significantly covaried with the seed ROI in a task-dependent manner. A second level analysis identified between-group differences in terms of regions that significantly covaried with the seed ROI during the task. Group analysis was carried out using FLAME, and resulting z -statistic images were thresholded using clusters determined by $Z > 2.3$ and a corrected-cluster significance threshold of $p = .05$ to control for multiple comparisons.

Conjunction analysis. Conjunction analysis was conducted by multiplying relevant group z -statistic maps (e.g., Control > SZ Liability x Control > BP Liability) in order to examine overlapping regions of aberrant activation and functional connectivity associated with liability to SZ and liability to BP. Conjunction analysis was performed on cluster-corrected z -statistic maps in order to control for multiple comparisons.

In order to compare the regional and network activation patterns associated with liability to both syndromes, the Dice Similarity Measure (DSM; Dice, 1945) was calculated. The DSM is a symmetric measure of the resemblance of two binary images and has been employed in previous work to measure the number of activated voxels that are shared between two fMRI images (Salimi-Khorshidi et al., 2009). The DSM coefficient ranges from 0 (indicating no overlap) to 1 (perfect overlap). The DSM coefficient was calculated for both activation and functional connectivity maps with the following equation:

$$\text{DSM} = (2 \times |A \cap B|) / (|A| + |B|)$$

where A represents the z-statistic activation map from the first contrast (e.g., Control > SZ Liability) and B represents the z-statistic activation map from the second contrast (e.g., Control > BP Liability).

Functional activation-performance analysis. To assess the relationship of performance and fMRI signal between subjects, a linear regression was performed predicting fMRI signal in select ROIs with performance as a factor using SAS version 9.2. Primary functional-performance analyses were conducted on signal in the right DLPFC given hypothesized activation-performance relationships in this region (Callicott et al., 2003; Karlsgodt et al., 2009). Group differences were examined using the interaction between the slopes of the relationship between performance and BOLD signal and tested for significance. To account for relatedness between co-twins, twin pairs were clustered to adjust standard errors for intragroup correlations of twin pairs.

Results

Tests of Sample Representativeness

The studied probands were comparable to the remainder of the twin proband population in terms of sex ($X^2(1) = 0.87, p = .35$), age at first hospital admission ($t(168) = -0.78, p = .44$), and total number of hospital admissions ($t(170) = -1.25, p = .21$). However, there was a marginal age effect in our sample ($t(187) = 1.89, p = .06$), such that studied probands were on average three years younger than the remainder of the twin proband population (Proband Participants' Mean \pm SD: 49.34 ± 11.55 ; Proband Non-Participants: 52.57 ± 10.15). To control for this potential bias, we included age as a covariate and matched groups on age.

Behavioral Data

Descriptive statistics for stSCAP performance indicators for each group are displayed in Table 2. There were no group differences in the analyses by delay period (Accuracy: $F(20,859) = 1.18, p = .27$; RT-Correct: $F(20,859) = 1.05, p = .40$; Omissions: $F(20,859) = 0.78, p = .74$), indicating that the performance of all groups was reduced in association with increased delays to similar degrees. When performance data was collapsed across delay, a pattern in which probands showed performance decrements compared with controls was observed. Mixed model tests of simple effects revealed significant group differences on accuracy ($F(4,859) = 4.13, p = .020$) and reaction time ($F(4,859) = 3.93, p = .010$) as well as trend-level differences on omissions ($F(4,859) = 2.17, p = .085$). Post-hoc t -tests revealed significant differences on accuracy between controls and SZ probands ($p = .049$, one-tailed) and marginal differences between controls and BP probands ($p = .060$, one-tailed). Control subjects did not differ from SZ or BP co-twins. This general pattern was consistent for reaction time and omissions.

stSCAP Task-Related Activation

As shown in Figure 3, subjects collapsed across groups showed overall significantly more activation of the canonical WMem network during encoding compared with retrieval phases of the stSCAP task, involving increased activation in bilateral occipital cortex (Peak MNI Coordinates: [34, -54, -18]), right dorsolateral prefrontal cortex (Peak MNI Coordinates: [46, 34, 16]), bilateral precentral gyrus (Peak MNI Coordinates: [28, 0, 50]), and bilateral parietal cortex (Peak MNI Coordinates: [50, -38, 42]) including the supramarginal gyrus, angular gyrus, and superior parietal lobule ($p < .05$ cluster-corrected). Subjects showed overall increased activation during retrieval compared with encoding phases in the medial frontal cortex (Peak MNI Coordinates: [4, 46, -12]) and posterior cingulate/precuneus (Peak MNI Coordinates: [-6, -56, 16]; $p < .05$ cluster-corrected), regions typically associated with default mode activity. When the statistical map of the retrieval phase was examined separately, activation was observed in the medial motor cortex (Peak MNI Coordinates: [0, 4, 46]; $p < .05$ cluster-corrected).

Results from within-group analyses conducted on the whole-brain level comparing encoding and retrieval trials are reported in Table 3. Control subjects exhibited widespread task-related activation in regions typically associated with WMem, including bilateral occipital cortex, right DLPFC, bilateral precentral gyrus, and bilateral parietal cortex during encoding phases relative to retrieval phases ($p < .05$, cluster-corrected). SZ and BP probands activated similar regions ($p < .05$, cluster-corrected) but to a lesser spatial extent, particularly in frontal regions. SZ and BP co-twins also exhibited activation in similar regions ($p < .05$, cluster-corrected).

During retrieval phases compared with encoding phases, SZ and BP probands showed pronounced activation in the medial prefrontal cortex and posterior cingulate ($p < .05$, cluster-corrected), suggesting failure to suppress these regions of the default mode during task

engagement. Control subjects activated similar regions ($p < .05$, cluster-corrected) but to a lesser spatial extent, particularly in the posterior cingulate cortex. While BP co-twins showed a similar pattern of default-related activity ($p < .05$, cluster-corrected), although to a lesser spatial extent than their proband counterparts, SZ co-twins did not show any significant regions of activation during retrieval trials compared with encoding trials ($p < .05$, cluster-corrected).

Whole-Brain Between-Group Activation during Encoding

Given distinct task-related networks associated with each WMem task phase, between-group activation was examined separately for the encoding and retrieval phases in order to maximize the number of activated voxels when examining between-group differences. Controls exhibited significantly greater activation during successful encoding of information in WMem relative to both proband groups ($p < .05$, cluster-corrected) in bilateral prefrontal cortex (Right Peak MNI Coordinates: [24, 8, 46], BA 6, Z -max = 3.72, p -corrected = .042, cluster size = 362; Left Peak MNI Coordinates: [-8, 42, 26], BA 9, Z -max = 4.16, p -corrected < .001, cluster size = 1029), bilateral angular gyrus (Right Peak MNI Coordinates: [44, -52, 14], BA 39, Z -max = 4.14, p -corrected < .001, cluster size = 1013; Left Peak MNI Coordinates: [-52, -64, 30], BA 39, Z -max = 4.31, p -corrected = .002, cluster size = 605), and precuneus (Peak MNI Coordinates: [-4, -52, 40], BA 7, Z -max = 4.18, p -corrected < .001, cluster size = 1064), with BP probands showing intermediate activation between SZ probands and control subjects in these regions (see Figure 4). There were no significant differences between SZ and BP probands ($p < .05$, cluster-corrected).

Liability to illness. Control subjects showed greater activation relative to non-affected co-twins during accurate encoding of information ($p < .05$, cluster-corrected) in the anterior cingulate (Peak MNI Coordinates: [0, 48, 24], BA 9, Z -max = 3.73, p -corrected = .018, cluster size = 427), left DLPFC (Peak MNI Coordinates: [-22, 44, 26], BA 9, Z -max = 3.22, p -corrected

= .023, cluster size = 343), and the left angular gyrus (Peak MNI Coordinates: [-38, -58, 34], BA 39, Z -max = 3.65, p -corrected = .030, cluster size = 387). There were no regions where co-twins showed significantly greater activation during encoding relative to controls.

Schizophrenia liability. Whole-brain analysis conducted using a linear contrast revealed significantly greater task-related activation during encoding in the right DLPFC (Peak MNI Coordinates: [46, 30, 24], BA 9, Z -max = 3.57, p -corrected < .001, cluster size = 687), anterior cingulate (Peak MNI Coordinates: [-8, 42, 26], BA 9, Z -max = 4.56, p -corrected < .001, cluster size = 939), precuneus (MNI Peak Coordinates: [-4, -52, 40], BA 7, Z -max = 2.12, p -corrected = .008, cluster size = 496) and bilateral parietal cortex (Left MNI Peak Coordinates: [-52, -64, 30], BA 39, Z -max = 4.11, p -corrected = .013, cluster size = 452; Right Peak MNI Coordinates: [50, -62, 36], BA 39, Z -max = 3.69, p -corrected < .001, cluster size = 745) in controls relative to SZ co-twins relative to SZ probands (p < .05, cluster-corrected). The z -statistic activation map illustrating areas where Controls > SZ Co-Twins > SZ is displayed in Figure 5A.

Bipolar disorder liability. Whole-brain analysis conducted using a linear contrast revealed significantly greater task-related activation during encoding in the left DLPFC (Peak MNI Coordinates: [-26, 40, 24], BA 9, Z -max = 3.55, p -corrected = .007, cluster size = 181), anterior cingulate (Peak MNI Coordinates: [-2, 44, 26], BA 9, Z -max = 4.35, p -corrected = .037, cluster size = 372), and left lateral parietal cortex including regions in the angular gyrus and supramarginal gyrus (Peak MNI Coordinates: [-44, -52, 36], BA 39, Z -max = 3.41, p -corrected = .009, cluster size = 484) in controls relative to BP co-twins relative to BP probands (p < .05, cluster-corrected, see Figure 5B).

Whole-Brain Between-Group Activation during Retrieval

Both proband groups exhibited greater activation during retrieval relative to control subjects ($p < .05$, cluster-corrected) in the posterior cingulate cortex (Peak MNI Coordinates: [-8, -52, 24], BA 31, Z -max = 3.84, p -corrected = .002, cluster size = 594), with BP probands showing activation in this region intermediate between SZ probands and controls, indicating significantly reduced task-related suppression of the default-mode during retrieval in probands relative to control subjects. There were no statistically significant regions showing greater activation in control subjects compared with proband groups.

Schizophrenia liability. Whole-brain analysis conducted using a linear contrast revealed significantly greater regional activation during retrieval in the posterior cingulate cortex (Peak MNI Coordinates: [-8, -52, 24], BA 31, Z -max = 4.22, p -corrected < .001, cluster size = 787) in SZ probands relative to SZ co-twins relative to control subjects, suggesting that failure to suppress this region of the default network during retrieval of information from WMem may be associated with liability to SZ. There were no statistically significant regions in the whole-brain analysis where control subjects activated more than SZ co-twins.

Bipolar disorder liability. Whole-brain analysis conducted using a linear contrast revealed significantly greater activation during retrieval in the thalamus (Peak MNI Coordinates: [-18, -32, 14], Z -max = 3.31, p -corrected = .005, cluster size = 343) and the left superior parietal lobule (Peak MNI Coordinates: [-28, -48, 36], Z -max = 3.17, p -corrected = .018, cluster size = 101) in controls relative to BP co-twins to BP probands. There were no statistically significant regions in the whole-brain analysis where BP co-twins activated more than control subjects.

Discriminant Function Analysis on Regions of Interest

A discriminant function analysis was performed to assess prediction of group membership (SZ, SZ co-twin, BP, BP co-twin, control) from regional activation during encoding trials in four ROIs selected to characterize the WMem network. One significant discriminant function was calculated and accounted for 80% of the between-group variability. The discriminant function maximally separated SZ and BP probands and non-affected co-twins from control subjects. The loading matrix of correlations (see Table 4) between predictor ROIs and the discriminant function suggested that activation in the right DLPFC and right superior parietal lobule best distinguishes between individuals carrying liability for illness (probands and co-twins) and controls.

Functional Connectivity Analysis

Functional connectivity within WMem circuitry. Functional connectivity during the WMem task was examined collapsing across encoding and retrieval trials in order to maximize power within a single-trial design. PPI analysis examined covariation between activation in four seed regions selected to characterize the WMem network (right DLPFC, right parietal, left DLPFC, left parietal) and every voxel in the brain. Peak MNI coordinates of clusters and local maxima from between-group whole-brain functional connectivity analyses ($Z > 2.3$, $p < .05$, cluster-corrected) are reported in Table 5. No differences were observed on functional connectivity measures between probands and control subjects in predicted fronto-parietal circuitry. However, given the possibility that medication status in probands may correct for altered connectivity patterns, we explored differences between co-twins and controls.

Non-affected co-twins showed a pattern of reduced fronto-parietal connectivity compared with control subjects (see Figure 7). Specifically, SZ co-twins exhibited weaker task-dependent

covariation between the right DLPFC and lateral parietal cortex and precuneus (Peak MNI Coordinates: [-24, -78, 36], BA 7, Z -max = 3.78, p -corrected = .031, cluster size = 384) compared with control subjects in whole-brain analysis. SZ co-twins also showed reduced functional connectivity relative to controls between the left DLPFC and bilateral parietal cortices and precuneus (Peak MNI Coordinates: [46, -50, 36], BA 40, Z -max = 4.45, p -corrected = .009, cluster size = 485). BP co-twins exhibited a similar pattern of reduced connectivity relative to control subjects between the left DLPFC and lateral occipital cortex (Peak MNI Coordinates: [54, -72, -2], BA 37, Z -max = 3.57, p -corrected = .029, cluster size = 390) and the lateral parietal cortex and precuneus (Peak MNI Coordinates: [-12, -70, 40], BA 7, Z -max = 3.92, p -corrected = .009, cluster size = 483). There were no significant differences between SZ co-twins and BP co-twins in terms of functional connectivity in whole-brain analysis.

Functional connectivity with limbic-related circuitry. Individuals carrying liability for BP showed a pattern of increased task-dependent covariation with limbic-related regions. BP probands showed increased functional connectivity between the left DLPFC and the posterior cingulate cortex/precuneus (Peak MNI Coordinates: [-14, -58, 12], BA 30, Z -max = 3.52, p -corrected = .009, cluster size = 479) compared with controls. Moreover, whole-brain analysis conducted using a linear contrast revealed significantly greater task-dependent covariation between the left DLPFC and bilateral insular cortex and superior and middle temporal gyrus (Right Peak MNI Coordinates: [44, -4, -4], BA 13, Z -max = 3.91, p -corrected = .006, cluster size = 520; Left Peak MNI Coordinates: [-58, -16, -6], BA 21, Z -max = 3.58, p -corrected = .039, cluster size = 368) in BP probands relative to BP co-twins relative to control subjects. A similar pattern of increased functional connectivity between the left parietal cortex and insular cortex (Peak MNI Coordinates: [-32, 20, 0], Z -max = 3.70, p -corrected = .032, cluster size = 382) was

observed in BP probands relative to BP co-twins relative to controls. Further, BP probands showed increased task-dependent covariation between the left parietal cortex and a cluster involving bilateral insular cortex, medial prefrontal cortex, and frontal pole (Peak MNI Coordinates: [-12, 52], -4, Z -max = 4.59, p -corrected < .001, cluster size = 1769), compared with SZ probands, suggesting the pattern of functional coupling with emotion-related regions is specific to liability for BP.

Conjunction Analysis

A conjunction map was created by multiplying the cluster-corrected z -statistic activation maps thresholded at $Z > 2.3$, p -corrected < .05 for controls > SZ liability and controls > BP liability during accurate encoding of information in working memory in order to examine overlapping areas of aberrant regional brain activation associated with liability to illness. As displayed in Figure 8, individuals carrying liability for illness showed common reductions of encoding-related activation in the bilateral angular gyrus/supramarginal gyrus (Left Peak MNI Coordinates: [-52, -62, 30]; Right Peak MNI Coordinates: [58, -40, 36]) and paracingulate gyrus/anterior cingulate cortex (Peak MNI Coordinates: [-4, 42, 26]) compared with control subjects. The Dice Similarity Measure was used to quantify voxelwise overlap between the thresholded images produced by the two contrasts. Consistent with the significant correspondence in the spatial localization of activation in each map (see Figure 8), the DSM coefficient revealed a substantial degree of overlap between the non-zero voxels in the two maps (DSM = 0.406).

Conjunction analysis was also applied to the cluster-corrected functional connectivity maps for Controls > SZ Co-Twins and Controls > BP Co-Twins thresholded at $Z > 1.96$, p -corrected < .05 in order to examine common alterations of fronto-parietal circuitry associated

with liability to illness. As displayed in Figure 7, individuals carrying liability for illness exhibited overlapping reductions in task-dependent prefrontal-parietal covariation relative to controls. The DSM coefficient revealed moderate overlap ($DSM = 0.227$) of covariation with the right DLPFC between co-twin groups relative to control subjects, particularly in the bilateral occipital cortices (Left Peak MNI Coordinates: [-22, -88, 0]; Right Peak MNI Coordinates: [16, -88, 0]). Additionally, common reductions in task-dependent covariation with the left DLPFC were observed between co-twin groups relative to controls in bilateral parietal cortices (Left Peak MNI Coordinates: [-16, -68, 38]; Right Peak MNI Coordinates: [46, -52, 38]). Consistent with the significant correspondence in the spatial localization of task-dependent covariation in each map (see Figure 7), the DSM coefficient revealed a substantial degree of overlap between the non-zero voxels in the two functional connectivity maps ($DSM = 0.424$).

Supplemental Analyses

Effects of lifetime history of psychosis. To test whether the observed behavioral and physiological WMem disturbances associated with liability to BP were attributable to a positive history of psychosis, we compared BP probands with a lifetime history of psychosis to BP probands without a history of psychosis. Parallel comparisons were made between co-twins of BP probands with a positive lifetime history of psychosis and co-twins of BP probands without such a history.

Analysis of behavioral data revealed no significant differences on stSCAP task accuracy between BP probands with a lifetime history of psychosis and BP probands without a history of psychosis. However, trend-level performance differences were observed between respective co-twin groups ($t(29) = 1.81, p = .08$, two-tailed), such that co-twins of BP probands with a positive lifetime history of psychosis performed worse than co-twins of BP probands without a lifetime

history of psychosis (Positive Psychosis History BP Co-Twins' Mean \pm SD: 70.6 ± 9.0 ; Negative Psychosis History BP Co-Twins: 76.4 ± 7.4).

Whole-brain fMRI analysis during encoding trials revealed no significant differences on regional activation between BP probands with a lifetime history of psychosis and BP probands without a psychosis history ($p < .05$, cluster-corrected). Likewise, no differences were observed between co-twins of BP probands with a positive psychosis history and co-twins of BP probands without a psychosis history ($p < .05$, cluster-corrected). However, linear trend analysis contrasting Controls > Co-Twins of BP Proband without Psychosis History > Co-Twins of BP Proband with Psychosis History revealed significant regions of increased activation in a cluster encompassing the right DLPFC (Peak MNI Coordinates: [28, 46, 26], BA 9, Z-max = 3.23, p -corrected = .003, cluster size = 575) and medial prefrontal cortex (Peak MNI Coordinates: [0, 48, 24], BA 9/10, Z-max = 3.76) as well as bilateral parietal cortex (Right Peak MNI Coordinates: [60, -42, 36], BA 40, Z-max = 4.20, p -corrected = .041, cluster size = 364; Left Peak MNI Coordinates: [-52, -64, 32], BA 39, Z-max = 3.93, p -corrected = .005, cluster size = 528), thus suggesting the BP co-twin effects may be driven in part by liability to psychosis. Moreover, controls showed increased activation compared with co-twins of BP probands with a positive psychosis history in the left parietal cortex (Peak MNI Coordinates: [-52, -64, 32], BA 39, Z-max = 3.80, p -corrected = .043, cluster size = 360). However, control subjects did not statistically differ from co-twins of BP probands without a history of psychosis in whole-brain analysis, further suggesting that BP co-twin – control differences may be driven by liability to psychosis in BP.

Whole-brain analysis during retrieval trials revealed no significant differences on regional activation between BP probands with a lifetime history and BP probands without a

history of psychosis. There were also no differences during retrieval between co-twins of BP probands with a positive lifetime history of psychosis and co-twins of BP probands without a history of psychosis. However, whole-brain analysis contrasting increasing liability to BP with psychosis (Controls > Co-twins of BP Proband without Psychosis History > Co-Twins of BP Proband with Psychosis History > BP Probands without Psychosis History > BP Probands with Psychosis History) revealed significant alterations in the bilateral prefrontal cortex (Right Peak MNI Coordinates: [16, 50, 22], BA 9, Z -max = 3.91, p -corrected < .001, cluster size = 1207; Left Peak MNI Coordinates: [-28, 20, 24], BA 9, Z -max = 3.58) and left parietal cortex (Peak MNI Coordinates: [-38, -32, 42], BA 40, Z -max = 3.40, p -corrected = .049, cluster size = 343), suggesting that liability to psychosis in BP is associated with increasing alterations in WMem circuitry. Of note, the above analyses were underpowered due to the small sample of co-twins of BP probands with a lifetime history of psychosis. The majority of BP probands with a history of psychosis were concordant twin pairs, leaving only one-third of non-affected co-twins of BP probands with such a history ($N=8$).

Functional activation-performance analysis. In the ROI regression analysis, the slope of the relationship between fMRI signal during encoding trials and average performance (percent correct) differed significantly between groups in the right DLPFC ($F(4,36) = 3.15$, $p = .02$; see Figure 6) and left DLPFC ($F(4,35) = 3.91$, $p < .01$), with trends in the bilateral parietal cortices (Right: $F(4,36) = 2.45$, $p = .06$; Left: $F(4,36) = 1.67$, $p = 0.17$). In the prefrontal regions, probands and non-affected co-twins differed significantly from controls (p 's < .0125; corrected for multiple comparisons, $.05/4 = .0125$), with trend-level significance for pairwise comparisons in the parietal regions (p 's < .06). There were no significant differences between the slopes of SZ

probands and BP probands and between the slopes of SZ co-twins and BP co-twins in any region examined. Results were equivalent when age and sex were included in the model as covariates.

Given the pattern of default-mode activity observed during retrieval trials, we examined the relationship between activation and performance during retrieval trials in the medial prefrontal cortex and precuneus/posterior cingulate cortex. The slopes of the relationship between fMRI signal and behavior did not differ significantly between groups in either of these regions.

Evaluation of dose-dependency. Linear trend analyses comparing controls to DZ and MZ co-twins were conducted on fMRI activation during encoding trials in four ROIs selected to characterize the WMem network (right DLPFC, left DLPFC, right parietal, left parietal). There were no significant linear effects for SZ liability on any task-related region examined (p 's > 0.05). MZ and DZ SZ co-twins did not differ from each other on any region. Similarly, there were no significant linear effects for BP liability on any task-related region examined (p 's > 0.05). MZ and DZ BP co-twins did not differ from each other. Of note, these analyses likely suffered from a lack of power due to the small cell sizes of co-twins split by zygosity.

In addition, parallel linear trend analyses were conducted on fMRI activation during retrieval in the medial prefrontal cortex and precuneus/posterior cingulate cortex. There were no significant linear effects on either ROI for SZ liability, and MZ and DZ SZ co-twins showed equivalent activation in these regions. Additionally, there were no significant linear effects on either ROI for BP liability. MZ and DZ BP co-twins did not differ from each other on activation in these regions.

Discussion

In view of emerging evidence demonstrating substantial genetic overlap between SZ and BP, we examined whether WMem dysfunction at the neural level represents shared genetic liability to these syndromes. To test a model of shared inheritance of WMem dysfunction, we assessed SZ and BP probands as well as their non-affected co-twins who carry susceptibility factors without overt expression of the illness on a spatial WMem paradigm. Lending support for a model of biological overlap, we observed significant hypoactivation in overlapping regions of the prefrontal and parietal cortex, along with overlapping reductions of functional connectivity in fronto-parietal circuitry, in affected and non-affected individuals with liability for SZ and BP compared with controls. Such neurophysiological alterations appear to be most pronounced during encoding phases of WMem compared with retrieval phases. To our knowledge, this is the first neuroimaging study to simultaneously examine twin pairs discordant for SZ and BP and thus provide direct evidence for endophenotypic overlap of shared WMem dysfunction.

Endophenotypic Overlap of Working Memory Dysfunction

Findings from this report support the hypothesis that cortical disruptions in spatial WMem reflect an expression of familial liability to SZ and BP. We observed substantial overlap in anomalous regional and network activation associated with liability to SZ and BP. As predicted, non-affected co-twins of both proband groups showed hypoactivation in prefrontal and parietal regions compared with control subjects. In particular, reduced regional activation in bilateral parietal cortex during accurate encoding of information in WMem appears to represent an area of shared liability-related dysfunction between SZ and BP. A conjunction analysis revealed significantly decreased BOLD response in overlapping regions of the bilateral parietal cortex during encoding phases of WMem in individuals carrying liability factors for SZ and BP

compared with controls. Observations of common alterations relative to control subjects suggest that physiological abnormalities in this region may serve as a shared endophenotypic marker for SZ and BP. Moreover, a discriminant function analysis effectively distinguished individuals carrying liability to both SZ and BP (probands and co-twins) but failed to predict SZ and BP status separately on the basis of regional activation within the WMem network, particularly in the right DLPFC and parietal cortex. Findings of overlapping anomalous regional and network activation during WMem performance may represent downstream effects of shared genetic liability to SZ and BP, possibly reflecting common genetic etiologies. These results indicate that cortical disruptions of WMem circuitry might mark familial susceptibility to both SZ and BP, thus contributing to emerging support of a transdiagnostic framework at the etiological level (Berrettini, 2004; Lichtenstein et al., 2009; Purcell et al., 2009).

The pattern of results in terms of functional activation for SZ co-twins was intermediate between SZ probands and controls, showing attenuated task-related regional abnormalities in the right DLPFC, anterior cingulate, and bilateral parietal cortex. Such findings are consistent with previous research showing intermediate disruptions of putative nodes of the WMem network in non-affected relatives of SZ patients (Callicott et al., 2003; Cannon et al., 2005; Glahn et al., 2006; Karlsgodt et al., 2007), thereby corroborating existing evidence of WMem dysfunction as a robust endophenotypic marker of SZ. That is, it appears that neural alterations in fronto-parietal circuitry may be related to genetic rather than disease-specific factors in SZ. Of note, the current findings suggest that liability-related alterations of WMem circuitry are specific to encoding phases, indicating that prior observations of WMem disruptions may have hinged on encoding-related deficiencies. The finding that effects are more significant on the right than the left

supports the idea that the right hemisphere is more strongly associated with spatial processing and thus with performance on the visuospatial WMem task.

Similar to the pattern observed in SZ, we found that BP co-twins showed hypoactivation intermediate between BP probands and controls during encoding phases of WMem in regions of the frontal and parietal cortex, specifically in the left DLPFC and left parietal cortex. Likewise, disruptions in fronto-parietal connectivity in BP co-twins were lateralized to the left hemisphere. The finding that BP effects were more significant on the left than on the right might mark a potential distinctive feature of liability to BP. The left lateralization may be related to linguistic rather than image-based encoding of the spatial stimuli or may reflect an attempt to utilize compensatory verbal strategies in order to complete task demands. Such an interpretation might be supported by (1) the finding of increased functional coupling with language processing regions (e.g., middle temporal gyrus) in BP co-twins compared with controls and (2) evidence from another study examining overlapping twin samples that demonstrated enhanced verbal facilities in individuals carrying liability to BP (Higier et al., submitted). Of note, structural (Kieseppa et al., 2003; McDonald et al., 2004) and functional (Drapier et al., 2008; Fusar-Poli et al., 2012) abnormalities previously reported for BP tend to be lateralized to the left hemisphere. Further, that disturbances of WMem circuitry were observed in euthymic BP probands as well as their non-affected co-twins suggests that WMem dysfunction might represent a trait marker of BP, seemingly related to liability features of the illness.

Additionally, we observed shared disruptions of fronto-parietal neural circuitry as assessed by functional connectivity analysis in individuals carrying liability for SZ and BP. A conjunction analysis revealed significant overlap in terms of reduced task-dependent functional coupling in fronto-parietal circuitry between non-affected co-twins of SZ and non-affected co-

twins of BP compared with controls. Such network disruptions appear to occur in overlapping regions within the fronto-parietal network, thereby implicating not only regional alterations but also disruptions in the overall coordination of WMem circuitry as shared endophenotypic markers. While prior research has demonstrated disruptions of distributed WMem networks in SZ probands and their non-affected relatives (Meyer-Lindenberg et al., 2001; Peled et al., 2001; Schlösser et al., 2003; Fornito et al., 2011), to our knowledge, this was the first study to evaluate functional connectivity patterns during WMem performance in BP probands and their co-twins. We found evidence for significant disruptions in fronto-parietal circuitry associated with liability to BP, although perhaps to a lesser degree than the disconnectivity observed in SZ (Karlsgodt et al., 2008). Common disruptions of fronto-parietal circuitry in both co-twin groups further implicate at least partially overlapping genetic etiologies.

Notably, despite significant overlap of WMem dysfunction, we found functional alterations to be relatively less pronounced in BP compared with SZ. The finding that BP probands exhibited attenuated disruptions relative to SZ probands is consistent with prior neuropsychological studies showing performance decrements to a lesser degree in BP (Seidman et al., 2002; Altshuler et al., 2004; Pirkola et al., 2005; Krabbendam et al., 2005; Daban et al., 2006; Glahn et al., 2006b; Green, 2006; Schretlen et al., 2007; Barrett et al., 2009; Reichenberg et al., 2009) and fMRI studies demonstrating cortical alterations (e.g., DLPFC hypoactivation) in BP intermediate between SZ and control subjects (Hamilton et al., 2009). Taken together, these results suggest significant phenotypic overlap of WMem dysfunction between SZ and BP with relatively less pronounced cortical alterations in BP than in SZ. However, we found some evidence that liability to psychosis in BP is associated with increasing alterations of WMem circuitry, consistent with prior reports indicating more pronounced neurocognitive impairments

in BP patients with psychotic features (Seidman et al., 2002; Altshuler et al., 2004; Badcock et al., 2005; Glahn et al., 2006b; Glahn et al., 2007). The finding that co-twins of BP probands with a history of psychosis showed more pronounced behavioral and cortical disruptions of WMem function suggests that liability to psychotic features in BP might contribute to the pattern of shared inheritance observed between SZ and BP. Notably, differential performance decrements in spatial WMem have been reported in bipolar I patients with a history of psychosis when compared to non-psychotic BP samples (Glahn et al., 2006b; Glahn et al., 2007). These findings provide converging evidence in support of recent psychiatric genetic studies suggesting that psychotic BP may delineate an informative subtype for biological investigations (Potash et al., 2003; Park et al., 2004; Maziade et al., 2005; Craddock & Owen, 2005; Schulze et al., 2006; Craddock & Sklar, 2009).

In contrast, failure to suppress the default mode during task engagement appears to be related to disease-related factors common across SZ and BP rather than overlapping liability-related factors. The finding that both proband groups showed increased retrieval-related activity in regions typically associated with the default mode network, such as the precuneus/posterior cingulate cortex, indicates phenotypic overlap of reduced task-related suppression of default mode regions during retrieval phases of WMem. Previous studies have demonstrated poor task-dependent modulation of the default network in patients with SZ (Pomarol-Clotet et al., 2008; Kim et al., 2009; Whitfield-Gabrieli et al., 2009) and BP (Drapier et al., 2008; Thermenos et al., 2010; Thermenos et al., 2011), with consistent findings of hyperactivation in medial prefrontal and posterior cingulate/precuneus cortex. This study suggests that such anomalous activation patterns within the default network might be related to retrieval-related disturbances, whereby SZ and BP patients may show difficulty inhibiting regions mediating the default mode in order to

provide a memory-guided response. Notably, dysfunction of the default network is thought to be related to cognitive deficits, with greater suppression and connectivity associated with better performance on attention-demanding tasks in healthy subjects (Weissman et al., 2006; Sambataro et al., 2010). This report suggests that increased engagement of the default mode during task performance may represent an area of phenotypic overlap between SZ and BP. Such findings highlight the importance of examining default-mode activity in addition to task-related activity in order to optimally characterize the pathophysiological disturbances related to illness factors.

Distinctions between Schizophrenia and Bipolar Disorder

While we found significant areas of overlap in terms of physiological dysfunction associated with liability to SZ and BP, some differences between these syndromes were observed. First, liability to BP appears to be distinctly associated with anomalous thalamic retrieval-related activity, consistent with prior structural and functional neuroimaging studies implicating fronto-striatal disturbances in BP (Bearden et al., 2001; McDonald et al., 2004; Adler et al., 2006; Selvaraj et al., 2012). Second, we observed left lateralization of DLPFC dysfunction in individuals carrying liability to BP, consistent with prior reports (Drapier et al., 2008; Hamilton et al., 2009; Fusar-Poli et al., 2012) and perhaps indicating symbolic or linguistic rather than image-based encoding of stimuli (Ungerleider et al., 1998). Third, failure to suppress the precuneus/posterior cingulate cortex during retrieval phases followed a pattern of inheritance for SZ, such that SZ probands showed less task-related modulation of this region than SZ co-twins, who in turn showed less modulation than control subjects. This finding is consistent with evidence showing hyperactivity as well as hyperconnectivity of the default network in SZ probands, and, to a lesser degree, their first-degree relatives compared with controls (Whitfield-

Gabrieli et al., 2009). While both proband groups exhibited hyperactivity in the precuneus/posterior cingulate relative to controls, activity in this region was not correlated with liability to BP.

Additionally, individuals carrying liability to BP appear to show increased functional connectivity with limbic-related regions. In addition to the disrupted network connectivity observed in fronto-parietal circuitry, we found increased functional connectivity with regions mediating emotion processing (e.g., insula, frontopolar cortex) in BP co-twins compared with controls. No other groups showed connectivity to these regions. The finding that BP co-twins exhibited task-related connectivity patterns with limbic-related regions corroborates other reports of hyperactivity during cognitive (WMem) challenge in regions thought to be involved in emotional processing, such as the ventral frontopolar prefrontal cortex, anterior cingulate, and insula (Adler et al., 2004; Drapier et al., 2008; Gruber et al., 2010; Thermenos et al., 2010; Thermenos et al., 2011; Jogia et al., 2011; Fusar-Poli et al., 2012), thus implicating functional alterations of anterior limbic networks in liability to BP. Moreover, neuroanatomical disturbances of these regions in BP have been reported previously (McDonald et al., 2004; Strakowski et al., 2005; Selvaraj et al., 2012). Taken together, these findings are largely consistent with hypotheses of impaired prefrontal modulation of anterior limbic system networks in BP (Adler et al., 2006).

Isolation to Encoding-Related Processes

A strength of the current study was that the single-trial WMem task allowed for the examination of encoding and retrieval aspects of WMem separately, thereby permitting inferences as to whether the observed differences in BOLD response were more pronounced during encoding aspects of WMem function. Functional neuroimaging studies have consistently

identified a circuitry for WMem function comprised of dorsolateral, middle, and inferior frontal gyri, anterior cingulate and medial premotor cortex, and posterior parietal cortex (Jonides et al., 1998; D'Esposito et al., 1999; Carter et al., 1999; Owen et al., 2005), consistent with our encoding-related activation findings. Findings across all groups suggest that the neural WMem network, including the right DLPFC and parietal regions, is engaged to a greater extent during encoding compared with retrieval phases. In contrast, we observed increased recruitment of medial prefrontal and precuneus/posterior cingulate cortex, regions typically associated with the default mode network, during retrieval compared with encoding phases of WMem.

In accordance with our hypothesis, we found evidence for endophenotypic overlap between SZ and BP in aberrant task-related activation during encoding but not retrieval trials of WMem processing. The finding that liability-related cortical disruptions of WMem circuitry were specific to the encoding phase is consistent with prior work showing pronounced encoding-related deficits in SZ and BP probands at behavioral and neural levels of analysis (Bearden et al., 2006; Glahn et al., 2006a; Bachman et al., 2009). Taken together, these findings suggest that disturbances of WMem in affected probands and their non-affected relatives may be related to encoding aspects of WMem function. Further, it is worth noting that encoding trials activated the canonical WMem network, involving prefrontal and parietal regions known to show neuropathological abnormalities in SZ (Goldman-Rakic & Selemon, 1997; Cannon et al., 2002; Cannon et al., 2005) and possibly in BP (Strakowski et al., 2005) based on evidence from neuroimaging and post-mortem studies. In this way, it is perhaps unsurprising that the pattern of endophenotypic overlap between SZ and BP emerged during encoding phases of WMem processing.

That fronto-parietal WMem dysfunction appears to be specific to the encoding phase of WMem has important implications for cognitive rehabilitation interventions. The present study findings suggest that intervention efforts focused on enhancing and teaching encoding strategies may prove to be maximally effective at reducing impairments of WMem in SZ and BP patients. Further, that WMem dysfunction was observed in both SZ and BP suggests that cognitive interventions may be applicable across disorders. Such interventions stand to not only ameliorate cognitive deficits but also improve functional outcomes in SZ and BP patients in light of evidence linking cognitive deficits with substantial impediments to role functioning in patient populations (Green, 1996; Green et al., 2000; Green, Kern, & Heaton, 2004; Green, 2006; Bearden et al., 2010; Torres et al., 2011), thus reducing the public health burden associated with these illnesses. There is some evidence suggesting that WMem training increases overall cognitive abilities and improves functional outcomes in healthy (Jaeggi et al., 2008) and patient populations (McGurk et al., 2009; Kern et al., 2009; Eack et al., 2010), with effects persisting over time (Hogarty et al. 2006). The finding that WMem dysfunction may at least in part reside in encoding-related deficiencies could inform the development and refinement of these intervention efforts (see Barch & Smith, 2008).

Behavioral Performance

As expected, both proband groups exhibited behavioral impairments of WMem performance compared with controls, thereby indicating phenotypic overlap in WMem dysfunction at the behavioral level of analysis. However, somewhat surprisingly, attenuated impairments were not observed in non-affected co-twins. The current task paradigm was designed not only to expose behavioral differences between groups but also to maximize the number of correct trials in order to analyze between-group differences in physiological activation

during task performance. Previous work from our laboratory using a similar task found significant performance decrements in probands at the selected memory set size (load of 3) and marginal differences in non-affected co-twins compared with controls (Glahn et al., 2003; Pirkola et al., 2005; Cannon et al., 2005). One important change in the task design in this study was that the delay periods and inter-trial intervals were slightly longer than previous versions, possibly diminishing behavioral deficits in co-twin groups. The jittered delay period was inserted in order to vary the relationship between encoding and retrieval trials in order to assess BOLD response separately by task phase. While prior evidence demonstrates proband-control performance differences at longer delay periods (Lee & Park, 2005), it is possible that the additional time to maintain information in WMem dampened any observed differences between non-affected co-twin siblings and controls.

Consistent with the current findings, most prior fMRI studies have observed DLPFC hypoactivation in probands relative to controls (SZ: Ragland et al., 1998; Barch et al., 2003; Cannon et al., 2005; Driesen et al., 2008; Scheuerecker et al., 2008; BP: Monks et al., 2004; Lagopoulos et al., 2007; Hamilton et al., 2009; Townsend et al., 2010), although hyperactivation has also been reported (SZ: Manoach et al., 1999; Callicott et al., 2000; Manoach et al., 2000; BP: Adler et al., 2004; Robinson et al., 2010; Jogia et al., 2011). To reconcile these differences, it has been suggested that activation in the DLPFC relates to WMem performance in an inverted-U shaped curve, with hypoactivation occurring when WMem load has exceed capacity (Callicott et al., 1999; Callicott et al., 2003b; Manoach, 2003a; Karlsgodt et al., 2007; Karlsgodt et al., 2009). To test this model, we assessed the relationship between functional activation in the right DLPFC during encoding trials and behavioral performance between-subjects. Findings suggest that the relationship between functional activation and performance follow a pattern of

inheritance in SZ and BP, such that decreased activation in probands relative to controls is associated with lower performance and increased activation with higher performance. A similar pattern was observed previously for liability to SZ (Karlsgodt et al., 2007), with the current findings suggesting this pattern of inheritance may also apply to BP. Moreover, despite comparable performance between co-twins and controls, significant alterations in BOLD response and network connectivity were observed, and correct-trials only were analyzed in whole-brain analysis, thus suggesting that cortical disruptions may be heritable even in the absence of performance differences.

Study Limitations and Future Directions

This study also has a number of limitations. First, although our sample sizes were larger than those typically included in other psychiatric functional imaging studies (Adler et al., 2004; Lagopoulos et al., 2007; Hamilton et al., 2009), primary tests of hypotheses collapsed across zygosity. It is possible that analyses splitting groups by zygosity may have been underpowered to detect subtle differences between MZ and DZ twins. Though co-twin groups showed hypoactivation and hypoconnectivity during WMem task performance relative to control subjects, there were no significant differences between MZ and DZ co-twins. Thus, we cannot definitely conclude a pattern of genetic inheritance, although results clearly indicate that non-affected co-twins show physiological dysfunction in cortical regions and networks subserving WMem function. Larger samples of co-twins discordant for SZ and BP are needed in order to parse the genetic and environmental contributions to these disruptions.

Second, interpretations regarding activation in regions of the default mode are limited in that our study did not include explicitly probe default mode activity using resting state data. The default network is thought to mediate task-independent brain function, comprising regions more

active during rest than during a wide range of cognitive tasks (Raichle et al., 2001; Greicus et al., 2003). Future studies should include rest trials in addition to task-related trials in order to adequately assess possible anti-correlations between task-related and default-mode activity. As such, the findings of group differences in default-mode activity during retrieval phases should be interpreted with caution. Future studies with resting conditions would allow for the direct comparison of task-related and default-mode activation maps.

Third, the task design employed in the current study did not parametrically vary WMem load, thereby precluding direct assessments of within- and between-group differences on the relationship between WMem capacity and BOLD activation. Analyzing individual loads (within-subject) would allow for a more thorough assessment of functional-behavioral relationships and comparisons of between- and within-group effects. For example, some evidence suggests that WMem impairments in euthymic BP patients are increasingly pronounced across load (Pan et al., 2011), suggesting that effects may have been stronger with larger memory set sizes. Given that we only examined a memory set size of three, it was not possible to assess individual differences in capacity with the current experimental paradigm. Future studies should consider task designs that parametrically vary load in order to assess WMem capacity at the individual subject level, probe group differences in the relationship between activation and performance more directly, and further explore the extent of WMem dysfunction associated with liability to illness across varying loads.

Additionally, our samples of SZ and BP probands had a relatively long duration of illness and a long history of medication use. It is unknown at present how medication history impacts BOLD response and connectivity of neural circuitry. While there were no differences between non-affected co-twins and control subjects on lifetime medication history in the current samples,

as expected, SZ and BP probands showed elevated rates of lifetime medication use. It is difficult to explicitly assess the impact of medication on BOLD response in the current study given that medication status is almost perfectly confounded with diagnostic group. However, previous findings of DLPFC hypoactivation in medication-free patients (Manoach, 2003; Scheuerecker et al., 2008; Phillips et al., 2008) suggest that the observed differences are likely not attributable to antipsychotics, although less is known about the impact of mood stabilizers on BOLD response. The findings of attenuated cortical alterations in BP co-twins compared with controls in the absence of medication differences suggests that study findings are likely unrelated to medication status. Nonetheless, the question of whether the observed findings are also present in the early stages of illness and whether observed functional deviations are related to medication history can be addressed by conducting similar studies in recent onset or unmedicated samples.

Finally, the delay trials of the stSCAP task in the current study were jittered and likely confounded with encoding and retrieval trials, possibly influencing BOLD response during these task phases. To explore the impact of the delay period on encoding and retrieval activation maps, we conducted a subanalysis in control subjects removing the delay regressor from the model. When delay trials were removed from the model, the canonical WMem network is activated by both encoding and retrieval trials, including the right DLPFC, bilateral precentral gyrus, and bilateral parietal cortex. This is in contrast to the retrieval map when the delay trials are modeled separately, which activates medial motor regions and the precuneus/posterior cingulate cortex. The encoding maps were equivalent in both models. Findings from this subanalysis indicate regions associated with encoding and retrieval phases are largely overlapping, with substantial overlap in the right DLPFC, bilateral precentral gyri, and bilateral parietal cortices. Encoding trials appeared to show increased activation in the occipital cortex compared with retrieval trials,

which is consistent with increased visual stimuli presented during this task phase. No regions showed distinctive activation during retrieval trials. This analysis was conducted in control subjects only in order to evaluate the impact of delay trials on encoding and retrieval maps, thereby preventing between-group comparisons at present. Future analyses will employ these models to estimate retrieval-related activity and assess between-group differences, with the caveat that leaving the delay period unmodeled essentially integrates maintenance-related activity with implicit baseline.

It appears that the delay period jitter in the current task paradigm may be insufficient to accurately model retrieval-related activation. That is, due to their temporal adjacency to the retrieval regressors, the delay regressors appear to extend temporally into the probe period, possibly leaving retrieval estimates with only late probe-related activity plus the hemodynamic undershoot. This may explain the observed patterns of default mode activity during retrieval phases. As such, interpretations regarding retrieval-related activation should be taken with caution. Given this limitation, and in view of evidence supporting proband deficits specific to encoding aspects of WMem function (Glahn et al., 2006a; Bearden et al., 2006; Bachman et al., 2009), primary comparisons in this study focused on encoding phases of WMem. Future studies should extend the delay period jitter in order to more accurately estimate retrieval-related activity.

Conclusion

In this study, we found evidence supporting endophenotypic overlap of physiological dysfunction as measured by functional activation and connectivity during WMem performance. As such, functional alterations during encoding phases of WMem appear to represent a shared feature of liability to SZ and BP. Specifically, we identified overlapping regions of hypoactivation and hypoconnectivity within fronto-parietal circuitry in probands and non-

affected co-twins compared with controls, a pattern that appears to be related to a common pathogenesis shared by SZ and BP. Additionally, we observed hyperactivation of the default mode network in both proband groups compared with controls, suggesting that failure to effectively modulate this network during retrieval phases of WMem may be related to disease-related factors shared across disorders. These findings are consistent with previous evidence indicating overlapping functional alterations in SZ and BP (e.g., Hamilton et al., 2009) and may inform models of neurobiological mechanisms underpinning the apparent biological overlap between SZ and BP, particularly in regards to encoding processes. In summary, this study provides evidence for WMem dysfunction as a key area of overlap between SZ and BP both at the endophenotypic level in terms of cortical alterations within fronto-parietal circuitry and at the phenotypic level in terms of poor task-related modulation of the default network. The elucidation of endophenotypic markers spanning diagnostic boundaries may inform genetic investigations, perhaps hastening the search for shared susceptibility genes.

Table 1. *Sociodemographic Characteristics by Group*

Characteristic	SZ Probands (N=30)		SZ Co-Twins (N=40)		BP Probands (N=35)		BP Co-Twins (N=31)		Controls (N=44)		Statistic	df	p-Value
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD			
Age (years)	48.3	11.5	49.7	11.2	49.4	10.4	49.9	10.7	46.5	8.8	$F = 1.35$	4,40	0.27
Education (years)	13.2	3.0	14.4	3.5	12.9	2.7	13.4	2.8	13.4	3.2	$F = 1.00$	4,33	0.38
YMRS	1.7	2.7	0.7 ^b	1.4	2.5 ^a	3.8	1.0 ^b	2.1	1.0 ^b	2.5	$F = 3.01$	4,41	0.03
HAM-D	8.2 ^a	6.0	2.7 ^c	2.7	4.7 ^b	7.3	2.8 ^c	4.6	1.9 ^c	2.7	$F = 9.60$	4,41	< .01
SAPS	18.4 ^a	20.0	0.8 ^b	1.8	2.6 ^b	5.9	0.8 ^b	2.3	0.6 ^b	2.1	$F = 25.02$	4,41	< .01
SANS	36.6 ^a	24.6	5.8 ^b	11.2	8.4 ^b	13.5	2.5 ^b	6.0	1.9 ^b	3.9	$F = 37.37$	4,39	< .01
GRF-Current	4.7 ^c	1.4	7.6 ^a	1.6	6.3 ^b	1.5	7.8 ^a	1.5	7.9 ^a	1.4	$F = 27.06$	4,41	< .01
	N	%	N	%	N	%	N	%	N	%			
Female	10	33.3	17	42.5	21	60.0	19	61.3	24	54.5	$F = 0.70$	4,41	0.60
Right-Handedness	24	80.0	35	87.5	32	91.4	30	96.8	40	90.9	$F = 1.04$	4,41	0.40
Medication Status											$F = 7.54$	3,38	< .01
Anti-Psychotic	19	63.3	1	2.5	10	28.6	1	3.2	0	0.0			
Mood Stabilizer	1	3.3	0	0.0	8	22.9	0	0.0	0	0.0			
Anti-Depressant	0	0.0	4	10.0	5	14.3	5	16.1	0	0.0			
Other or None	10	33.3	35	87.5	12	34.3	25	80.6	44	100.0			

Note. Statistical tests are based on mixed effects models including twin pair as a random effect and diagnostic group as a fixed effect. Means with different superscripts differ significantly at $\alpha < .05$ by the Bonferroni multiple comparisons (e.g., $a > b > c$). Medication status was coded in a hierarchical manner according to severity (anti-psychotics > mood stabilizers > anti-depressants > other or none). Abbreviations: YMRS=Young Mania Ratings Scale; HAM-D=Hamilton Rating Scale for Depression; SAPS=Scale for the Assessment of Positive Symptoms; SANS=Scale for the Assessment of Negative Symptoms; GRF=Global Role Functioning.

Table 2. *Single-Trial Spatial Capacity Working Memory Task Performance by Group*

	SZ Probands		SZ Co-Twins		BP Probands		BP Co-Twins		Controls		F-Value	df	p-Value
	(N=30)		(N=40)		(N=35)		(N=31)		(N=44)				
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD			
% Correct	70.6	9.1	76.4	11.4	70.1	9.8	74.9	8.1	74.2	10.4	4.13	4,859	< 0.01
% Omissions	10.1	7.7	6.4	7.9	9.1	7.9	6.7	6.6	7.2	6.9	2.17	4,859	0.07
RT-Correct ^a	1208.5	150.0	1154.7	187.8	1197.0	180.3	1149.1	196.0	1143.8	147.8	3.93	4,859	0.01

Note. Means are based on raw scores. Statistical tests are based on mixed effects repeated measures models including twin pair as a random effect, age and sex as covariates, and diagnostic group and delay period as fixed effects. ^aInteraction term for sex by group was included in the model. RT-Correct=Reaction Time for Correct Trials.

Table 3. *Task-Specific Within-Group Activation Coordinate Locations of Clusters and Local Z-Maxima*

Task Phase	Contrast	MNI Peak Coordinates			No. voxels	$p_{\text{corrected}}$	Z max
		X	Y	Z			
Encoding > Retrieval	SZ Probands	34	-58	-18	1509	8.34E-07	4.60
		50	-38	42	1486	9.54E-07	5.27
		-32	-64	-14	1020	5.30E-05	4.42
		-50	-34	40	879	1.99E-04	4.56
	SZ Co-Twins	34	-54	-18	21707	1.40E-45	6.66
		54	10	26	1176	1.32E-05	4.82
	BP Probands	32	-70	36	21084	9.81E-45	6.41
		-56	2	22	550	5.98E-03	4.39
	BP Co-Twins	28	-66	50	15991	5.07E-37	6.43
		54	6	24	477	1.38E-02	4.60
	Controls	32	-68	26	21589	1.40E-45	6.99
		50	8	28	2560	3.75E-10	5.88
4		14	50	1731	1.19E-07	4.90	
Retrieval > Encoding	SZ Probands	4	-60	30	2591	3.04E-10	5.80
		6	58	-4	1864	5.96E-08	4.37
	SZ Co-Twins	-	-	-	-	-	-
		BP Probands	-6	-56	16	820	3.54E-04
	BP Co-Twins	-6	56	-8	814	3.75E-04	4.01
		8	56	14	698	1.21E-03	3.69
	Controls	0	-44	32	406	3.23E-02	3.52
		-2	48	-10	948	1.03E-04	5.50
		0	-48	30	458	1.73E-02	3.60

Table 4. *Results of Discriminant Function Analysis*

ROI entered in discriminant analysis	Correlation with discriminant function	F (df)
rPAR	0.801	4.34* (4,175)
rDLPFC	0.749	3.78* (4,175)
IPAR	0.299	2.27 (4,175)
IDLPFC	0.169	1.86 (4,175)
Canonical R	0.265	
Eigenvalue	0.076	
χ^2	18.717* (df = 16)	
% variance	79.7	

Note. * $p < .05$. Abbreviations: ROI=region-of-interest; rPAR=right parietal cortex; rDLPFC=right dorsolateral prefrontal cortex; IPAR=left parietal cortex; IDLPFC=left dorsolateral prefrontal cortex.

Table 5. *Peak Coordinates of Clusters and Local Maxima from Whole-Brain Functional Connectivity Analyses with Four Seed Regions*

Contrast	rDLPFC					rPAR					IDLDFC					IPAR				
	MNI Coordinates					MNI Coordinates					MNI Coordinates					MNI Coordinates				
	X	Y	Z	$p_{corrected}$	Z_{max}	X	Y	Z	$p_{corrected}$	Z_{max}	X	Y	Z	$p_{corrected}$	Z_{max}	X	Y	Z	$p_{corrected}$	Z_{max}
SZ > Control	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Control > SZ	-54	-16	-14	2.60E-02	4.24	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
SZ Co-Twin > Control	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Control > SZ Co-Twin	-24	-78	36	3.10E-02	3.78	-	-	-	-	-	4	-64	48	1.79E-07	4.25	-	-	-	-	-
											46	-50	36	8.81E-03	4.45					
BP > Control	-	-	-	-	-	58	4	16	4.55E-02	3.92	-14	-58	12	9.49E-03	3.52	-	-	-	-	-
Control > BP	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
BP Co-Twin > Control	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Control > BP Co-Twin	-	-	-	-	-	-	-	-	-	-	-12	-70	40	9.03E-03	3.92	-	-	-	-	-
											54	-72	-2	2.94E-02	3.57					
SZ > BP	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
BP > SZ	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-12	52	-4	5.96E-08	4.59
SZ Co-Twin > BP Co-Twin	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
BP Co-Twin > SZ Co-Twin	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Note. Seed regions selected to characterize the working memory network. Coordinates displayed were statistically significant at $Z > 2.3$, $p < .05$, cluster-corrected. Abbreviations: rPAR=right parietal cortex; rDLPFC=right dorsolateral prefrontal cortex; lPAR=left parietal cortex; lDLPFC=left dorsolateral prefrontal cortex.

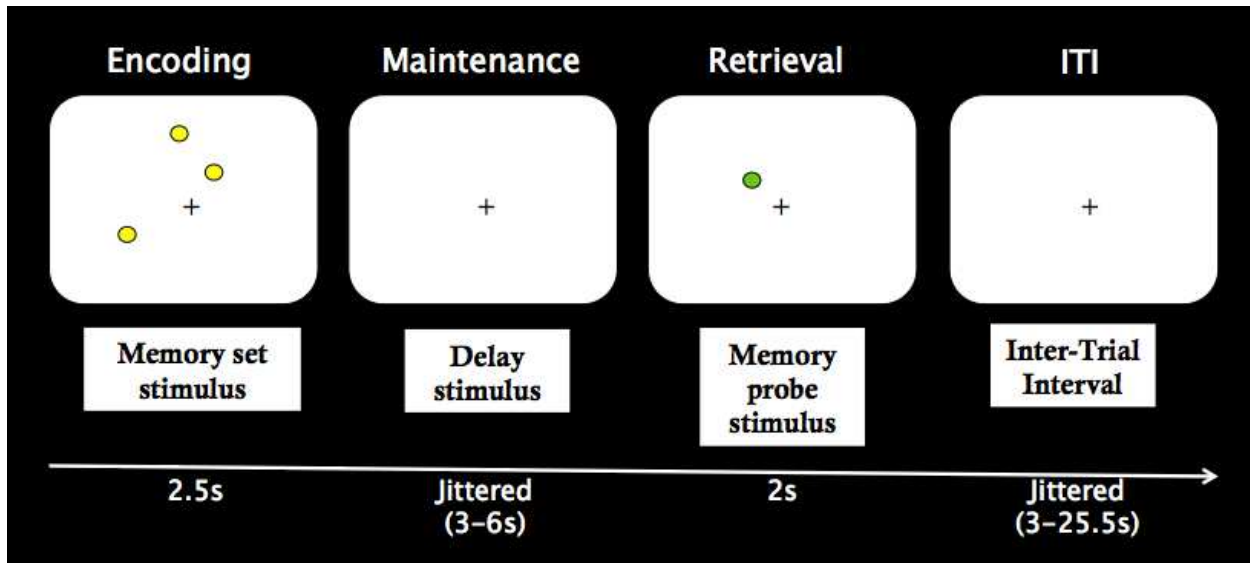


Figure 1. Single-Trial Spatial Capacity Working Memory Task Paradigm. Participants were shown three yellow target circles positioned pseudo-randomly around a central fixation. After a jittered delay period, participants were shown a single green probe circle and were asked to determine if the green probe circle was in the same position as one of the yellow target circles. The task was comprised of 26 trials; half were true positive (correct answer ‘yes’) trials and the other half were true negative (correct answer ‘no’) trials.

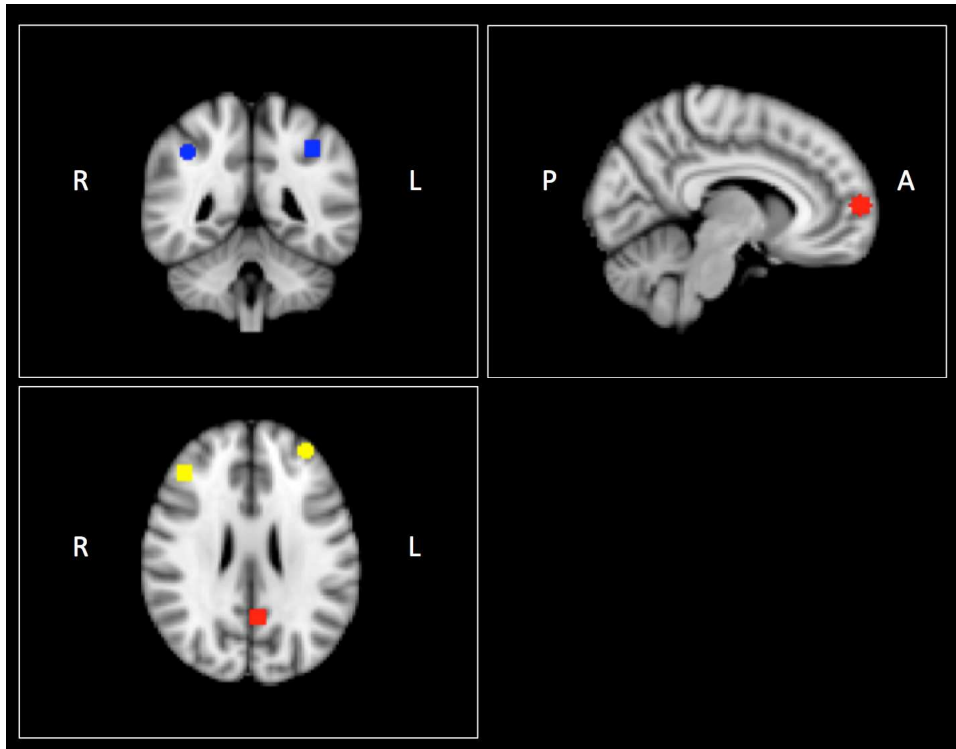


Figure 2. Functional Regions-of-Interest. Derived from the all subjects, all trial types contrasts to allow each group to contribute to the definition of the region-of-interest (ROI). The t -statistic map for this contrast was thresholded at $T_{\infty} > 1.96$ (2-tailed, $p < .05$). From this thresholded map, the peak activation voxels were identified using Brodmann's and anatomical landmarks, and a 6mm sphere was applied. Four ROIs were selected to characterize the working memory network (bilateral dorsolateral prefrontal cortex in yellow and bilateral parietal cortex in blue) and two to characterize the default-mode network (medial prefrontal cortex and precuneus/posterior cingulate cortex in red). L=left; R=right; A=anterior; P=posterior.

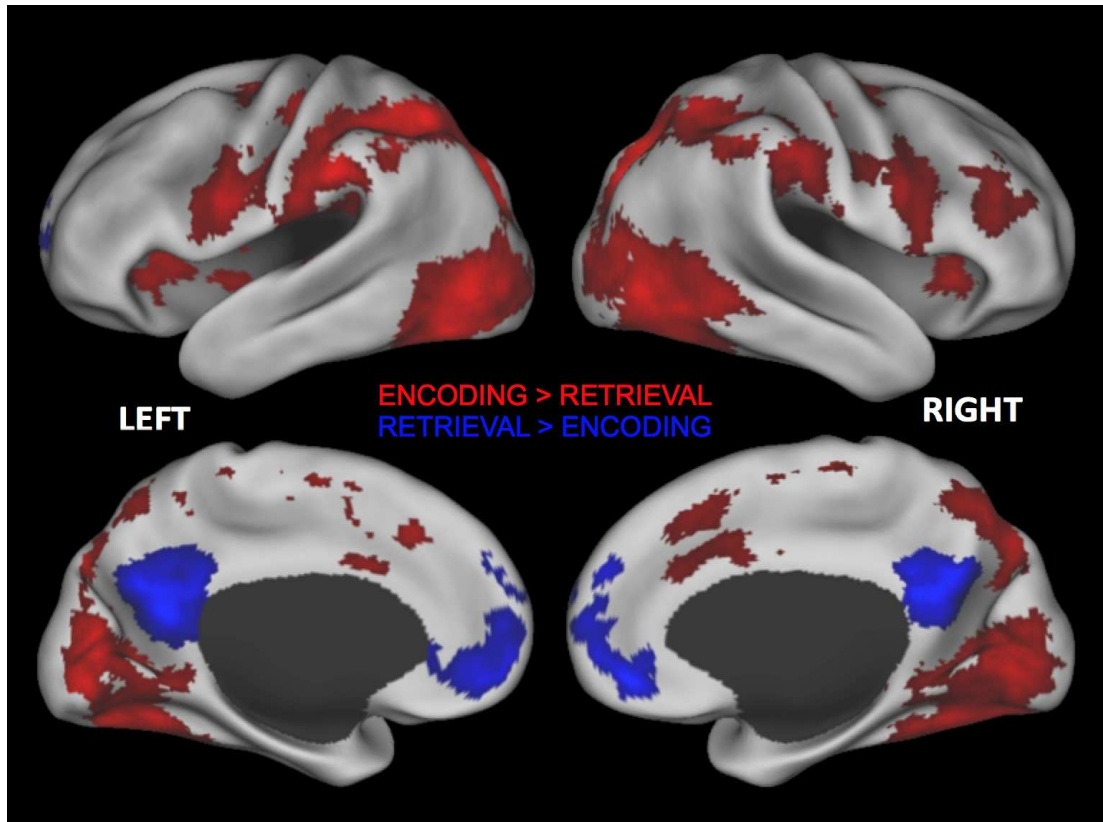


Figure 3. Working Memory Task Phase Effects. Regions showing significant activation in encoding relative to retrieval trials are shown in red. Regions showing significant activation in retrieval relative to encoding trials are shown in blue. Statistical maps derived across all groups and thresholded at $Z > 2.3$, $p > 0.05$, cluster corrected.

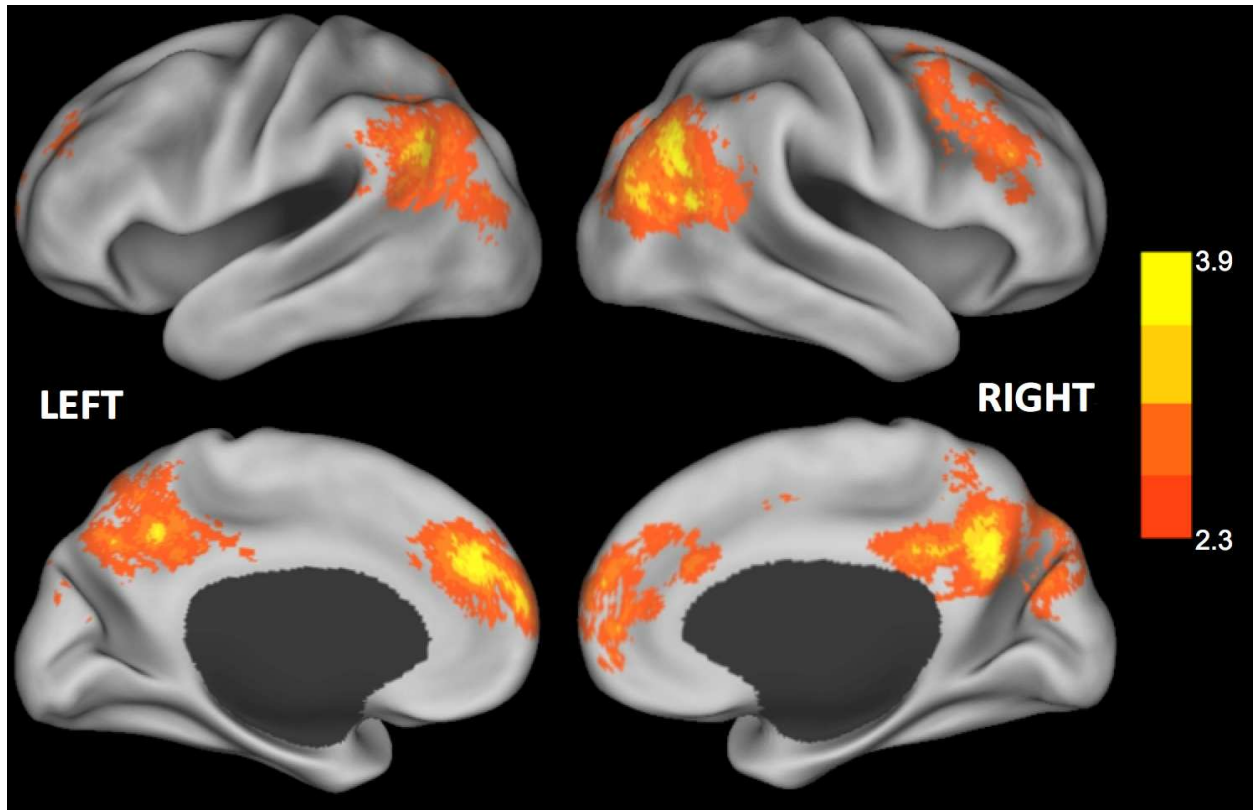


Figure 4. Regional Activation of Controls > Bipolar Probands > Schizophrenia Probands during Encoding Trials. Statistical map derived from a linear contrast and displayed at $Z > 2.3$, $p > 0.05$, cluster corrected. Color bar indicates Z statistic values. L=left; R=right.

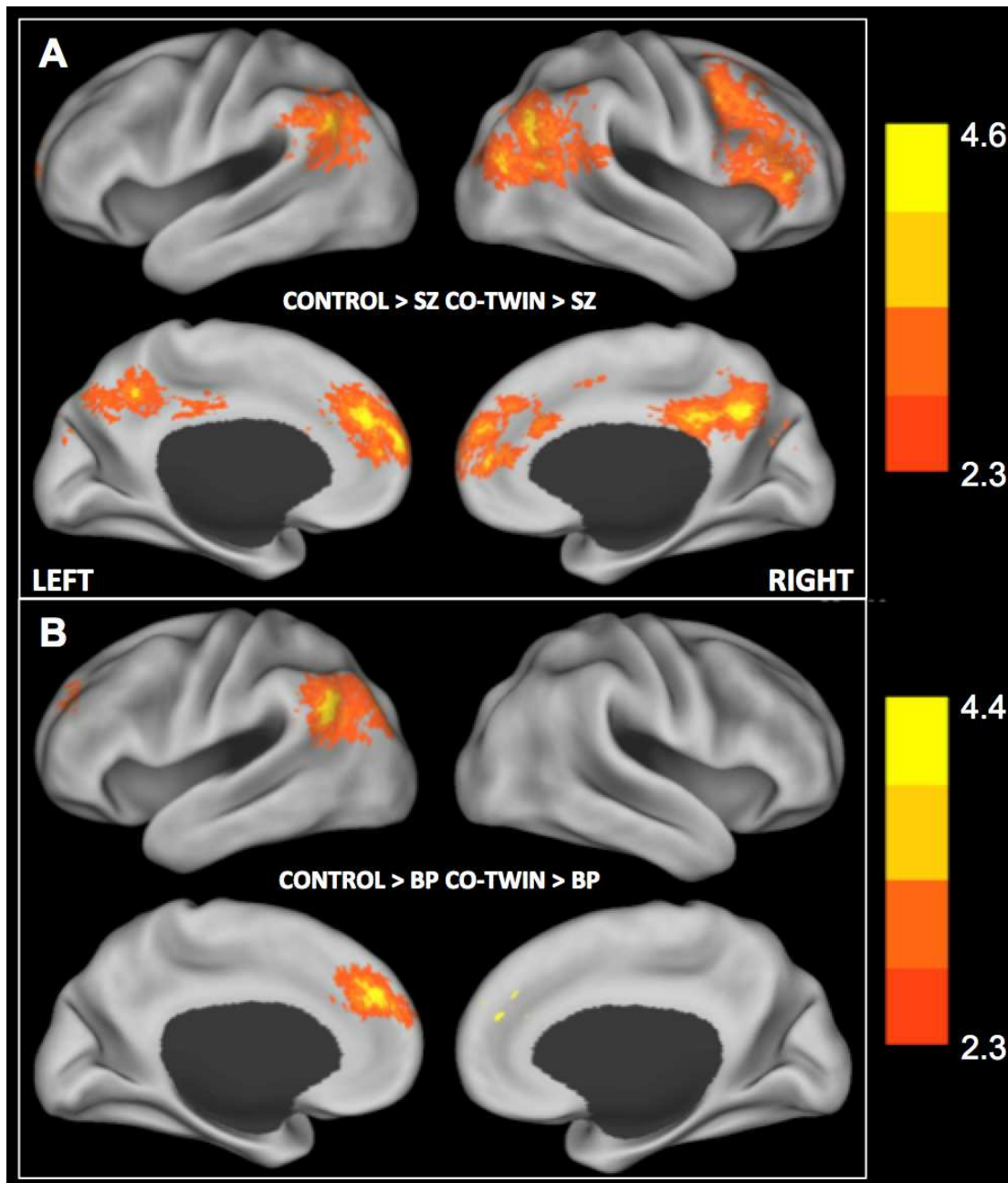


Figure 5. Regional activation associated with liability to illness during encoding trials. Panel A shows Controls > Schizophrenia Co-twins > Schizophrenia Probands. Panel B shows Controls > Bipolar Co-twins > Bipolar Probands. Statistical maps derived from linear contrasts and thresholded at $Z > 2.3$, $p > 0.05$, cluster corrected. Color bar indicates Z statistic values. L=left; R=right.

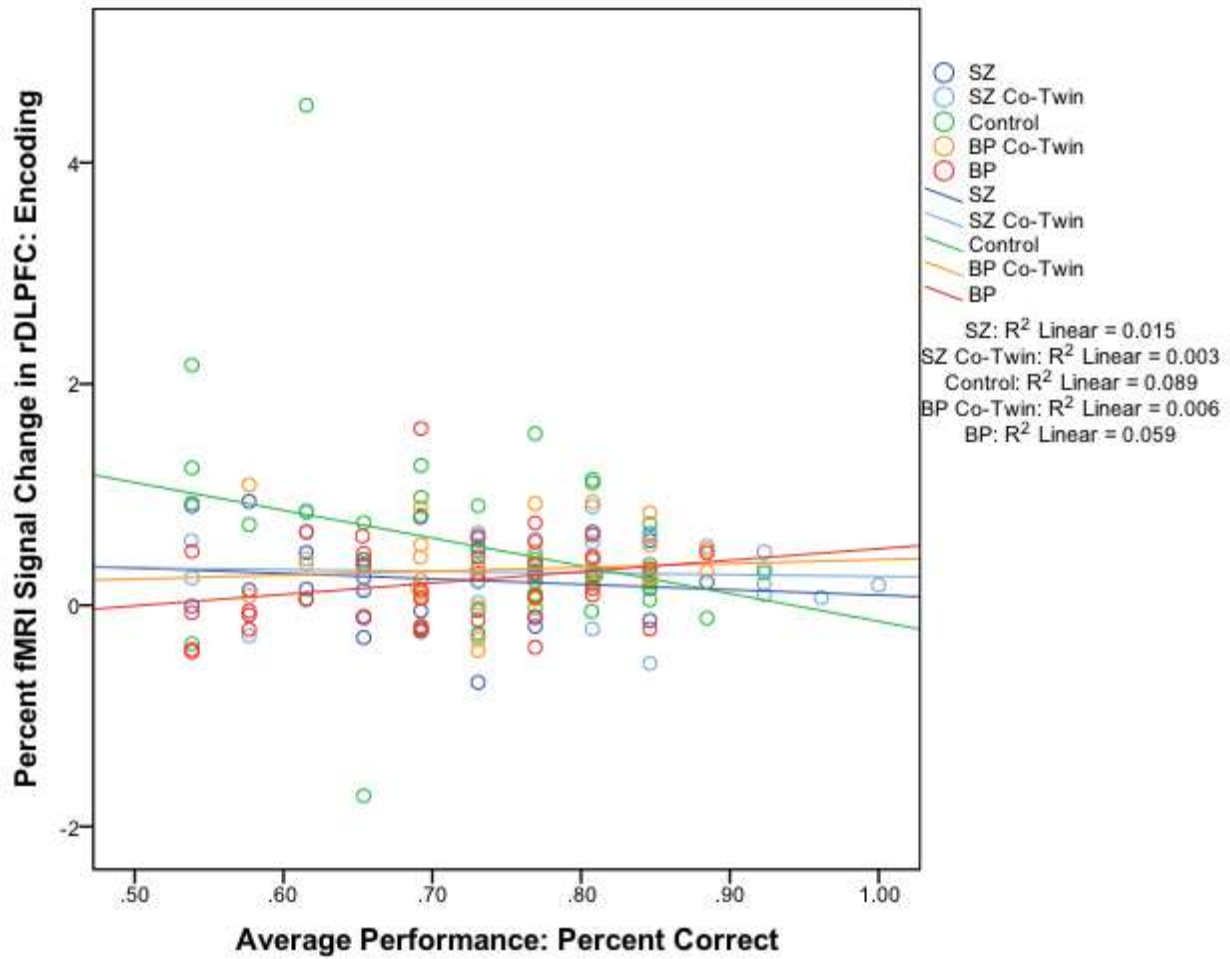


Figure 6. Relationship between Behavioral Performance and Activation in the Right Dorsolateral Prefrontal Cortex during Encoding Trials. Regression analysis predicting percent signal change in the rDLPFC (BA 9, MNI Coordinates: [42, 34, 24]) during successful encoding trials with behavioral performance. Group differences were examined using the interaction between the slopes of the relationship of performance and BOLD signal.

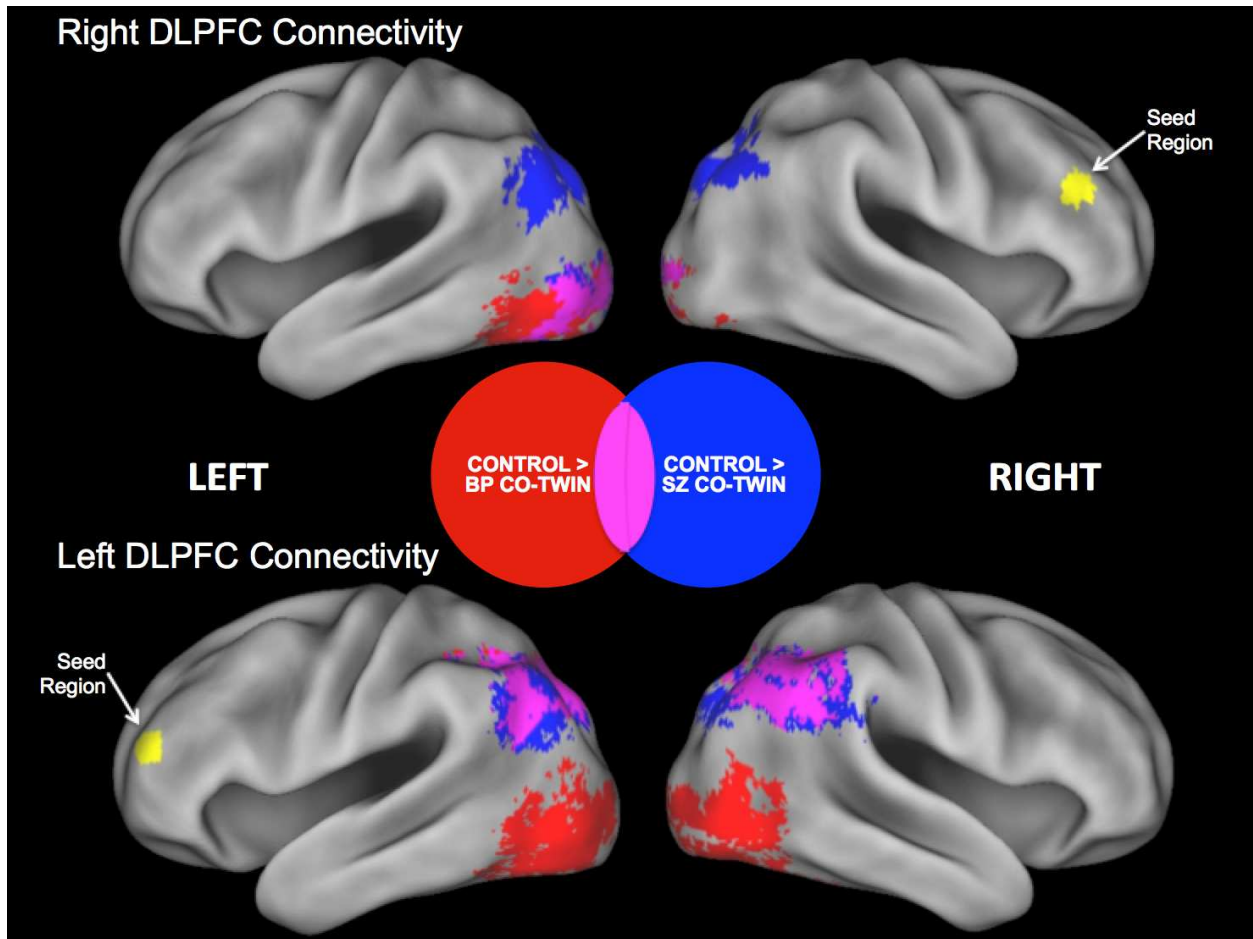


Figure 7. Reduced Fronto-Parietal Connectivity among Non-Affected Co-Twins Relative to Control Subjects. Overlaid functional connectivity maps for Controls > Schizophrenia Co-Twins (shown in blue) and Controls > Bipolar Co-Twins (shown in red). Top row shows functional connectivity with the right dorsolateral prefrontal cortex (DLPFC). Bottom row shows functional connectivity with the left DLPFC. Statistical maps are thresholded at $Z > 1.96$, p -corrected $< .05$ for visualization.

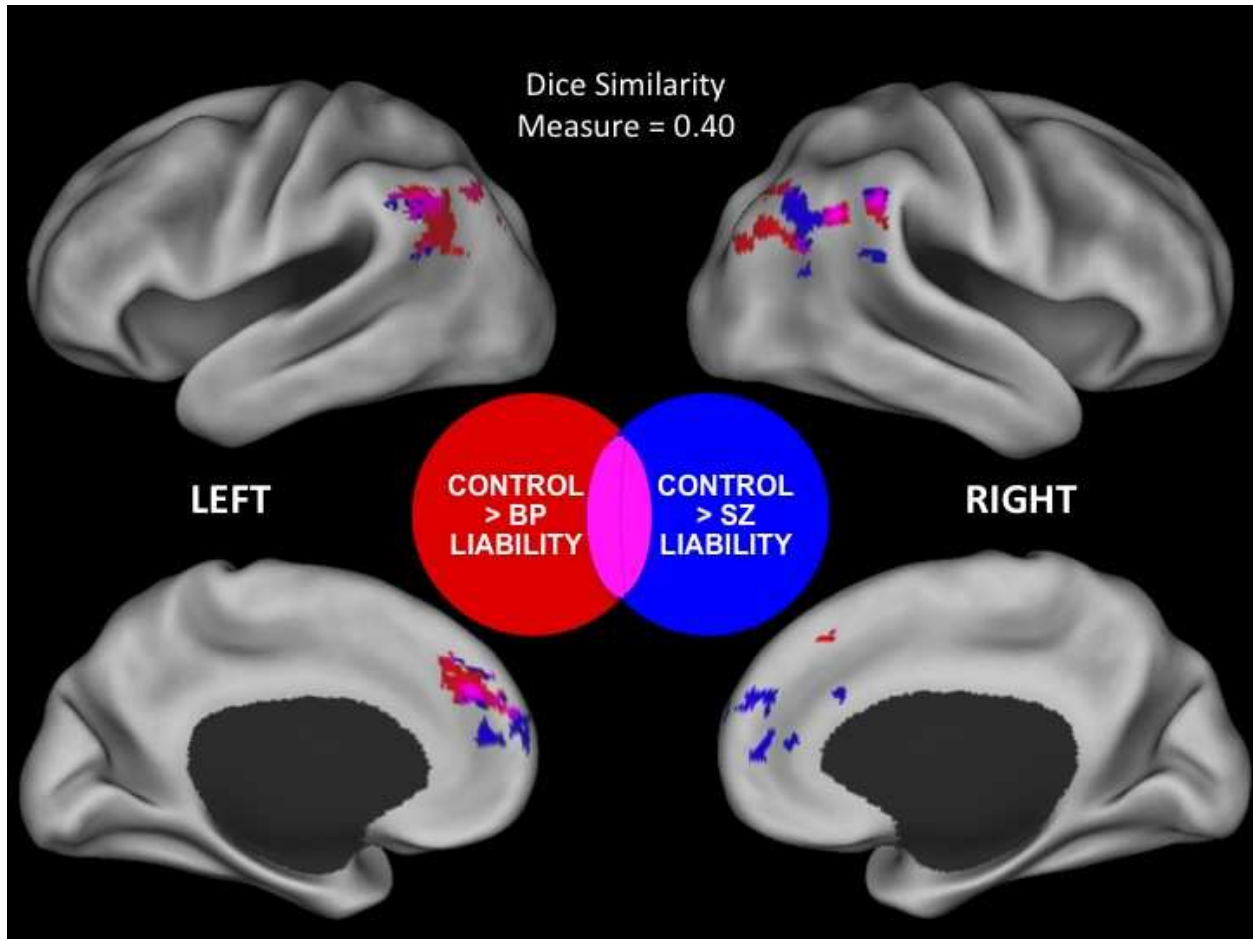


Figure 8. Overlapping Encoding-Based Deviations from Control Subjects among Individuals Carrying Liability for Schizophrenia and Bipolar Disorder. Overlaid encoding maps for Controls > Schizophrenia Liability (shown in blue) and Controls > Bipolar Liability (shown in red). Statistical maps are thresholded at $Z > 2.3$, $p > 0.05$, cluster corrected.

References

- Abecasis, G.R., Cardon, L.R., Cookson, W.O. (2000). A test of association for quantitative traits in nuclear families. *Am J Hum Genet* 66(1), 279-292.
- Adler, C.M., DelBello, M.P., Strakowski, S.M. (2006). Brain network dysfunction in bipolar disorder. *CNS Spectr* 11(4), 312-320.
- Adler, C.M., Holland, S.K., Schmithorst, V., Tuchfarber, M.J., Strakowski, S.M. (2004). Changes in neuronal activation in patients with bipolar disorder during performance of a working memory task. *Bipolar Disord* 6, 540-549.
- Altshuler, L.L., Bearden, C.E., Green, M.F., van Gorp, W., Mintz, J. (2008). A relationship between neurocognitive impairment and functional impairment in bipolar disorder: A pilot study. *Psychiatry Res* 157, 289-293.
- Altshuler, L.L., Ventura, J., van Gorp, W.G., Green, M.F., Theberge, D.C., Mintz, J. (2004). Neurocognitive function in clinically stable men with bipolar I disorder or schizophrenia and normal control subjects. *Biol Psychiatry* 56(8), 560-569.
- Andreasen, N.C. (1983). *Scale for the Assessment of Negative Symptoms (SANS)*. Iowa City, Iowa, University of Iowa.
- Andreasen, N.C. (1984). *Scale for the Assessment of Positive Symptoms (SAPS)*. Iowa City, Iowa, University of Iowa.
- Andreasen, N.C., O'Leary, D.S., Flaum, M., Nopoulos, P., Watkins, G.L., Boles Ponto, L.L., Hichwa, R.D. (1997). Hypofrontality in schizophrenia: distributed dysfunctional circuits in neuroleptic-naïve patients. *Lancet* 349(9067), 1730-1734.
- Arts, B., Jabben, N. Krabbendam, L., van Os, J. (2008). Meta-analyses of cognitive functioning in euthymic patients and their first-degree relatives. *Psychol Med* 38, 771-785.

- Bachman, P., Kim, J., Yee, C.M., Therman, S., Manninen, M., Lonnqvist, J., Kaprio, J., Huttunen, M.O., Naatanen, R., Cannon, T.D. (2009). Efficiency of working memory encoding in twins discordant for schizophrenia. *Psychiatry Research: Neuroimaging* 174(2), 97-104.
- Badcock, J.C., Michie, P.T., Rock, D. (2005). Spatial working memory and planning ability: Contrasts between schizophrenia and bipolar I disorder. *Cortex* 41(6), 753-763.
- Baddeley, A. (2003). Working memory: Looking back and looking forward. *Nat Rev Neurosci* 4, 829-839.
- Balanza-Martinez, V., Rubio, C., Selva-Vera, G., Martinez-Aran, A., Sanchez-Moreno, J., Salazar-Fraile, J., Vieta, E., Tabares-Seisdedos, R. (2008). Neurocognitive endophenotypes (endophenocognitypes) from studies of relatives of bipolar disorder subjects: A systematic review. *Neurosci and Biobehav Rev* 32(8), 1426-1438.
- Barch, D.M. (2005). The cognitive neuroscience of schizophrenia. *Ann Rev Clin Psychol* 1, 321-353.
- Barch, D.M., Sheline, J.G., Csernansky, J.G., Snyder, A.Z. (2003). Working memory and prefrontal cortex dysfunction: Specificity to schizophrenia compared with major depression. *Biol Psychiatry* 53(5), 376-384.
- Barch, D.M., Smith, E. (2008). The cognitive neuroscience of working memory: Relevance to CNTRICS and schizophrenia. *Biol Psychiatry* 64, 11-17.
- Barrett, S.L., Kelly, C., Bell, R., King, D.J. (2008). Gender influences the detection of spatial working memory deficits in bipolar disorder. *Bipolar Disord* 10(5), 647-654.

- Barrett, S.L., Mulholland, C.C., Cooper, S.J., Rushe, T.M. (2009). Patterns of neurocognitive impairment in first-episode bipolar disorder and schizophrenia. *British J Psychiatr* 195, 67-72.
- Baumann, B., Bogerts, B. (1999). The pathomorphology of schizophrenia and mood disorders: similarities and differences. *Schizophr Res* 39(2), 141-148.
- Bearden, C.E., Glahn, D.C., Monkul, E.S., Barrett, J., Najt, P., Kaur, S., Sanches, M., Villarreal, V., Bowden, C., Soares, J.C. (2006). Sources of declarative memory impairment in bipolar disorder: mnemonic processes and clinical features. *Psychiatric Res* 40, 47-58.
- Bearden, C.E., Hoffman, K.M., Cannon, T.D. (2001). The neuropsychology and neuroanatomy of bipolar affective disorder: A critical review. *Bipolar Disord* 3(3), 106-153.
- Bearden, C.E., Reus, V.I., Freimer, N.B. (2004). Why genetic investigation of psychiatric disorders is so difficult. *Curr Opin Genet Deve* 14(3), 280-286.
- Bearden, C.E., Woogen, M., Glahn, D.C. (2010). Neurocognitive and neuroimaging predictors of clinical outcome in bipolar disorder. *Curr Psychiatry Rep* 12, 499-504.
- Benes, F.M., McSparren, J., Bird, E.D., SanGiovanni, J.P., Vincent, S.L. (1991). Deficits in small interneurons in prefrontal and cingulate cortices of schizophrenic and schizoaffective patients. *Arch Gen Psychiatry* 48(11), 996-1001.
- Berrettini, W. (2004). Bipolar disorder and schizophrenia: convergent molecular data. *Neuromolecular Med* 5(1), 109-117.
- Blokland, G.A.M., McMahon, K.L., Hoffman, J., Zhu, G., Meredith, M., Martin, N.G., Thompson, P.M., de Zubicaray, G.I., Wright, M.J. (2008). Quantifying the heritability of task-related brain activation and performance during the N-back working memory task: A twin fMRI study. *Biol Psychiatry* 79(1), 70-79.

- Bora, E., Yucel, M., Pantelis, C. (2009). Cognitive endophenotypes of bipolar disorder: A meta-analysis of neuropsychological deficits in euthymic patients and their first-degree relatives. *J Affect Disord* 113, 1-20.
- Brambilla, P., Harenski, K., Nicoletti, M., Mallinger, A.G., Frank, E., Kupfer, D.J., Keshavan, M.S., Soares, J.C. (2001). Differential effects of age on brain gray matter in bipolar patients and healthy individuals. *Neuropsychobiology* 43(4), 242-247.
- Bramon, E., Sham, P.C. (2001). The common genetic liability between schizophrenia and bipolar disorder: A review. *Curr Psychiatry Rep* 3(4), 332-337.
- Buckholtz, J.W., Myere-Lindenberg, A. (2012). Psychopathology and the human connectome: Toward a transdiagnostic model of risk for mental illness. *Neuron* 74(6), 990-1104.
- Burdick, K.E., Goldberg, J.F., Harrow, M., Faull, R.N., Malhotra, A.K. (2006). Neurocognition as a stable endophenotype in bipolar disorder and schizophrenia. *J Nerv Ment Dis* 194(4), 255-260.
- Cairo, T.A., Liddle, P.F., Woodward, T.S., Ngan, E.T.C. (2004). The influence of working memory load on phase specific patterns of cortical activity. *Cogn Brain Res* 21(3), 377-387.
- Callicott, J.H., Bertolino, A., Mattay, V.S., Langheim, F.J., Duyn, J., Coppola, R., Goldberg, T.E., Weinberger, D.R. (2000). Physiological dysfunction of the dorsolateral prefrontal cortex in schizophrenia revisited. *Cereb Cortex* 10(11), 1078-1092.
- Callicott, J.H., Egan, M.F., Mattay, V.S., Bertolino, A., Bone, A.D., Verchinski, B., Weinberger, D.R. (2003a). Abnormal fMRI response of the dorsolateral prefrontal cortex in cognitively intact siblings of patients with schizophrenia. *Am J Psychiatry* 160, 709-719.

- Callicott, J.H., Mattay, V.S., Verchinski, B.A., Marenco, S., Egan, M.F., Weinberger, D.W. (2003b). Complexity of prefrontal cortical dysfunction in schizophrenia: more than up or down. *Am J Psychiatry* 160(12), 2209-2215.
- Cannon, T.D., Gasperoni, T.L., van Erp, T.G.M., Rosso, I.M. (2001). Quantitative neural indicators of liability to schizophrenia: Implications for molecular genetic studies. *Am J Med Genetic* 105, 16-19.
- Cannon, T.D., Glahn, D.C., Kim, J., van Erp, T.G.M., Karlsgodt, K., Cohen, M.S., Nuechterlein, K.H., Bava, S., Shirinyan D. (2005). Dorsolateral prefrontal cortex activity during maintenance and manipulation of information in working memory in patients with schizophrenia. *Arch Gen Psychiatry* 62, 1071-1080.
- Cannon, T.D., Huttunen, M.O., Lonnqvist, J., Tuulio-Henriksson, A., Prikola, T., Glahn, D., Finkelstein, J., Hietanen, M., Kaprio, J., Koskenvuo, M. (2000). The inheritance of neuropsychological dysfunction in twins discordant for schizophrenia. *Am Soc Human Genetics* 67, 369-382.
- Cannon, T.D., Kaprio, J., Lonnqvist, J., Huttunen, M., Koskenvuo, M. (1998a). The genetic epidemiology of schizophrenia in a Finnish twin cohort: A population-based modeling study. *Arch Gen Psychiatry* 55(1), 67-74.
- Cannon, T.D., Keller, M.C. (2006). Endophenotypes in the genetic analyses of mental disorders. *Annu Rev Clin Psychol* 2, 267-290.
- Cannon, T.D., Mednicr, S.A., Parnas, J., Schulsinger, F., Praestholm, J., Vestergaard, A. (1993). Developmental brain abnormalities in the offspring of schizophrenic mothers. I. Contributions of genetic and perinatal factors. *Arch Gen Psychiatry* 50(7), 551-564.

- Cannon, T.D., Thompson, P.M., van Erp, T.G.M., Huttunen, M., Lonnqvist, J., Kaprio, J., Toga, A.W. (2006). Mapping heritability and molecular genetic associations with cortical features using probabilistic brain atlases. *Neuroinformatics 4*(1), 5-19.
- Cannon, T.D., Thompson, P.M., van Erp, T.G., Toga, A.W., Poutanen, V.P., Huttunen, M., Lonnqvist, J., Standerskjold-Nordenstam, C.G., Narr, K.L., Khaledy, M., Zoumalan, C.I., Dail, R., Kaprio, J. (2002). Cortex mapping reveals regionally specific patterns of genetic and disease-specific gray-matter deficits in twins discordant for schizophrenia. *Proc Natl Acad Sci 99*(5), 3228-3233.
- Cannon, T.D., van Erp, T.G.M., Huttunen, M., Lönqvist, J., Salonen, O., Valanne, L., Poutanen, V-P., Standerstskjöld-Nordenstam, C-G., Gur, R.E., Yan, M. (1998b). Regional gray matter, white matter, and cerebrospinal fluid distributions in schizophrenic patients, their siblings, and controls. *Arch Gen Psychiatry 55*, 1084-1091.
- Cannon, T.D., Zorrilla, L.E., Shtasel, D., Gur, R.E., Gur, R.C., Marco, E.J., Moberg, P. Price, R.A. (1994). Neuropsychological functioning in siblings discordant for schizophrenia and healthy volunteers. *Arch Gen Psychiatry 51*(8), 651-661.
- Cardno, A.G., Rijdsdijk, F.V., Sham, P.C., Murray, R.M., McGuffin, P. (2002). A twin study of genetic relationships between psychotic symptoms. *Am J Psychiatry 159*, 539-545.
- Carter, C.S., Botvinick, M.M., Cohen, J.D. (1999). The contribution of the anterior cingulate cortex to executive processes in cognition. *Rev Neurosci 10*, 49-57.
- Carter, C., Robertson, L., Nordahl, T., Chaderjian, M., Kraft, L., O'Shoro-Celaya, L. (1996). Spatial working memory deficits and their relationship to negative symptoms in unmedicated schizophrenia patients. *Biol Psychiatry 40*, 930-932.

- Chafee, M.V., Goldman-Rakic, P.S. (1998). Matching patterns of activity in primate prefrontal areas 8a and parietal area 7ip during a spatial working memory task. *J Neurophysiol* 79(6), 2919-2940.
- Clark, L., Iversen, S.D., Goodwin, G.M. (2002). Sustained attention deficit in bipolar disorder. *British J Psychiatr* 180, 313-319.
- Clark, L., Sarna, A., Goodwin, G.M., (2005). Impairment of executive function but not memory in first-degree relatives of patients with bipolar I disorder and in euthymic patients with unipolar depression. *Am J Psychiatry* 162, 1980-1982.
- Cohen, J.D., Perlstein, W.M., Braver, T.S., Nystrom, L.E., Noll, D.C., Jonides, J., Smith, E.E. (1997). Temporal dynamics of brain activation during a working memory task. *Nature* 386, 604-607.
- Condray, R., Steinhauer, S.R., van Kammen, D.P., Kasperek, A. (1996). Working memory capacity predicts language comprehension in schizophrenic patients. *Schizophr Res* 20(1-2), 1-13.
- Cornblatt, B., Auther, A., Niendam, T., Smith, C., Zingberg, J., Bearden, C., Cannon, T.D. (2007). Preliminary findings for two new measures of social and role functioning in the prodromal phase of schizophrenia. *Schizophr Bull* 33(3), 688-702.
- Coryell, W., Leon, A.C., Turvey, C., Akiskal, H.S., Mueller, T., Endicott, J. (2001). The significance of psychotic features in manic episodes: A report from the NIMH collaborative study. *J Affect Disord* 67, 79-88.
- Cotter, D., Pariante, C., Everall, I. (2001). Glial cell abnormalities in major psychiatric disorders: The evidence and implications. *Brain Res Bull* 55, 585-595.

- Courtney, S.M., Petit, L., Maisog, J.M., Ungerleider, L.G., Haxby, J.V. (1998). An area specialized for spatial working memory in human frontal cortex. *Science* 279, 1347-1351.
- Courtney, S.M., Ungerleider, L.G., Keil, K., Haxby, J.V. (1997). Transient and sustained activity in a distributed neural system for human working memory. *Nature* 386, 608-611.
- Craddock, N., O'Donovan, M.C., Owen, M.J. (2006). Genes for schizophrenia and bipolar disorder? Implications for psychiatric nosology. *Schizophr Bull* 32, 9-16.
- Craddock, N., Owen, M.J. (2005). The beginning of the end for the Kraepelinian dichotomy. *British J Psychiatr* 186, 364-366.
- Craddock, N., Sklar, P. (2009). Genetics of bipolar disorder: Successful start to a long journey. *Trends in Genetics* 25(2), 99-105.
- Curtis, C.E., D'Esposito, M. (2003). Persistent activity in the prefrontal cortex during working memory. *Trends in Cogn Neurosci* 7(9), 415-423.
- Curtis, C.E., D'Esposito, M. (2006). Selection and maintenance of saccade goals in the human frontal eye fields. *J Neurophysiology* 95, 3923-3927.
- Daban, C., Martinez-Aran, A., Torrent, C., Tabares-Seisdedos, R., Balanza-Martinez, V., Salazar-Fraile, J., Selva-Vera, G., Vieta, E. (2006). Specificity of cognitive deficits in bipolar disorder versus schizophrenia: A systematic review. *Psychother Psychosom* 75, 72-84.
- Daviss, S.R., Lewis, D.A. (1995). Local circuit neurons of the prefrontal cortex in schizophrenia: Selective increase in the density of calbindin-immunoreactive neurons. *Psychiatry Res* 59, 81-96.

- D'Esposito, M., Postle, B.R., Ballard, D., Lease, J. (1999). Maintenance versus manipulation of information held in working memory: An event-related fMRI study. *Brain Cogn* 41(1), 66-86.
- Dice, L.R. (1945). Measures of the amount of ecologic association between species. *Ecology* 26(3), 297-302.
- Drapier, D., Surguladze, S., Marshall, N., Schulze, K., Fern, A., Hall, M-H., Walshe, M., Murray, R.M., McDonald, C. (2008). Genetic liability for bipolar disorder is characterized by excess frontal activation in response to a working memory task. *Biol Psychiatry* 64(6), 513-520.
- Drevets, W.C., Price, J.L., Simpson, J.R., Todd, R.D., Reich, T., Vannier, M., Raichle, M.E. (1997). Subgenual prefrontal cortex abnormalities in mood disorders. *Nature* 386(24), 824-827.
- Driesen, N.R., Leung, H.C., Calhoun, V.D., Constable, R.T., Gueorguieva, R., Hoffman, R., Skudlarski, P., Goldman-Rakic, P.S., Krystal, J.H. (2008). Impairment of working memory maintenance and response in schizophrenia: Functional magnetic resonance imaging evidence. *Biol Psychiatry* 64(12), 1026-1034.
- Eack, S.M., Pogue-Geile, M.F., Greenwald, D.P., Hogarty, S.S., Keshavan, M.S. (2010). Mechanisms of functional improvement in a 2-year trial of cognitive enhancement therapy for early schizophrenia. *Psychol Med* 41(6), 1253-1261.
- Ferrier, I.N., Chowdhury, R., Thompson, J.M., Watson, S., Young, A.H. (2004). Neurocognitive function in unaffected first-degree relatives of patients with bipolar disorder: A preliminary report. *Bipolar Disord* 6(4), 319-322.

- First, M.B., Gibbon, M., Spitzer, R.L., Williams, J.W.B., Benjamin, L.S. (1997). *Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II)*. Washington, D.C.: American Psychiatric Press, Inc.
- First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.W.B. (2002). *Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition (SCID-I/P)*. New York: Biometrics Research, New York State Psychiatric Institute.
- Fleming, K., Goldberg, T.E., Binks, S., Randolph, C., Gold, J.M., Weinberger, D.R. (1997). Visuospatial working memory in patients with schizophrenia. *Biol Psychiatry* 41(1), 43-49.
- Fornito, A., Yoon, J., Zalesky, A., Bullmore, E.T., Carter, C.S. (2011). General and specific functional connectivity disturbances in first-episode schizophrenia during cognitive control performance. *Biol Psychiatry* 70(1), 64-72.
- Frangou, S., Haldane, M., Roddy, D., Kumari, V. (2005). Evidence for deficit in tasks of ventral, but not dorsal, prefrontal executive function as an endophenotypic marker for bipolar disorder. *Biol Psychiatry* 58(10), 838-839.
- 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. *Eur Psychiatry* 23(4), 300-308.
- Friston, K., Buechel, C., Fink, G., Morris, J., Roll, E., Dolan, R.J. (1997). Psychophysiological and modulatory interactions in neuroimaging. *NeuroImage* 6(3), 218-229.
- Funahashi, S., Bruce, C.J., Goldman-Rakic, P.S. (1993). Dorsolateral prefrontal lesions and oculomotor delayed-response performance: Evidence for mnemonic “scotomas.” *J Neurosci* 13(4), 1479-1497.

- Fusar-Poli, P., Howes, O., Bechdolf, A., Borgwardt, S. (2012). Mapping vulnerability to bipolar disorder: A systematic review and meta-analysis of neuroimaging studies. *J Psychiatry Neurosci* 37(3), 170-184.
- Gershon, E.S., DeLisi, L.E., Hamovit, J., Nurnberger, J.I. Jr., Maxwell, M.E., Schreiber, J., Dauphinais, D., Dingman, C.W. 2nd, Guroff, J.J. (1988). A controlled family study of chronic psychoses: Schizophrenia and schizoaffective disorder. *Arch Gen Psychiatry* 45, 328-336.
- Gilvarry, C.M., Russel, A., Hemsley, D. Murray, R.M. (2001a). Neuropsychological performance and spectrum personality traits in the relatives of patients with schizophrenia and affective psychosis. *Psychiatr Res* 101, 89-100.
- Gilvarry, C.M., Russel, A., Jones, P., Sham, P., Hemsley, D., Murray, R.M. (2001b). Verbal fluency in patients with schizophrenia and affective psychoses and their first-degree relatives. *Psychol Med* 31, 695-704.
- Glahn, D.C., Almas, L., Barguil, M., Hare, E., Peralta, J.M., Kent, J.W., Dassori, A., Contreras, J., Pacheco, A., Lanzagorta, N., Nicolini, H., Raventos, H., Escamilla, M.A. (2010). Neurocognitive endophenotypes for bipolar disorder in multiplex multigenerational families. *Arch Gen Psychiatry* 67(2), 168-177.
- Glahn, D.C., Bearden, C.E., Barguil, M., Barrett, J., Reichenberg, A., Bowden, C.L., Soares, J.C., Velligan, D.I. (2007). The neurocognitive signature of psychotic bipolar disorder. *Biol Psychiatry* 62(18), 910-916.
- Glahn, D.C., Barrett, J., Bearden, C.E., Mintz, J., Green, M.F., Monkul, E.S., Najt, P., Soares, J.C., Velligan, D.I. (2006a). Dissociable mechanisms for memory impairment in bipolar disorder and schizophrenia. *Psychol Med* 36, 1085-1095.

- Glahn, D.C., Bearden, C.E., Cakir, S., Barrett, J.A., Najt, P., Monkul, E.S., Maples, N., Velligan, D.I., Soares, J.C. (2006b). Differential working memory impairment in bipolar disorder and schizophrenia: Effects of a lifetime history of psychosis. *Bipolar Disord* 8(2), 117-123.
- Glahn, D.C., Bearden, C.E., Niendam, T.A., Escamilla, M.A. (2004). The feasibility of neuropsychological endophenotypes in the search for genes associated with bipolar affective disorder. *Bipolar Disord* 6(3), 171-182.
- Glahn, D.C., Kim, J., Cohen, M.S., Poutanen, V-P., Therman, S., Bava, S., van Erp, T.G.M., Manninen, M., Huttunen, M., Lönnqvist, J., Standerskjöld-Nordenstam, C.G., Cannon, T.D. (2002). Maintenance and manipulation in spatial working memory: Dissociations in the prefrontal cortex. *NeuroImage* 17, 201-213.
- Glahn, D.C., Ragland, J.D., Abramoff, A., Barrett, J., Laird, A.R., Bearden, C.E., Velligan, D.I. (2005). Beyond hypofrontality: A quantitative meta-analysis of functional neuroimaging studies of working memory in schizophrenia. *Human Brain Mapping* 25(1), 60-69.
- Glahn, D.C., Therman, S., Manninen, M., Huttunen, M., Kaprio, J., Lönnqvist, J., Cannon, T.D. (2003). Spatial working memory as an endophenotype for schizophrenia. *Biol Psychiatry* 53(7), 624-626.
- Gold, J.M., Carpenter, C., Randolph, C. Goldberg, T.E., Weinberger, D.R. (1997). Auditory working memory and Wisconsin Card Sorting Test performance in schizophrenia. *Arch Gen Psychiatry* 54(2), 159-165.
- Goldman-Rakic, P.S. (1994). Working memory dysfunction in schizophrenia. *J Neuropsychiatry Clin Neurosci* 6(4), 348-357.

- Goldman-Rakic, P.S. (1995). Architecture of the prefrontal cortex and the central executive. *Ann NY Acad Sci* 769, 71-83.
- Goldman-Rakic, P.S., Selemon, L.D. (1997). Functional and anatomical aspects of prefrontal pathology in schizophrenia. *Schizophr Bull* 23(3), 437-458.
- Gooding, C.G., Tallent, K.A. (2001). The association between antisaccade task and working memory task performance in schizophrenia and bipolar disorder. *J Nerv Ment Dis* 189, 8-16.
- Goswami, U., Sharma, A., Varma, A., Gulrajani, C., Ferrier, I.N., Young, A.H., Gallagher, P., Thompson, J.M., Moore, P.B. (2009). The neurocognitive performance of drug-free and medicated euthymic bipolar patients do not differ. *Acta Psychiatr Scand* 120(6), 456-463.
- Gottesman, I.I., Gould, T.D. (2003). Quantitative neural indicators of liability to schizophrenia: Implications for molecular genetic studies. *Am J Psychiatry* 105(1), 16-19.
- Gourovitch, M.L., Torrey, E.F., Gold, J.M., Randolph, C., Weinberger, D.R., Goldberg, T.E. (1999). Neuropsychological performance of monozygotic twins discordant for bipolar disorder. *Biol Psychiatry* 45(5), 639-646.
- Green, M.F. (1996). What are the functional consequences of neurocognitive deficits in schizophrenia? *Am J Psychiatry* 153(3), 321-330.
- Green, M.F. (2006). Cognitive impairment and functional outcome in schizophrenia and bipolar disorder. *J Clin Psychiatry* 67(10), e12.
- Green, M.F., Kern, R.S., Braff, D.L., Mintz, J. (2000). Neurocognitive deficits and functional outcome in schizophrenia: Are we measuring the “right stuff?” *Schizophr Bull*, 119-136.
- Green, M.F., Kern, R.S., Heaton, R.K. (2004). Longitudinal studies of cognition and functional outcomes in schizophrenia: implications for MATRICS. *Schizophr Res* 72, 41-51.

- Greicius, M.D., Krasnow, B., Reiss, A.L., Menon, V. (2003). Functional connectivity in the resting state brain: A network analysis of the default mode hypothesis. *Proc Natl Acad Sci* 100(1), 253-258.
- Gruber, S.A., Rosso, I.M., Yurgelun-Todd, D. (2008). Neuropsychological performance predicts clinical recovery in bipolar patients. *J Affect Disord* 105, 253-260.
- Gruber, O., Tost, H., Henseler, I., Schmael, C., Scherk, H., Ende, G., Ruf, M., Falkai, P., Rietschel, M. (2010). Pathological amygdala activation during working memory performance: Evidence for a pathophysiological trait marker in bipolar affective disorder. *Human Brain Mapping* 31(1), 115-125.
- Gur, R.E., Calkins, M.E., Gur, R.C., Horan, W.P., Nuechterlein, K.H., Seidman, L.J., Stone, W.S. (2007). The consortium on the genetics of schizophrenia: Neurocognitive endophenotypes. *Schizophr Bull* 33(1), 49-68.
- Häfner, H., Maurer, K., Trendler, G., an der Heiden, W., Schmidt, M., Könnecke, R. (2005). Schizophrenia and depression: Challenging the paradigm of two separate diseases – A controlled study of schizophrenia, depression and healthy controls. *Schizophr Res* 77(1), 11-24.
- Hamilton, M. (1960). A rating scale for depression. *J Neurol Neurosurg Psychiatry* 23, 56-62.
- Hamilton, L.S., Altshuler, L.L., Townsend, J., Bookheimer, S.Y., Phillips, O.R., Fischer, J., Woods, R.P., Mazziotta, J.C., Toga, A.W., Nuechterlein, K.H., Narr, K.L. (2009). Alterations in functional activation in euthymic bipolar disorder and schizophrenia during a working memory task. *Human Brain Mapping* 30(12), 3958-3969.

- Hannelius, U., Gherman, L., Ville-Veikko, M., Liindstedt, A., Zucchelli, M., Lagerberg, C., Tybring, G., Kere, H., Lindgren, C.M. (2007). Large-scale zygosity testing using single nucleotide polymorphisms. *Twin Res Hum Genet* 10(4), 604-625.
- Hasler, G., Drevets, W.C., Gould, T.D., Gottesman, I.I., Manji, H.K. (2006). Toward constructing an endophenotype strategy for bipolar disorders. *Biol Psychiatry* 60, 93-105.
- Hartman, M., Steketee, M.C., Silva, S., Lanning, K., McCann, H. (2003). Working memory and schizophrenia: Evidence for slowed encoding. *Schizophr Res* 59, 99-113.
- Higier, R.G., Jimenez, A.M., Hultman, C.M., Borg, J., Roman, C., Kizling, I., Larsson, H., Cannon, T.D. (In Press). Enhanced neurocognitive functioning and positive temperament in twins discordant for bipolar disorder. *Am J Psychiatry*.
- Hirayasu, Y., Shenton, M.E., Salisbury, D.F., Kwon, J.S., Wible, C.G., Fischer, I.A., Yurgelun-Todd, D., Zarate, C., Jolesz, F.A., McCarley, R.W. (1999). Subgenual cingulate cortex volume in first-episode psychosis. *Am J Psychiatry* 156(7), 1091-1093.
- Hoff, A.L., Shukla, S., Aronson, T., Cook, B., Ollo, C., Baruch, S., Jandorf, L., Schwartz, J. (1990). Failure to differentiate bipolar disorder from schizophrenia on measures of neuropsychological function. *Schizophr Res* 3(4), 253-260.
- Hogarty, G.E., Greenwald, D.P., Eack, S.M. (2006). Durability and mechanism effects of cognitive enhancement therapy. *Psychiatr Serv* 57(12), 1751-1757.
- Ivleva, E.I., Morris, D.W., Osuji, J., Moates, A.F., Carmody, T.J., Thaker, G.K., Cullum, M., Tamminga, C.A. (2012). Cognitive endophenotypes of psychosis within dimension and diagnosis. *Psychiatry Res* 196(1), 38-44.
- Jaeggi, S.M., Buschkuhl, M., Jonides, J., Perrig, W.J. (2008). Improving fluid intelligence with training on working memory. *Proc Natl Acad Sci* 105(19), 6829-6833.

- Jamrozinski, K., Gruber, O., Kemmer, C., Falkai, P., Scherk, H. (2009). Neurocognitive functions in euthymic bipolar patients. *Acta Psychiatr Scand* 119(5), 365-374.
- Jogia, J., Dima, D., Kumari, V., Frangou, S. (2011). Frontopolar cortical inefficiency may underpin reward and working memory dysfunction in bipolar disorder. *World J Biol Psychiatry* (doi:10.3109/15622975.2011.585662)
- Jonides, J. Schumacher, E.H., Smith, E.E., Koeppe, R.A., Awh, E., Reuter-Lorenz, P.A., Marshuetz, C., Willis, C.R. (1998). The role of parietal cortex in verbal working memory. *J Neurosci* 18(13), 5026-5034.
- Karlsgodt, K.H., Glahn, D.C., van Erp, T.G., Therman, S., Huttunen, M., Manninen, M., Kaprio, J., Cohen, M.S., Lönqvist, J., Cannon, T.D. (2007). The relationship between performance and fMRI signal during working memory in patients with schizophrenia, unaffected co-twins, and control subjects. *Schizophr Res* 89, 191-197.
- Karlsgodt, K.H., Kochunov, P., Winkler, A.M., Laird, A.R., Almasy, L., Duggirala, R., Olvera, R.L., Fox, P.T., Blangero, J., Glahn, D.C. (2010). A multimodal assessment of the genetic control over working memory. *J Neurosci* 30(24), 8197-8202.
- Karlsgodt, K.H., Sanz, J., van Erp, T.G., Bearden, C.E., Nuechterlein, K.H., Cannon, T.D. (2009). Re-evaluating dorsolateral prefrontal cortex activation during working memory in schizophrenia. *Schizophr Res* 108(1-3), 143-150.
- Karlsgodt, K.H., Sun, D., Jimenez, A.M., Lutkenhoff, E.S., Willhite, R., van Erp, T.G., Cannon, T.D. (2008). Developmental disruptions in neural connectivity in the pathophysiology of schizophrenia. *Development and Psychopathology* 20(4), 1297-1327.
- Keck, P.E., McElroy, S.L., Havens, J.R., Altshuler, L.L., Nolen, W.A., Frye, M.A., Suppes, T., Denicoff, K.D., Kupka, R., Leverich, G.S., Rush, A.J., Post, R.M. (2003). Psychosis in

- bipolar disorder: Phenomology and impact on morbidity and course of illness. *Compr Psychiatry* 44, 263-269.
- Keefe, R.S.E., Lees-Roitman, S.E., Dupre, R.L. (1997). Performance of patients with schizophrenia on a pen and paper visuospatial working memory task with short delay. *Schizophr Res* 26, 9-14.
- Keefe, R.S.E., Lees-Roitman, S.E., Harvey, P.D., Dupre, R.L., Prieto, D.M., Davidson, M., Davis, K.L. (1995). A pen-and-paper human analogue of a monkey prefrontal cortex activation task: Spatial working memory in patients with schizophrenia. *Schizophr Res* 17, 25-33.
- Kendler, K.S., Diehl, S.R. (1993). The genetics of schizophrenia: A current, genetic epidemiologic perspective. *Schizophr Bull* 19, 261-284.
- Keri, S., Kelemen, O., Benedek, G., Janka, Z. (2001). Different trait markers for schizophrenia and bipolar disorder: A neurocognitive approach. *Psychol Med* 31, 915-922.
- Kern, R.S., Glynn, S.M., Horan, W.P., Marder, S.R. (2009). Psychosocial treatments to promote functional recovery in schizophrenia. *Schizophr Bull* 35, 347-361.
- Kieseppä, T., Tuulio-Henriksson, A., Haukka, J., van Erp, T., Glahn, D., Cannon, T.D., Partonen, T., Kaprio, J., Lönnqvist, J. (2005). Memory and verbal learning functions in twins with bipolar I disorder, and the role of information-processing speed. *Psychol Med* 35, 205-215.
- Kieseppä, T., van Erp, T.G.M., Haukka, J., Partonen, T., Cannon, T., Poutanen, V-P., Kaprio, J., Lönnqvist, J. (2003). Reduced left hemispheric white matter volume in twins with bipolar I disorder. *Biol Psychiatry* 54(9), 896-905.

- 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. *Schizophr Res* 68, 173-187.
- Kim, D.I., Manoach, D.S., Mathalon, D.H., Turner, J.A., Mannell, M., Brown, G.G., Ford, J.M., Gollub, R.L., White, T., Wible, C., Belger, A., Bockholt, H.J., Clark, V.P., Lauriello, J., O'Leary, D., Meuller, B.A., Lim, K.O., Andreasen, N., Potkin, S.G., Calhoun, V.D. (2009). Dysregulation of working memory and default-mode networks in schizophrenia using independent component analysis, an fBIRN and MCIC study. *Human Brain Mapping* 30(11), 3795-3811.
- Krabbendam, L., Arts, B. van Os, J., Aleman, A. (2005). Cognitive functioning in patients with schizophrenia and bipolar disorder: A review. *Schizophr Res* 80, 137-149.
- Kraepelin, E. (1919). *Manic depressive insanity and paranoia*. (trans. R.M. Barclay). Edinburgh: Livingstone.
- Kremen, W.S., Faraone, S.V., Seidman, L.J., Pepple, J.R., Tsuang, M.T. (1998). Neuropsychological risk indicators for schizophrenia: A preliminary study of female relatives of schizophrenic and bipolar patients. *Psychiatry Res* 79, 227-240.
- Lagopoulos, J., Ivanovski, B., Malhi, G.S. (2007). An event-related functional MRI study of working memory in euthymic bipolar disorder. *J Psychiatry Neurosci* 32, 174-184.
- Lee, J., Park, S. (2005). Working memory impairments in schizophrenia: A meta-analysis. *J Abnormal Psychol* 114(4), 599-611.
- Lichtenstein, P., Yip, B.H., Björk, C., Pawitan, Y., Cannon, T.D., Sullivan, P.F., Hultman, C.M. (2009). Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: A population-based study. *Lancet* 373(9659), 234-239.

- Lin, P-I., Mitchell, B.D. Approaches for unraveling the joint genetic determinants of schizophrenia and bipolar disorder. *Schizophr Bull* 34(4), 791-797.
- Lopez-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. *Biol Psychiatry* 52(2), 93-100.
- Ludvigsson J.F., Andersson, E., Ekblom, A., Feychting, M., Kim, J.L., Reuterwall, C., Heurgren, M., Olausson, P.O. (2011). External review and validation of the Swedish national inpatient register. *BMC Public Health* 11, 450-465.
- Maher, B.A., Manschreck, T.C., Woods, B.T., Yurgelun-Todd, D.A., Tsuang, M.T. (1994). Frontal brain volume and context effects in short-term recall in schizophrenia. *Biol Psychiatry* 37(3), 144-150.
- Maier, W., Höfgen, B. Zobel, A., Rietschel, M. (2005). Genetic models of schizophrenia and bipolar disorder: Overlapping inheritance or discrete genotypes? *Eur Arch Psychiatry Clin Neurosci* 255, 159-166.
- Maier, W., Lichtermann, D., Franke, P., Heun, R., Falkai, P., Rietschel, M. (2002). The dichotomy of schizophrenia and affective disorders in extended pedigrees. *Schizophr Res* 57, 259-266.
- Manoach, D.S. (2003a). Prefrontal cortex dysfunction during working memory performance in schizophrenia: Reconciling discrepant findings. *Schizophr Res* 60, 285-298.
- Manoach, D.S., Greve, D.N., Lindgren, K.A., Dale, A.M. (2003b). Identifying regional activity associated with temporally separated components of working memory using event-related functional MRI. *NeuroImage* 20(3), 1670-1684.

- Manoach, D.S., Gollub, R.L., Benson, E.S., Searl, M.M., Goff, D.C., Halpern, E., Saper, C.B., Rauch, S.L. (2000). Schizophrenic subjects show aberrant fMRI activation of dorsolateral prefrontal cortex and basal ganglia during working memory performance. *Biol Psychiatry* 48(2), 99-109.
- Manoach, D.S., Press, D.Z., Thangaraj, V., Searl, M.M., Goff, D.C., Halpern, C.B., Saper, S., Warach, S. (1999). Schizophrenic subjects activate dorsolateral prefrontal cortex during a working memory task as measured by fMRI. *Biol Psychiatry* 45(9), 1128-1137.
- Martinez-Aran, A., Vieta, E., Colom, F., Reinares, M., Benabarre, A., Gasto, C., Salamero, M. (2000). Cognitive dysfunctions in bipolar disorder: Evidence of neuropsychological disturbance. *Psychother Psychosom* 69, 2-18.
- Maziade, M., Roy, M.-A., Chagnon, Y.C., Cliche, D., Fournier, J.-P., Montgrain, N., Dion, C., Lavallee, J.-C., Garneau, Y., Gingras, N., Nicole, L., Pires, A., Ponton, A.-M., Potvin, A., Wallot, H., Merette, C. (2005). Shared and specific susceptibility loci for schizophrenia and bipolar disorder: A dense genome scan in Eastern Quebec families. *Molecular Psychiatry* 10(5), 486-499.
- Merikangas, K.R., Chakravarti, A., Moldin, S.O., Araj, H., Blangero, J.C., Burmeister, M. *et al.* (2002). Future of genetics of mood disorders research. *Biol Psychiatry* 52, 457-477.
- Meyer-Lindenberg, A., Poline, J.-B., Kohn, P.D., Holt, J.L., Egan, M.F., Weinberger, D.R., Berman, K.F. (2001). Evidence for abnormal cortical functional connectivity during working memory in schizophrenia. *Am J Psychiatry* 158, 1809-1817.
- McDonald, C., Bullmore, E.T., Sham, P.C., Chitnis, X., Wickham, H., Bramon, E., Murray, R.M. (2004). Association of genetic risks for schizophrenia and bipolar disorder with specific and generic brain structural endophenotypes. *Arch Gen Psychiatry* 61, 974-984.

- McDonough-Ryan, P., DelBello, M., Shear, P.K., Ris, M.D., Soutullo, C., Strakowski, S.M. (2002). Academic and cognitive abilities in children of parents with bipolar disorder: A test of the nonverbal learning disability model. *J Clin Exper Neuropsychol* 24(3), 280-285.
- McGrath, J., Chapple, B., Wright, M. (2001). Working memory in schizophrenia and mania: Correlation with symptoms during the acute and sub-acute phases. *Acta Psychiatr Scand* 103, 181-188.
- McGuffin, P., Rijdsdijk, F., Andrew, M., Sham, P., Katz, R., Cardno, A. (2003). The heritability of bipolar affective disorder and the genetic relationship to unipolar depression. *Arch Gen Psychiatry* 60(5), 497-502.
- McGurk, S.R., Mueser, K.T., DeRosa, T.J., Wolfe, R. (2009). Work, recovery, and comorbidity in schizophrenia: A randomized controlled trial of cognitive remediation. *Schizophr Bull* 35, 319-335.
- McIntosh, A.M., Whalley, H.C., McKirdy, J., Hall, J., Sussman, J.E.D., Shankar, P., Johnstone, E.C., Lawrie, S.M. (2008). Prefrontal function and activation in bipolar disorder and schizophrenia. *Am J Psychiatry* 165, 378-384.
- Monks, P.J., Thompson, J.M., Bullmore, E.T., Suckling, J., Brammer, M.J., Williams, S.C., *et al.* (2004). A functional MRI study of working memory task in euthymic bipolar disorder: Evidence for task-specific dysfunction. *Bipolar Disord* 6, 550-564.
- Mortensen, P.B., Pedersen, C.B. Melbye, M., Mors, O., Ewald, H. (2003). Individual and familial risk factors for bipolar affective disorders in Denmark. *Arch Gen Psychiatry* 60, 1209-1215.

- Munafò, M.R., Bowes, L., Clark, T.G., Flint, J. (2005). Lack of association of the COMT (Val^{158/108}Met) gene and schizophrenia: A meta-analysis of case-control studies. *Mol Psychiatry* 10, 765-770.
- Mur, M., Portella, M.J., Martínez-Arán, A., Pifarré, A., Vieta, E. (2007). Persistent neuropsychological deficit in euthymic bipolar patients: Executive function as a core deficit. *J Clin Psychiatry* 68, 1078-1086.
- Noga, J.T., Vladoar, K., Torrey, E.F. (2001). A volumetric magnetic resonance imaging study of monozygotic twins discordant for bipolar disorder. *Psychiatry Res* 106(1), 25-34.
- O'Donovan, M.C., Craddock, N., Norton, N., Williams, H., Peirce, T., Moskvina, V., Nikolov, I., Hamshere, M., Carroll, L., Georgieva, L. *et al.* (2008). Identification of loci associated with schizophrenia by genome-wide association and follow-up. *Nat Genet* 40, 1053-1055.
- Owen, M.J., Craddock, N., Jablensky, A. (2007). The genetic deconstruction of psychosis. *Schizophr Bull* 33, 905-911.
- 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), 49-59.
- Pan, Y-J., Hsieh, M.H., Liu, S-K. (2011). Visuospatial working memory deficits in remitted patients with bipolar disorder: Susceptibility to the effects of GABAergic agonists. *Bipolar Disord* 13(4), 365-376.
- Park, S., Holzman, P.S. (1992). Schizophrenics show spatial working memory deficits. *Arch Gen Psychiatry* 49(12), 975-982.
- Park, S., Holzman, P.S. (1993). Association of working memory deficit and eye tracking dysfunction in schizophrenia. *Schizophr Res* 11(1), 55-61.

- Park, S., Holzman, P.S., Goldman-Rakic, P.S. (1995). Spatial working memory deficits in the relatives of schizophrenic patients. *Arch Gen Psychiatry* 52(10), 821-828.
- Park, N., Juo, S.H., Cheng, R., Liu, J., Loth, J.E., Lilliston, B., Nee, J., Grunn, A., Kanyas, K., Lerer, B., Endicott, J., Gilliam, T.C., Baron, M. (2004). Linkage analysis of psychosis in bipolar pedigrees suggests novel putative loci for bipolar disorder and shared susceptibility with schizophrenia. *Molecular Psychiatry* 9(12), 1091-1099.
- Peled, A., Geva, A.B., Kremen, W.S., Blankfeld, H.M., Esfandiari, R., Nordahl, T.E. (2001). Functional connectivity and working memory in schizophrenia: An EEG study. *International J Neurosci* 106, 47-61.
- Perlstein, W.M., Carter, C.S., Noll, D.C., Cohen, J.D. (2001). Relation of prefrontal cortex dysfunction to working memory and symptoms in schizophrenia. *Am J Psychiatry* 158, 1105-1113.
- Petrides, M. (2000). The role of the mid-dorsolateral prefrontal cortex in working memory. *Exp Brain Res* 133, 44-54.
- Phillips, M.L., Travis, M.J., Fagiolini, A., Kupfer, D.J. (2008). Medication effects in neuroimaging studies of bipolar disorder. *Am J Psychiatry* 165, 313-320.
- Phillips, M.L., Vieta, E. (2007). Identifying functional neuroimaging biomarkers of bipolar disorder: Toward DSM-V. *Schizophr Bull* 33(4), 893-904.
- Pirkola, T., Tuulio-Henriksson, A., Glahn, D.C., Kieseppa, T., Haukka, J., Kaprio, J., Lonnqvist, J., Cannon, T.D. (2005). Spatial working memory function in twins with schizophrenia and bipolar disorder. *Biol Psychiatry* 58(12), 930-936.
- Pomarol-Clotet, E., Salvador, R., Sarro, S., Gomar, J., Vila, F., Martinez, A., Guerrero, A., Ortiz-Gil, J., Sans-Sansa, B., Capdevila, A., Cebamanos, J.M., McKenna, P.J. (2008). Failure

- to deactivate in the prefrontal cortex in schizophrenia: Dysfunction of the default mode network? *Psychol Med* 38, 1185-1193.
- Postle, B.R., Berger, J.S., Taich, A.M., D'Esposito, M. (2000). Activity in human frontal cortex associated with spatial working memory and saccadic behavior. *J Cogn Neurosci* 12, 2-14.
- Potash, J.B., Zandi, P.P., Willour, V.L., Lan, T.-H., Huo, Y., Avramopoulos, D., Shugart, Y.Y., MacKinnon, D.F., Simpson, S.G., McMahon, F.J., DePaulo Jr., J.R., McInnis, M.G. (2003). Suggestive linkage to chromosomal regions 13q31 and 22q12 in families with psychotic bipolar disorder. *Am J Psychiatry* 160(4), 680-686.
- Potkin, S.G., Turner, J.A., Brown, G.G., McCarthy, G., Greve, D.N., Glover, G.H., Manoach, D.S., Belger, A., Diaz, M., Wible, C.G., Ford, J.M., Mathalon, D.H., Gollub, R., Lauriello, J., O'Leary, D., van Erp, T.G.M., Toga, A.W., Preda, A., Kim, K.O. (2009). Working memory and DLPFC inefficiency in schizophrenia: The FBIRN study. *Schizophr Bull* 35(1), 19-31.
- Purcell, S.M., Wray, N.R., Stone, J.L., Visscher, P.M., O'Donovan, M.C., Sullivan, P.F., Sklar, P. (2009). Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature* 460, 748-752.
- Quraishi, S., Frangou, S. (2002). Neuropsychology of bipolar disorder: A review. *J Affect Disord* 72(3), 209-226.
- Raichle, M.E., MacLeod, A.M., Snyder, A.Z., Powers, W.J., Gusnard, D.A., Shulman, G.L. (2001). A default mode of brain function. *Proc Natl Acad Sci* 98, 676-682.
- Ragland, J.D., Gur, R.C., Glahn, D.C., Censits, D.M., Smith, R.J., Lazarev, M.G., Alavi, A., Gur, R.E. (1998). Frontotemporal cerebral blood flow change during executive and declarative

- memory tasks in schizophrenia: a positron emission tomography study. *Neuropsychology* 12(3), 399-413.
- Rajkowska, G. (2000). Postmortem studies in mood disorders indicate altered numbers of neurons and glial cells. *Biol Psychiatry* 48, 766-777.
- Ranganath, C., D'Esposito, M. (2005). Directing the mind's eye: Prefrontal, inferior, and medial temporal mechanisms for visual working memory. *Cur Opin Neurobiol* 15(2), 175-182.
- Reichenberg, A., Harvey, P.D. (2007). Neuropsychological impairments in schizophrenia: Integration of performance-based and brain imaging findings. *Psychol Bull* 133(5), 833-858.
- Reichenberg, A., Harvey, P.D., Bowie, C.R., Mojtabai, R., Rabinowitz, J., Heaton, R.K., Bromet, E. (2009). Neuropsychological function and dysfunction in schizophrenia and psychotic affective disorders. *Schizophr Bull* 35(5), 1022-1029.
- Robinson, J.L., Bearden, C.E., Monkul, E.S., Tordesillas-Gutierrez, D., Velligan, D.I., Frangou, S., Glahn, D.C. (2009). Fronto-temporal dysregulation in remitted bipolar patients: An fMRI delayed-non-match-to-sample (DNMS) sample. *Bipolar Disord* 11(4), 351-360.
- Robinson, L.J., Thompson, J.M., Gallagher, P., Goswami, U., Young, A.H., Ferrier, I.N., Moore, P.B. (2006). A meta-analysis of cognitive deficits in euthymic patients with bipolar disorder. *J Affect Disord* 93, 105-115.
- Rowe, J.B., Toni, I., Josephs, O., Frackowiak, R.S.J., Passingham, R.E. (2000). The prefrontal cortex: Response selection or maintenance within working memory? *Science* 288(5471), 1656-1660.
- Rund, B.R., Melle, I., Friis, S., Johannessen, J.O., Larsen, T.K., Midboe, L.J., Opjordsmoen, S., Simonsen, E., Vaglum, P., McGlashan, T. (2007). The course of neurocognitive

- functioning in first-episode psychosis and its relation to premorbid adjustment, duration of untreated psychosis, and relapse. *Schizophr Res* 91, 132-140.
- Rypma, B., D'Esposito, M. (1999). The roles of prefrontal brain regions in components of working memory: Effects of memory load and individual differences. *Proc Natl Acad Sci* 96(11), 6558-6563.
- Salimi-Khorshidi, G., Smith, S.M., Keltner, J.R., Wager, T.D., Nichols, T.E. (2009). Meta-analysis of neuroimaging data: a comparison of image-based and coordinate-based pooling of studies. *NeuroImage* 45(3), 810-823.
- Sambataro, F., Murty, V.P., Callicott, J.H., Tan, H-Y., Das, S., Weinberger, D.R., Mattay, V.S. (2010). Age-related alterations in default mode network: Impact on working memory performance. *Neurobiol Aging* 31(5), 839-852.
- Savitz, J.B., Solms, M., Ramesar, R.S. (2005). Neurocognitive function as an endophenotype for genetic studies of bipolar affective disorder. *Neuromolecular Med* 7, 275-286.
- Sax, K.W., Strakowski, S.M., Zimmerman, M.E., DelBello, M., Keck, P.E., Hawkins, J.M. (1999). Frontosubcortical neuroanatomy and the continuous performance test in mania. *Am J Psychiatry* 156, 139-141.
- Saykin, A.J., Gur, R.C., Gur, R.E., Mozley, P.D., Mozley, L.H., Resnick, S.M., Kester, D.B., Stafiniak, P. (1991). Neuropsychological function in schizophrenia: Selective Impairment in Memory and Learning. *Arch Gen Psychiatry* 48(7), 618-624.
- Saykin, A.J., Shtasel, D.L., Gur, R.E., Kester, D.B., Mozley, L.H., Stafiniak, P., Gur, R.C. (1994). Neuropsychological deficits in neuroleptic naïve patients with first-episode schizophrenia. *Arch Gen Psychiatry* 51(2), 124-131.

- Scheuerecker, J., Ufer, S., Zipse, M., Frodi, T., Koutsouleris, N., Zetzsche, T., Wiesmann, M., Albrecht, J., Bruckmann, H., Schmitt, G., Möller, H.J., Meisenzahi, E.M. (2008). Cerebral changes and cognitive dysfunctions in medication-free schizophrenia – An fMRI study. *Psychiatry Res* 42, 469-476.
- Schlösser, R., Gesierich, T., Kaufmann, B., Vuvurevic, G., Hunsche, S., Gawehn, J., Stoeter, P. (2003). Altered effective connectivity during working memory performance in schizophrenia: A study with fMRI and structural equation modeling. *NeuroImage* 19(3), 751-763.
- Schretlen, D.J., Cascella, N.G., Meyer, S.M., Kingery, L.R., Testa, S.M., Munro, C.A., Pulver, A.E., Rivkin, P., Rao, V.A., Diaz-Asper, C.M., Dickerson, F.B., Yolken, R.H., Perlson, G.D. (2007). Neuropsychological functioning in bipolar disorder and schizophrenia. *Biol Psychiatry* 62(2), 179-186.
- Schulze, T.G., Hedeker, D., Zandi, P., Rietschel, M., McMahon, F.J. (2006). What is familial about familial bipolar disorder? Resemblance among relatives across a broad spectrum of phenotypic characteristics. *Arch Gen Psychiatry* 63(12), 1368-1376.
- Schurhoff, F., Szoke, A., Meary, A., Bellivier, F., Rouillon, F., Pauls, D., Leboyer, M. (2003). Familial aggregation of delusional proneness in schizophrenia and bipolar pedigrees. *Am J Psychiatry* 160, 1313-1319.
- Seidman, L.J., Kremen, W.S., Koren, D., Faraone, S.V., Goldstein, J.M., Tsuang, M.T. (2002). A comparative profile analysis of neuropsychological functioning in patients with schizophrenia and bipolar psychoses. *Schizophr Res* 53, 31-44.
- Seidman, L.J., Yurgelun-Todd, D., Kremen, W.S., Woods, B.T., Goldstein, J.M., Faraone, S.V., Tsuang, M.T. (1994). Relationship of prefrontal and temporal lobe MRI measures to

- neuropsychological performance in chronic schizophrenia. *Biol Psychiatry* 35(4), 235-246.
- Selemon, L.D., Rajkowska, G., Goldman-Rakic, P.S. (1995). Abnormally high neuronal density in the schizophrenic cortex: A morphometric analysis of prefrontal area 9 and occipital area 17. *Arch Gen Psychiatry* 53(10), 805-820.
- Selemon, L.D., Rajkowska, G., Goldman-Rakic, P.S. (1998). Elevated neuronal density in prefrontal area 46 in brains from schizophrenic patients: Applications of a three-dimensional, stereologic counting method. *J Compar Neurol* 392, 402-412.
- Selvaraj, S., Arnone, D., Job, D., Stanfield, A., Farrow, T.F.D., Nugent, A.C., Scherk, H., Gruber, O., Chen, X., Sachdev, P.S., Dickstein, D.P., Malhi, G.S., Ha, T.H., Phillips, M.L., McIntosh, A.M. (2012). Grey matter differences in bipolar disorder: A meta-analysis of voxel-based morphometry studies. *Bipolar Disord* 14, 135-145.
- Silver, H., Feldman, P., Bilker, W., Gur, R.C. (2003). Working memory deficit as a core neuropsychological dysfunction in schizophrenia. *Am J Psychiatry* 160(10), 1809-1816.
- Smith, M.J., Barch, D.M., Csernansky, J.G. (2009). Bridging the gap between schizophrenia and psychotic mood disorders: Relating neurocognitive deficits to psychopathology. *Schizophr Res* 107, 69-75.
- Smith, E.E., Jonides, J., Marshuetz, C. Koeppel, R.A. (1998). Components of verbal working memory: evidence from neuroimaging. *Proc Natl Acad Sci* 95(3), 876-82.
- Snitz, B.E., MacDonald, A.W. III, Carter, C.S. (2006). Cognitive deficits in unaffected first-degree relatives of schizophrenia patients: A meta-analytic review of putative endophenotypes. *Schizophr Bull* 32(1), 179-194.

- Srimal, R., Curtis, C.E. (2008). Persistent neural activity during the maintenance of spatial position in working memory. *NeuroImage* 39, 455-468.
- Stone, M., Gabrieli, J.D.E., Stebbins, G.T., Sullivan, E.V. (1998). Working and strategic memory deficits in schizophrenia. *Neuropsychology* 12(2), 278-288.
- Strakowski, S.M., Delbello, M.P., Adler, C.M. (2005). The functional neuroanatomy of bipolar disorder: A review of neuroimaging findings. *Mol Psychiatry* 10, 105-116.
- Sullivan, P.F., Kendler, K.S., Neale, M.C. (2003). Schizophrenia as a complex trait: Evidence from a meta-analysis of twin studies. *Arch Gen Psychiatry* 60(12), 1187-1192.
- Sweeney, J.A., Kmiec, J.A., Kupfer, D.J. (2000). Neuropsychological impairments in bipolar and unipolar mood disorders on the CANTAB neurocognitive battery. *Biol Psychiatry* 48, 674-685.
- Takeda, K., Funahashi, S. (2002). Prefrontal task-related activity representing visual cue location or saccade direction in spatial working memory tasks. *J Neurophysiology* 87(1), 567-588.
- Thermenos, H.W., Goldstein, J.M., Milanovic, S.M., Whitfield-Gabrieli, S., Makris, N., LaViolette, P., Koch, J.K., Faraone, S.V., Tsuang, M.T., Buka, S.L., Seidman, L.J. (2010). An fMRI study of working memory in persons with bipolar disorder or at genetic risk for bipolar disorder. *Am J Med Genet Part B* 153B, 120-131.
- Thermenos, H.W., Makris, N., Whitfield-Gabrieli, S., Brown, A.B., Giuliano, A.J., Lee, E.H., Faraone, S.V., Tsuang, M.T., Seidman, L.J. (2011). A functional MRI study of working memory in adolescents and young adults at genetic risk for bipolar disorder: Preliminary findings. *Bipolar Disord* 13(3), 272-286.
- Torres, I.J., Boudreau, V.G., Yatham, L.N. (2007). Neuropsychological functioning in euthymic bipolar disorder: A meta-analysis. *Acta Psychiatr Scand* 116, 17-26.

- Torres, I.J., DeFreitas, C.M., DeFreitas, V.G., Bond, D.J., Kunz, M., Honer, W.G., Lam, R.W., Yatham, L.N. (2011). Relationship between cognitive functioning and 6-month clinical and functional outcome in patients with first manic episode bipolar I disorder. *Psychol Med* 41, 971-982.
- 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 Res: Neuroimaging* 182(1), 22-29.
- Tsuang, M.T., Stone, W.S., Faraone, S.V. (2000). Toward reformulating the diagnosis of schizophrenia. *Am J Psychiatry* 157(7), 1041-1050.
- Tsuang, M.T., Winokur, G., Crowe, R.R. (1980). Morbidity risks of schizophrenia and affective disorders among first degree relatives of patients with schizophrenia, mania, depression, and surgical conditions. *Br J Psychiatry* 137, 497-504.
- Tuulio-Henriksson, A., Arajärvi, R., Partonen, T., Haukka, J., Varilo, M., Schreck, M., Cannon, T.D., Lönnqvist, J. (2003). Familial loading associates with impairment in visual span among healthy siblings of schizophrenia patients. *Biol Psychiatry* 54(6), 623-628.
- Tuulio-Henriksson, A., Haukka, J., Partonen, T., Varilo, T., Paunio, T., Ekelund, J., Cannon, T.D., Meyer, J.M., Lönnqvist, J. (2002). Heritability and number of quantitative trait loci of neurocognitive functions in families with schizophrenia. *Am J Med Genet* 114, 483-490.
- Toulopoulou, T., Picchioni, M.M., Ribchester, T., Hua Hull, M., Murray, R.M. (2005). Neurocognitive deviations in twins with schizophrenia and their unaffected co-twins. *Schizophr Bull* 31, 279.
- Ungerleider, L.G., Courtney, S.M., Haxby, J.V. (1998). A neural system for human visual working memory. *Proc Natl Acad Sci* 95, 883-890.

- Valles, V., Van Os, J., Guillamat, R., Gutierrez, B., Campillo, M. Gento, P., Fananas, L. (2000). Increased morbid risk for schizophrenia in families of in-patients with bipolar illness. *Schizophr Res* 42(2), 83-90.
- Weissman, D.H., Roberts, K.C., Visscher, K.M., Woldorff, M.G. (2006). The neural basis of momentary lapses in attention. *Nat Neurosci* 9, 971-978.
- Whitfield-Gabrieli, S., Thermenos, H.W., Milanovic, S., Tsuang, M.T., Faraone, S.V., McCarley, R.W., Shenton, M.E., Green, A.I., Nieto-Castanon, A., LaViolette, P., Wojcik, J., Gabrieli, J.D.E., Seidman, L.J. (2009). Hyperactivity and hyperconnectivity of the default network in schizophrenia and in first-degree relatives of persons with schizophrenia. *Proc Natl Acad Sci* 106(4), 1279-1284.
- Williams, H.J. Craddock, N., Russo, G., Hamshere, M.L., Moskvina, V., Dwyer, S., Smith, R.L., Green, E., Grozeva, D., Holmans, P., Owen, M.J., O'Donovan, M.C. (2011). Most genome-wide significant susceptibility loci for schizophrenia and bipolar disorder reported to date cross-traditional diagnostic boundaries. *Hum Mol Genet* 20(2), 387-391.
- Williams, H.J., Norton, N., Dwyer, S., Moskvina, V., Nikolov, I., Carroll, L., Georgieva, L., Williams, N.M., Morris, D.W., Quinn, E.M. *et al.* (2011). Fine mapping of ZNF804A and genome-wide significant evidence for its involvement in schizophrenia and bipolar disorder. *Mol Psychiatry* 16, 429-441.
- Young, R.C., Biggs, J.T., Ziegler, V.E., Meyer, D.A. (1978). A rating scale for mania: reliability, validity and sensitivity. *British J Psychiatr* 133, 429-435.
- Zala, T., Joyce, C., Szöke, A., Schürhoff, F., Pillon, B. Komano, O., Perez-Diaz, F., Bellivier, F., Alter, C., Dubois, B., Rouillon, F., Houde, O., Leboyer, M. (2007). Executive

dysfunctions as potential markers of familial vulnerability to bipolar disorder and schizophrenia. *Psychiatry Res* 121(3), 207-217.

Zammit, S., Allebeck, P., David, A.S., Dalman, C., Hemmingsson, T., Lundberg, I., Lewis, G. (2004). A longitudinal study of premorbid IQ score and risk of developing schizophrenia, bipolar disorder, severe depression, and other nonaffective psychoses. *Arch Gen Psychiatry* 61, 354-360.

Zubieta, J-K., Huguelet, P., O'Neil, R.L., Giordani, B.J. (2001). Cognitive function in euthymic bipolar I disorder. *Psychiatry Res* 102(1), 9-20.