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Title: Connectome Signatures of Neurocognitive Abnormalities in Euthymic Bipolar I Disorder

Article Type: Original Article

Keywords: Bipolar Disorder; connectome; cognition; MRI; Go/NoGo task, response inhibition

Abstract: Objectives: Connectomics have allowed researchers for the first time to study integrative patterns of neural connectivity in humans. Yet, it is unclear how connectomics may elucidate structure-function relationships in bipolar I disorder (BPI). Expanding on our previous structural connectome study, here we used an overlapping sample with additional psychometric and fMRI data to relate structural connectome properties to both fMRI signals and cognitive performance. Methods: 42 subjects completed a neuropsychological (NP) battery covering domains of processing speed, verbal memory, working memory, and cognitive flexibility. 32 subjects also had fMRI data performing a Go/NoGo task. Results: Bipolar participants had lower NP performance across all domains, but only working memory reached statistical significance. In BPI participants, processing speed was significantly associated with both white matter integrity (WMI) in the corpus callosum and interhemispheric network integration. Mediation models further revealed that the relationship between interhemispheric integration and processing speed was mediated by WMI, and processing speed mediated the relationship between WMI and working memory. Bipolar subjects had significantly decreased BA47 activation during NoGo vs. Go. Significant predictors of BA47 fMRI activations during the Go/NoGo task were its nodal path length (left) and its nodal clustering coefficient (right). Conclusions: This study suggests that structural connectome changes underlie abnormalities in fMRI activation and cognitive performance in euthymic BPI subjects. Results support that BA47 structural connectome changes may be a trait marker for BPI. Future studies are needed to determine if these "connectome signatures" may also confer a biological risk and/or serve as predictors of relapse.

***Cover Letter**

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RE: JPR5764 – "Connectome Signatures of Neurocognitive Abnormalities in Euthymic Bipolar I Disorder"

Dear Dr. Schatzberg,

We thank you for the opportunity to revise and re-submit the above-referenced manuscript. We would like to thank the reviewers for their very helpful comments and insightful recommendations. We have made the suggested changes in this revision. We incorporated as many additional comments into the main manuscript as possible but could not comprehensively include all suggested additions due to word limits. Thanks to their expert opinions, we believe that this paper is now much improved, and we hope it will be of substantial interest to researchers in the fields of both computational neuroimaging and bipolar disorder if accepted.

In the following, please find our point-by-point response to the reviewers' comments (in **bold**) and the corresponding changes (highlighted in yellow) in the revised manuscript.

We look forward to your positive feedback regarding this revised manuscript.

Sincerely,

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***Response to Reviewers**

Reviewer #1:

1. The sample size is small and the number of analyses is fairly large, including between group comparisons of multiple neurocognitive domains, fMRI (whole brain and with small volume correction), structural connectomics, as well as correlations between these variables. In addition, there are different numbers of subjects in the total sample, the NP and fMRI sample, which is the smallest (16 versus 16). I wonder whether the analytical plan is not overly ambitious considering the sample size. This might lead to both false negative as well as false positive findings.

We have clarified the limitations of the small sample size in the Discussion section, emphasizing the probability of false negative and false positive findings.

"First, our findings should be interpreted in the context of a relatively small sample size as some subjects had missing neuropsychological measurements or fMRI data, and as a result may have decreased our power to detect more subtle group differences or correlations contributing to possible false negative findings."

2. The bipolar and control groups differed in multiple relevant variables. Aside from the diagnosis, the groups differed in exposure to medications (greater in the bipolar group) and education (lower in the bipolar group). In addition, whereas lifetime history of substance abuse was an exclusion criterion in the control group, bipolar subjects with a past history of alcohol or drug use disorder could participate if they were sober for >3 months. These between group differences make it difficult to interpret the results as an effect of bipolar diagnosis.

The reviewer correctly points out the difference between control and bipolar groups. All group difference analyses were controlled for years of education. Differences in medication load are inherent in comparing a treated clinical group and a non-clinical comparison group and this is mentioned as a limitation to the study. With regards to substance abuse history, substance abuse is a very common comorbidity with bipolar disorder with lifetime prevalence rates up to 60% (Cassidy et al, Bipolar Disorders 2001). To institute the same criterion for the bipolar group would have significantly limited our sample. Nonetheless, we appreciate the reviewers' points and we have incorporated them as limitations of the study as highlighted below:

"Third, limitations pertaining to our sample characteristics should be acknowledged. While we carefully screened all participants with a diagnostic interview and operationalized euthymic mood at time of scan, our bipolar participants were predominantly medicated and our control participants were not screened for psychiatric illnesses in their first-degree relatives. While medications reportedly have limited impact on fMRI and DTI findings in bipolar disorder (Hafeman et al. , 2012), future research should examine whether those on medication have different modularity than non-medicated bipolar subjects. In addition, a substantial number of bipolar subjects had a history of (but not current) substance use disorders so the impact of this common comorbidity on our results cannot be ruled out (Cassidy et al. , 2001)."

3. The authors performed correction for multiple comparisons in their neuroimaging analyses. However, they also ran a number of other between group comparisons in addition to calculating many correlation coefficients. It would be important to specify the number of hypotheses tested and to correct for this number.

We thank the reviewer for bringing up this important point. We have added multiple comparison correction of the correlational analyses using the false discovery rate (for all measures) and we now report q-values in addition to p-values. Additionally, we have noted that the r-values represent medium-to-large effect sizes for all of our findings, providing a complementary way to assess the significance of the results.

4. The neurocognitive battery does not tie well with the introduction or the fMRI analyses. In addition, this study did not find differences between the groups in some of the neurocognitive domains/tests, which have consistently been reported as abnormal in BD. This may be a result of the small sample size, as mentioned in item 1.

We agree with the sample size issue as addressed in Item 1. With regards to the neurocognitive battery, we have information in the Introduction about the domains in the cognitive battery to relate it to the fMRI analysis. For example, the Introduction refers to previous studies that have identified cognitive deficits in the domains of executive function and verbal memory which are assessed by the neurocognitive battery. In addition, response inhibition, assessed by the Go-NoGo fMRI task, is also related to the Stroop task which is included in the neurocognitive battery.

5. The discussion would need to be toned down. For example, structural as well as functional changes in the BA47 have been reported not only in bipolar, but also in many other neuropsychiatric disorders. In absence of patients with other diagnoses, some of the speculations about this being an imaging marker for bipolarity (page 15, paragraph 2) seem a little too strong.

We thank the reviewer for this point. As a result, we have toned down the discussion to be more in line with the results of the study. As an example, we have edited the sentence cited by the reviewer:

*"Taken these findings as a whole, we thus hypothesize that structural connectome properties in BA47 may potentially serve as an imaging marker for neurocognitive abnormalities associated with mood disorders as supported by: a) structure connectome abnormalities are predictors for functional activation and neurocognitive deficits seen in BPI, b) there is a negative association between functional activation and the number of prior manic episodes (Pompei, Jogia, 2011), and c) other studies support BA47 hypo-activation as a trait marker of bipolarity (Altshuler, Bookheimer, 2005, Hajek, Alda, 2013a).***"**

Reviewer #2:

1. Abstract: Please add a sentence highlighting the take home message of this paper and the relevance of the current findings in terms of future directions. The authors should refer to DTI prior to mentioning FA, and explain acronyms such as FA before using this term.

We have adjusted the language to remove acronyms and used the more descriptive term "white matter integrity". A statement highlighting the take home message and relevance for future directions is highlighted in the updated abstract reprinted below:

"Abstract

Objectives: *Connectomics have allowed researchers for the first time to study integrative patterns of neural connectivity in humans. Yet, it is unclear how connectomics may elucidate structure-function relationships in bipolar I disorder (BPI). Expanding on our previous structural connectome study, here we used an overlapping sample with additional psychometric and fMRI data to relate structural connectome properties to both fMRI signals and cognitive performance.* ***Methods:*** *42 subjects completed a neuropsychological (NP) battery covering domains of processing speed, verbal memory, working memory, and cognitive flexibility. 32 subjects also had fMRI data performing a Go-NoGo task.* ***Results:*** *Bipolar participants had lower NP performance across all domains, but only working memory reached statistical significance. In BPI participants, processing speed was significantly associated with both white matter integrity (WMI) in the corpus callosum and interhemispheric network integration. Mediation models further revealed that the relationship between interhemispheric integration and processing speed was mediated by WMI, and processing speed mediated the relationship between WMI and working memory. Bipolar subjects had significantly decreased BA47 fMRI activation during NoGo vs. Go. Significant predictors of BA47 activations during the Go-NoGo task were its nodal path length (left) and its nodal clustering coefficient (right).* ***Conclusions:*** *This study suggests that structural connectome changes underlie abnormalities in fMRI activation and cognitive performance in euthymic BPI subjects. Results support that BA47 structural connectome changes may be a trait marker for BPI. Future studies are needed to determine if these "connectome signatures" may also confer a biological risk and/or serve as predictors of relapse."*

2. Introduction: Could the authors please provide a summary of their previous findings "Leow et al. 2013" and provide some context in terms of relevance of the findings and why is it important merging these measures?

We have expanded the section in the Introduction summarizing the results of our previous study and linking it to the goals of the present study as reprinted below:

"In the first published connectome study in euthymic BPI, our group demonstrated impairments in white matter integrity in the corpus callosum and reduced interhemispheric brain network efficiency (Leow et al. , 2013). Furthermore, using a novel in-house technique called PLACE (path length associated community estimation), we have shown that brain modular structures differ between euthymic BPI and healthy control subjects, especially in default mode network (DMN) regions (Gadelkarim et al. , 2013). While these findings were associated with clinical characteristics such as duration of illness and number of mood episodes, it is unclear whether

these structural connectome abnormalities are associated with cognitive differences and functional connectivity in bipolar disorder."

3. Methodology:

a. Connectome analyses and words such as "hemispherical integration" or "nodal integration" should be described or at least explained in the introduction to help the unfamiliar reader understand why such analyses are important.

b. In the discussion, the authors could also provide a better interpretation of what reduced nodal length or hemispherical integration really means in terms of neural, cognitive and global functioning.

We have provided more information in the Introduction to explain network efficiency and how that relates to brain network integration. In addition, we have provided additional references addressing the relationship of interhemispheric integration to functioning as outlined in the passages below:

Introduction:

"Connectomics have recently emerged as an exciting area in brain research. Borrowing techniques from graph theory in mathematics, connectomics examine the brain as a "graph" or network and allow us to gain insight into the collective and integrative patterns of all the connections in the brain (instead of specific connections linking few select regions of interest). Specifically, data analysis using connectomics may assess network efficiency, clustering, and modularity. It is thought that highly efficient networks require shorter graph distances or "path lengths" for different regions to communicate. These measures of efficiencies can apply to whole brain (global efficiency or characteristic path length) or specific brain regions (nodal efficiency or path length). Network efficiency can be enhanced by greater network integration, whereby distributed information is easily combined throughout the brain with strategically placed connections (Rubinov and Sporns, 2010)."

Discussion:

"Post-hoc mediation analyses further revealed that the relationship between interhemispheric integration/FA in the corpus callosum and working memory is mediated by processing speed. This finding is consistent with previous reports in the literature. Almost two decades ago, Pettigrew and Miller identified an abnormal "sticky" interhemispheric switch in bipolar patients (Pettigrew and Miller, 1998). More recently, a large multicenter diffusion imaging study revealed interhemispheric disconnectivity in bipolar patients, particularly in those with psychotic symptoms (Sarrazin et al. , 2014). In addition, white matter integrity has been associated with processing speed in a number of studies in bipolar disorder (Bearden et al. , 2011) and in late-life depression (Mettenburg et al. , 2012, Shimony et al. , 2009). The present study adds to this growing literature by providing a multimodal approach linking structural disconnectivity to

cognitive deficits in euthymic bipolar disorder."

"The present study adds to the literature by linking structure connectome to functional activation in this region, demonstrating that the more locally segregated and/or the less globally integrated BA47 is, the less activated it is during response inhibition, and are abnormal in euthymic bipolar disorder. As stronger local segregation/clustering and less global integration indicate less efficient information transfer, this may explain the observed longer reaction times for both the Go and NoGo conditions for our bipolar subjects."

c. Could the authors please describe their DTI data collection and measurements to a greater extent than done in this paper? Also why did they use FA? What about other parameters?

We have provided more detailed information about the DTI data collection in our Supplemental Materials. We used FA as this was the primary measure employed in our previous analysis. To reduce the number of analyses (see Reviewer #1, point #1), we did not look at other DTI-derived parameters but used the most commonly reported measure of white matter of integrity FA .

4. ROI: Could the authors explain the selection of the brain region? Why only BA47? Why not ACC, for instance (given the choice of the task)? This region has a special role in monitoring and is involved in both reward and mood regulation, which are also impaired in BD.

Given prior work from our group (Altshuler et al., 2005; Vizueta et al., 2012, Foland et al., 2008) as well as meta-analytic fMRI studies (Chen et al. 2011; Hajek et al. 2013) reporting a reduction in activation in inferior frontal gyrus (corresponding to BA47) in bipolar patients across all mood states, we hypothesized that reduced BA47 activation may be a trait marker of bipolar disorder. In the current study, we selected the Go-NoGo response inhibition fMRI paradigm as we have previously shown that it robustly activates bilateral BA47 in both healthy controls and the bipolar population (Townsend et al., 2012; Penfold et al., 2014), and thereby would enable us to test the hypothesis that our sample of bipolar I euthymic subjects would demonstrate significantly reduced BA47 activation compared to matched controls. While the reviewer is correct that the Go-NoGo paradigm activates additional regions other than BA47 including the ACC and striatal regions, the ACC was not a formal hypothesis in the present study. Given our small sample size and our decision to conduct only a priori ROI analyses, we therefore did not include an ROI analysis of the ACC. However, to be consistent with previous Go-NoGo work, we present the results of our whole-brain between-group analyses as shown in Figure 2. Given the reviewer's query of an ACC ROI analysis, we have reread the recent meta-analysis of fMRI activations in 30 studies investigating response inhibition in bipolar disorder (Hajek et al., 2013), which did not find a functional abnormality in the ACC across bipolar mood states nor in bipolar euthymia alone. While the results of this meta-analysis support an a priori ROI analysis of BA47, future research utilizing larger samples, however, should investigate functional and structural abnormalities in other regions in addition to the BA47.

5. Results: I would recommend that the authors present their findings based on the following structure:

a. Cognitive performance overall;

b. Structural findings;

c. Functional findings (subsection "functional activation" and "behavioral findings");

d. Connectome analyses;

e. Further RTs and/or accuracy levels for all neuropsychological tasks and the fmri task should be shown in a table; p-values should be included.

We thank the reviewer for this suggestion and we have rearranged the Results section accordingly. We also now present the additional reaction time/performance data to Table 2.

6. Discussion:

a. In the discussion the authors are encouraged to discuss what a reduced FA would mean based on their theoretical model. Further, they state that "working memory and FA in the genu were mediated by processing speed". Since the working memory tasks included in this paper were time based isn't this result almost intuitive? Would this result remain the same if working memory tasks had not been time-based?

We appreciate the reviewer's comment but would like to clarify the nature of the working memory domain. While some of the tests were indeed timed tests (i.e. processing speed and cognitive flexibility), the working memory domain performance was not based on time, but based on the total score obtained on the task. Because of this, we would argue our results showing that processing speed mediates the relationship between working memory and FA (representing white matter integrity) are novel and important findings supporting the take-home message that structural connectivity abnormalities underlie neurocognitive deficits in euthymic bipolar patients. To address the reviewer's comment, we have clarified in the Methods section that the working memory domain is based on total score, not time to complete.

b. Also, how do the current findings differ from those observed in older populations? Could the authors comment on the model of accelerated aging in relation to BD? I am mentioning this given that processing speed is bound to worsen over time. Could the authors be observing in BD a pattern of results similar to that observed in early dementia?

We thank the reviewer bringing up a very intriguing notion that processing speed deficits (especially related to white matter integrity) may represent a pattern of accelerated aging. Impaired processing speed has been reported in late-life bipolar disorder but not in association with significant differences (compared to controls) or changes (over time) in FA (Delaloye et al, IJGP 2011). However, it is possible that a pattern of accelerated aging exists in bipolar disorder and this is an area in need of further evaluation.

c. Additional comments could be made in the discussion in terms of:
i. Will the reported abnormalities change over time? In particular, do the authors think that BD-related neuropsychological impairment worsens over time, and if so why?

It is unclear whether the cognitive abnormalities presented in this cross-sectional study would change over time. There have been some longitudinal studies suggesting that neuropsychological deficits in bipolar disorder are stable (Strejilevich et al, J. Affect. Disord. 2015). One recent study demonstrated that newly diagnosed bipolar patients show an increase in cognitive performance over a 12-month period (Torres et al, Bipolar Disord 2014). The nature of the longitudinal course of cognitive dysfunction in bipolar disorder is likely influenced by a number of factors such as number of previous mood episodes, medication load, age of onset, etc. Due to word limits, we are not able to add this to the Discussion section.

ii. How/can these findings be generalized to BD II or other mood disorder populations?

While it is beyond of the scope of the present study to comment specifically on other mood disorders, we have cited studies in the Discussion that have found similar results in other mood disorder populations in the selected passages below:

"White matter integrity has been associated with processing speed in a number of studies in bipolar disorder (Bearden et al. , 2011) and in late-life depression (Mettenburg et al. , 2012, Shimony et al. , 2009). "

"Taken these findings as a whole, we thus hypothesize that structural connectome properties in BA47 may potentially serve as an imaging marker for neurocognitive abnormalities associated with mood disorders as supported by: a) structure connectome abnormalities are predictors for functional activation and neurocognitive deficits seen in BPI, b) there is a negative association between functional activation and the number of prior manic episodes (Pompei, Jogia, 2011), and c) other studies support BA47 hypo-activation as a trait marker of bipolarity (Altshuler, Bookheimer, 2005, Hajek, Alda, 2013a). Such a hypothesis is most relevant when one considers that there have been virtually no imaging or neuropsychological predictors of recurrence in bipolar disorder, except for clinical presentations themselves (e.g., a review article concluded that stressful events, higher numbers of prior episodes, shorter between-episode intervals, and persistence of affective symptoms predict relapse) (Altman et al. , 2006). Additionally, there are also no practical prospective predictors for the nature of the next acute mood episode (mania vs depression). Such major limitations not only exist in our understanding of bipolar disorder, but also in mood disorders in general (to address such limitations in MDD, e.g., the PReDICT trial is recently launched to identify predictors of treatment response and future recurrence) (Dunlop et al. , 2012)."

iii. The authors use heterogeneous techniques to measure neurocognitive functioning. While cognitive testing is a direct observation of brain function, one could say that fMRI and DTI measures are indirect measures of neural functioning. For instance, fMRI measures could be affected by hemodynamic changes associated with medical comorbidities (highly common in BD) and DTI may be affected by differing levels of water in the brain. Could the authors comment on these potential confounding effects?

The reviewer is correct in stating that fMRI and DTI are indirect measures of neural function as compared to more direct observation of brain function employed in cognitive testing. The reviewer is also correct in pointing out that medical comorbidities can impact the neuroimaging modalities employed in our study. However, these same medical co-morbidities can also affect the more direct measures obtained via neuropsychological testing in the same way. For example, cerebrovascular risk factors have been shown to have a detrimental effect on FA values as well as cognitive domains like processing speed (Shimony et al, Biol. Psych 2009; Segura et al, BMC Neurol. 2010).

iv. Could the authors explain how changes in BA 47 would affect the cortico-limbic functioning? How would the current findings explain mood and behavioral abnormalities observed in BD?

BA47 has direct projections to limbic areas via the uncinate fasciculus (Steffens et al, 2011 PLOS One). While the focus of the present study focused on the cognitive implications of abnormal BA47 function, we cite a number of studies associated with clinical features of BD in the Discussion section:

"A large meta-analysis study also supports right BA47 hypo-activation as a trait marker in bipolarity (Hajek, Alda, 2013a). Furthermore, it has been recently argued that structural changes in right BA47 reflect biological risk for bipolarity (Hajek et al. , 2013c), while another study reported a negative association between BA47 functional activation and the number of prior manic episodes (Pompei et al. , 2011)."

7. Overall:

a. Page 12: The authors refer to a "conditional process model." Could they please describe this approach in the methods and explain why they selected it?

The conditional process model is described in more detail in the Methods section reprinted below:

"To examine the relationship between significant variables of interest in a post-hoc mediation analyses, we used the conditional process modelling tool PROCESS (Hayes, 2012). Conditional process modeling is the analytical integration of mediation and moderation analysis and provides an efficient way to assess direct and indirect effects in a variety of models. "

b. fMRI analyses: Were reaction times during the go/no go task during the fMRI investigation included as a covariate in the fMRI analyses?

Reaction times during the go/no go fMRI task were not included as a covariate in the original version of the manuscript. However, in this revision, as stated on page 8, to examine group differences (control > bipolar, bipolar>control) in brain activation, adjusted for overall reaction time (RT) mean, we now additionally ran the model including overall RT as a covariate. The results are shown in Supplementary Figure 2 and are summarized in the text on page 12. The significant reduction in right BA47 in bipolar subjects relative to controls remained significant after adjusting for overall reaction time (RT) in the whole-brain analysis (panel A of Supplementary Figure 2). Additionally, activation in BA47 did not demonstrate neither a positive RT effect nor a negative RT effect in the whole-brain analysis (panel B of Supplementary Figure 2).

c. Page 14: I would recommend that the authors clarify/rewrite what they mean by "consistent with known…speed." It is a vague and somewhat confusing statement.

We have removed this statement from the manuscript.

d. Illustrations, Table 1: The authors report results for the NP and BD sample and HC. Are the HC samples reported here age/gender matched counterparts? Please clarify.

The NP sample is a subset of healthy control (HC) and bipolar subjects with neuropsychological data. The healthy controls are age and gender matched in each sample subset.

Connectome Signatures of Neurocognitive Abnormalities in Euthymic Bipolar I Disorder

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Abstract

Objectives: Connectomics have allowed researchers for the first time to study integrative patterns of neural connectivity in humans. Yet, it is unclear how connectomics may elucidate structure-function relationships in bipolar I disorder (BPI). Expanding on our previous structural connectome study, here we used an overlapping sample with additional psychometric and fMRI data to relate structural connectome properties to both fMRI signals and cognitive performance. **Methods:** 42 subjects completed a neuropsychological (NP) battery covering domains of processing speed, verbal memory, working memory, and cognitive flexibility. 32 subjects also had fMRI data performing a Go/NoGo task. **Results:** Bipolar participants had lower NP performance across all domains, but only working memory reached statistical significance. In BPI participants, processing speed was significantly associated with both white matter integrity (WMI) in the corpus callosum and interhemispheric network integration. Mediation models further revealed that the relationship between interhemispheric integration and processing speed was mediated by WMI, and processing speed mediated the relationship between WMI and working memory. Bipolar subjects had significantly decreased BA47 activation during NoGo vs. Go. Significant predictors of BA47 fMRI activations during the Go/NoGo task were its nodal path length (left) and its nodal clustering coefficient (right). **Conclusions:** This study suggests that structural connectome changes underlie abnormalities in fMRI activation and cognitive performance in euthymic BPI subjects. Results support that BA47 structural connectome changes may be a trait marker for BPI. Future studies are needed to determine if these “connectome signatures” may also confer a biological risk and/or serve as predictors of relapse.

Keywords: Bipolar Disorder, connectome, cognition, MRI, Go/NoGo task, response inhibition

Introduction

There has been increasing evidence of impaired cognitive function associated with bipolar I disorder (BPI) even in the context of stable, euthymic mood indicative of trait dysfunction. Early studies by our group (Altshuler et al. , 2004) and others (Goldberg and Chengappa, 2009, Martínez-Arán et al. , 2004) have demonstrated specific neurocognitive deficits in the executive and verbal memory domains in BPI. However, recent meta-analyses in euthymic bipolar patients have shown that cognitive impairments with medium-to-large effect sizes exist across all cognitive domains examined with the exception of intellectual/verbal ability (Lee et al. , 2014, Mann-Wrobel et al. , 2011, Torres et al. , 2007).

Functional neuroanatomical correlates have been suggested to underlie the persistent cognitive dysfunction. For example, functional magnetic resonance imaging (fMRI) studies of euthymic bipolar patients reveal aberrant patterns of activation in the ventral prefrontal cortex while performing the Stroop (Blumberg et al. , 2003, Strakowski et al. , 2005) and GoNo response inhibition task (Hajek et al. , 2013a, Townsend et al. , 2012). Abnormal activation patterns in the insular and cingulate cortices have also been observed in association with poor performance on tasks that activate attention networks (Sepede et al. , 2012, Strakowski et al. , 2004). In a large meta-analysis encompassing over 600 bipolar patients, right inferior frontal gyrus hypoactivation, congruent with a trait marker of bipolar disorder, was the most common abnormal activation pattern associated with response inhibition tasks (Hajek, Alda, 2013a).

While many studies have assessed relationships of regional gray matter volumes with neuropsychiatric function (Kozicky et al. , 2013, Zimmerman et al. , 2006) and few recent studies have correlated executive dysfunction with white matter integrity abnormalities in select frontal-subcortical circuits using diffusion tensor imaging (DTI)(Linke et al. , 2013, Oertel-Knochel et al. , 2014), there have been very few studies systematically relating white matter connectivity alterations to cognitive dysfunction in BPI.

Connectomics have recently emerged as an exciting area in brain research. Borrowing techniques from graph theory in mathematics, connectomics examine the brain as a "graph" or network and allow us to gain insight into the collective and integrative patterns of all the connections in the brain (instead of specific connections linking few select regions of interest). Specifically, data analysis using connectomics may assess network efficiency, clustering, and modularity. It is thought that highly efficient networks require shorter graph distances or "path lengths" for different regions to communicate. These measures of efficiencies can apply to whole brain (global efficiency or characteristic path length) or specific brain regions (nodal efficiency or path length). Network efficiency can be enhanced by greater network integration, whereby distributed information is easily combined throughout the brain with strategically placed connections (Rubinov and Sporns, 2010). Network clustering refers to the degree to which nodes in a graph tend to cluster together. Modularity describes how the brain is organized into distinct modules either based on functional characteristics (i.e. the salience network) or structural features (brain regions linked by white matter fiber

tracts). In the first published connectome study in euthymic BPI, our group demonstrated impairments in white matter integrity in the corpus callosum and reduced interhemispheric brain network efficiency (Leow et al. , 2013). Furthermore, using a novel in-house technique called PLACE (path length associated community estimation), we have shown that brain modular structures differ between euthymic BPI and healthy control subjects, especially in default mode network (DMN) regions (Gadelkarim et al. , 2013). While these findings were associated with clinical characteristics such as duration of illness and number of mood episodes, it is unclear whether these structural connectome abnormalities are associated with cognitive differences and functional connectivity in bipolar disorder.

The purpose of the present study was to examine whether white matter integrity and structural connectome properties in euthymic BPI subjects relate to their neurocognitive profiles or abnormal fMRI activation patterns in the ventrolateral prefrontal cortex (BA47) during executive function tasks. We hypothesized that cognitive performance and patterns of fMRI activation would be significantly correlated with (and predicted by) white matter integrity measured using DTI and/or connectome properties in the ventrolateral prefrontal cortex. Specifically, we expected to see better cognitive performance associated with higher fractional anisotropy (FA; a general DTI-derived measure of white matter integrity), greater network efficiency, and more consistent modularity.

Materials and Methods

Participants

Participants provided written informed consent in accordance with the Institutional Review Board at the University of California, Los Angeles (UCLA). Subjects with Bipolar I Disorder, currently euthymic, were recruited through the UCLA Mood Disorders Clinic and through local advertising. Control subjects were recruited by advertisement in local newspapers and campus flyers.

The total sample (N=47) consisted of 24 participants with DSM-IV diagnosed bipolar I disorder (13 male and 11 female; mean age: 43.0 ±12.1) and 23 healthy controls (11 male and 12 female; mean age: 43.2 ±10.8). The sample has been previously reported in (Gadelkarim, Ajilore, 2013, Leow, Ajilore, 2013). All participants completed the Structured Clinical Interview for DSM-IV Axis I Disorders, Research Version (SCID)(Spitzer et al. , 1992) to confirm a bipolar I disorder diagnosis or absence thereof. At the time of image acquisition, all subjects were in an euthymic state, operationally defined as a score of less than 7 on both the Young Mania Rating Scale (YMRS) (Young et al. , 1978) and the Hamilton Rating Scale for Depression (HAM-D) (Hamilton, 1980) as well as an absence of any mood episodes within 30 days of the scan.

Control subjects were excluded if they had a current or past psychiatric diagnosis (including history of substance abuse). Bipolar subjects with a past history of alcohol or drug use disorder could participate if they were sober for >3 months, as confirmed by self-report. Exclusion criteria for all subjects included left-handedness, head injury with

loss of consciousness > 5 min, ferrous metal implants, neurologic illness, and pregnancy. Course of illness information (i.e., bipolar illness duration, prior history of manic and depressive episodes) was obtained by self-report and confirmed by reference to psychiatric care records when available.

None of the participants were on lithium. At the time of the MRI scan, 7 bipolar participants were on valproic acid, 1 on carbamazepine, 3 on lamotrigine, 14 on antipsychotic medications, 8 on SSRI antidepressant medications, 5 on other antidepressant medications, and 3 on benzodiazepine. Two bipolar participants were not on any psychotropic medications.

Neuropsychological Battery

42 subjects (NP sample, 20 control and 22 bipolar) underwent a neuropsychological battery that consisted of a total of 12 tests assessing domains of processing speed (DKEFS(Delis, 2001) Number Sequencing, Letter Sequencing, Letter Fluency, and Category Fluency), verbal memory (California Verbal Learning Test(Delis et al. , 2000) or CVLT), working memory (WAIS(Wechsler, 1997) Digit Span Backwards, Letter-Number Sequencing, Digit Span Sequencing, and Symbol Span total scores), and cognitive flexibility (DKEFS Stroop Inhibition/Switching, Category Switching Accuracy, and Trails Number-Letter Sequencing). Raw scores were converted to z-scores using the means and standard deviations of the control group. Cronbach's alpha calculated for each domain were 0.61 for processing speed, .79 for verbal memory, 0.74 for working memory, and 0.53 for cognitive flexibility.

Go/NoGo fMRI Paradigm

In addition to the neurocognitive tests, a subset of 32 subjects (fMRI sample, 16 control and 16 bipolar) completed a Go/NoGo fMRI task that probes response inhibition. The Go/NoGo paradigm involved visually monitoring a series of pictures presented one at a time (112 trials). For the first 10-sec of the initial fixation phase, subjects viewed a gray screen with “Get Ready” in the center followed by a 20-sec phase with a fixation cross. Following this initial 30-sec fixation block, participants were given eight alternating 30-sec blocks of Go and NoGo conditions presented in the order ABABABAB, with a 20-sec rest at the end. Each Go condition (Block A) began with a 2-sec instruction “Push for every picture,” followed by 14 picture trials consisting of a variety of Spiderman pictures presented in a pseudorandom sequence. Each NoGo condition (Block B) began with a 2-sec instruction “Push only when you see Spiderman,” following which subjects were presented randomly with Spiderman 50% of the time and the Green Goblin 50% of the time, thus requiring subjects to either press the button or refrain from responding to Green Goblin (NoGo stimulus). Stimulus presentation within both Go and NoGo blocks lasted 2-sec without an inter-stimulus interval. Prior to scanning, participants completed a brief practice session in order to become familiar with the task.

Functional Magnetic Resonance Imaging Acquisition

The Go/NoGo fMRI scan was acquired using a T2*-weighted echo planar imaging (EPI) gradient-echo pulse sequence with integrated parallel acquisition technique (IPAT), with TR=2500ms, TE=25ms, flip angle=78°, Matrix 64 x 64, F OV=192 mm, in-plane voxel size=3 mm isotropic, slice thickness=3 mm, 0.75 mm gap, and 30 total interleaved

slices. The total sequence time was 4 min and 48 sec, with 112 volumes acquired. For co-registration to the EPI images, structural images aligned to the anterior and posterior commissure were acquired with the following parameters: TR=5000ms, TE=34ms, flip angle=90°, Matrix 128x128, FOV=192mm, in-plane voxel size 1.5 x 1.5 x 3.0 mm, slice thickness=3 mm, and 30 total slices.

Diffusion Tensor Imaging Acquisition

Subjects were scanned on a 3T Siemens Trio scanner (Siemens Medical Systems, Germany). Sixty contiguous axial brain slices were collected using the following parameters: 64 diffusion-weighted (b=1000s/mm^2) and 1 non-diffusion weighted scan; field of view (FOV) 190mm by 190mm; voxel size 2x2x2mm; TR=8400ms; TE=93ms. High-resolution structural images were acquired using T1-weighted magnetization-prepared rapid-acquisition gradient echo (MPRAGE; FOV 250mm by 250 mm; voxel size: 1x1x1mm; TR=1900ms, TE=2.26ms, flip angle=9°, matrix = 256 x 256, and total sequence time 6 min and 50 sec). Further details on the FA analysis and structural brain network construction are provided in supplementary materials.

fMRI Data Analyses

fMRI data processing methods are detailed in the supplementary materials. For the first-level analyses, Go and NoGo blocks were modeled separately for each subject. The fMRI statistics were analyzed using the general linear model (GLM), with six motion parameter estimates modeled as covariates of no interest. Then contrasts were created to compare activation during the NoGo blocks against the Go blocks to obtain a

statistical map for each subject. The NoGo minus Go contrast was the main focus of the fMRI analysis, as this represents activation related to response inhibition. Higher-level statistics were conducted using FLAME (FMRIB's Local Analysis of Mixed Effects) stage 1 and stage 2 (Beckmann et al. , 2003, Woolrich, 2008, Woolrich et al. , 2004), with a height threshold of $Z > 2.3$ and cluster probability of $P < 0.05$ corrected (Worsley, 2001). To examine group differences (control > bipolar, bipolar>control) in brain activation, adjusted for overall reaction time (RT) mean, we additionally ran the model including overall RT as a covariate.

Region of Interest (ROI) Analyses

To preclude "double-dipping" and not bias our ROI selection (Kriegeskorte et al. , 2009), we functionally-defined our *a priori* VLPFC ROIs using coordinates from an independent sample of healthy subjects performing similar Go/NoGo response inhibition tasks. For Brodmann area (BA) 47, the coordinate used to create the 5 mm sphere originated from an average of peak voxels reported in three studies all using Go/NoGo tasks in healthy subjects (Mazzola-Pomietto et al. , 2009, Menon et al. , 2001, Nakata et al. , 2008). The right BA47 sphere was centered at (42, 24, -12) and a mirror image was created for the left BA47 sphere (-42, 24, -12). The peaks of the resulting ROI masks are further comparable to those reported in a recent meta-analysis of response inhibition in bipolar disorder (Hajek et al. , 2013b). FEATQuery was then used to extract the time course from these regions in order to calculate mean percent signal change for NoGo minus Go during the Go/NoGo fMRI paradigm.

Statistical analysis

Analysis of Demographic and Cognitive Variables

Statistical analysis of demographic variables was performed using SPSS. Group differences in categorical and continuous demographic variables were computed using 2-tailed Fisher's exact and independent *t*-tests. Group differences in cognitive performance were conducted using analysis of covariance (ANCOVA) controlling for years of education. Statistical significance was defined at $\alpha=0.05$. To examine the relationship between significant variables of interest in a post-hoc mediation analyses, we used the conditional process modelling tool PROCESS (Hayes, 2012). Conditional process modeling is the analytical integration of mediation and moderation analysis and provides an efficient way to assess direct and indirect effects in a variety of models.

Go/NoGo *Behavioral Data Analysis*

Behavioral data were unavailable for one control participant. For each group, means and standard deviations were computed for accuracy and response times for the Go and NoGo conditions. Differences in accuracy and response time were tested independently using chi-square and independent samples t-tests, respectively, with diagnosis (bipolar, healthy comparison) as the between-subject factor. For accuracy, the measures could not be analyzed as continuous variables due to a ceiling effect whereby only a few distinct values were observed. Consistent with a recent Go/NoGo study in bipolar subjects and healthy controls (Penfold et al. , 2014) whereby a non-normal distribution was also observed due to the fact that the majority of subjects made

few or no errors, accuracy was dichotomized into two groups (high and low performance) and differences were assessed using a chi-square test.

Associations with Brain Network Metrics

Two-tailed Pearson's bivariate correlations were used to analyze associations between FA values, brain network metrics, and cognitive domain z-scores. Correlations results were adjusted using the false discovery rate (Benjamini and Hochberg, 1995). To analyze connectome-based predictors of Go/NoGo related activation in BA47, linear regression models were tested with lateral orbitofrontal (OFC/BA47) network metrics as predictor variables (path length, clustering coefficient, nodal network efficiency, and the PLACE-based consistency metric V) with BA47 activation levels as the outcome variable. V quantifies how an individual's brain connectome modularly differs from that of the average healthy control; V values are between 0 and 1, with 0 indicating that the individual does not share any modular similarity with the average healthy control.

Results

Subject Characteristics

There were no significant group differences in age or gender in the total sample (n = 47), NP sample (n = 42) or fMRI sample (n=32) (Table 1). Education was significantly higher in the control group across all samples and included as a covariate in group comparisons.

Cognitive Performance

NP cognitive and behavioral performance

Results for the NP cognitive and fMRI behavioral performance are presented in Table 2. Bipolar participants had lower performance across all four NP cognitive domains, but only working memory reached statistical significance (F = 4.6, p = .04, df = 1) (Figure 1). There were no significant between-group differences in accuracy for either the Go or NoGo conditions. Reaction times for the Go and NoGo conditions were significantly faster for controls relative to the bipolar group.

Structural Connectivity

NP cognitive domain associations with corpus callosum white matter integrity

In our prior study, we found selective white matter impairment in the corpus callosum (CC) (Leow, Ajilore, 2013). Across the total sample, processing speed was significantly correlated with CC FA in the genu and body (r = .43, p = .004, q = .048, df = 40; r = .36, p = .019, q = .072, df = 40 respectively). Working memory was also significantly correlated with CC FA in the genu and splenium (r = .40, p = .009, q = .054, df = 40; r = .35, p = .024, q = .072, df = 40 respectively). Processing speed associations were primarily driven by strong correlations in the bipolar group across all three segments of the corpus callosum (Supplementary Figure 1). While there were no significant correlations within the control group, processing speed in the bipolar group significantly correlated with FA in the genu (r = .62, p = .002, q = .048, df = 20), body (r = .56, p = .007, q =.084, df = 20) and but not in the splenium (r =.45, p = .035, q = .28, df = 20). All significant correlations found represented medium-to-large effect sizes. There were no significant associations for verbal memory or cognitive flexibility across the total sample

or within subject groups.

Functional Connectivity

ROI and between-group whole-brain functional MRI results

Given our *a priori* hypothesis, we conducted a region-of-interest (ROI) analysis in the left and right BA47 during response inhibition (No-Go minus Go). Bipolar subjects had significantly decreased BA47 activation during No-Go minus Go (overall p = .045), driven primarily by the right BA47 (control: .241 ±.117 vs. bipolar: -.241±.117, p = .013) versus the left (control: .267 ±.123 vs. bipolar: -.017±.123, p = .146) (Figure 2A). Results of the whole-brain analysis (Figure 2B) during response inhibition (No-Go minus Go) similarly revealed significant hypoactivation in the right BA47 region in the bipolar group relative to healthy subjects ($Z>2.0$, $p<0.05$ corrected). The significant reduction in right BA47 in bipolar subjects relative to controls remained significant after adjusting for overall reaction time (RT) in the whole-brain analysis (panel A of Supplementary Figure 2). Additionally, activation in BA47 did not demonstrate neither a positive RT effect nor a negative RT effect in the whole-brain analysis (panel B of Supplementary Figure 2).

Connectome Analyses

NP cognitive domain associations with global connectome properties

Examining correlations between cognitive performance and global connectome properties (interhemispheric path length and efficiency), there were no significant associations across the total sample. However, in the bipolar group, similar to the results with corpus callosum FA, processing speed was significantly negatively

associated with interhemispheric path lengths (r = -.50, p = .017, q = .068, df = 20) and significantly positively associated with interhemispheric efficiencies (r = .54, p = .012, q = .068, df = 20) (Figure 3). As with the FA results, the correlation strengths represent medium-to-large effect sizes. To synthesize our significant findings, we constructed a conditional process model and found that the relationship between interhemispheric integration and processing speed was mediated by FA in the genu of the corpus callosum and processing speed mediated the relationship between FA and working memory (Figure 4a).

fMRI Associations with orbitofrontal local connectome properties

Linear regression analyses for determining significant predictors of BA47 activation during the Go/NoGo task revealed that left BA47 activation was associated with lateral OFC path length (β = -.40, p = .03) and right BA47 activation was significantly predicted by right lateral OFC clustering coefficient (β = -.50, p = .004) (Supplementary Figure 3). Left lateral OFC path length was also significantly correlated with Go and NoGo reaction times (Go: r = .56, p = .001, df = 30; NoGo: r = .46, p = .01, df = 30); Right lateral OFC clustering coefficients did not correlate with Go/NoGo accuracy or reaction times. In the conditional process analysis, left BA47 activation was a significant mediator of the relationship between left BA47 nodal path length and Go/NoGo reaction times (Figure 4b).

Discussion

This study represents the first imaging study that maps structure to function in bipolar disorder using cutting-edge graph-theoretical brain connectomics. Our results suggest

that structural connectome property of path length mediates are associated neurocognitive performance in BA47 during a Go/NoGo task (and that structural connectome abnormalities of longer BA47 path length may underlie neurocognitive and fMRI activation abnormalities in euthymic bipolar subjects).

This study builds on our previous study (Leow, Ajilore, 2013) investigating structural connectome in this population, where we found reduced white matter integrity in the corpus callosum and related inter-hemispheric integration deficits. Here, using an overlapping sample we additionally map structure to function by taking advantage of psychometric and fMRI data available to us in a subset of study participants.

First, using data from neuropsychological testing, we compared four neurocognitive domains including processing speed, verbal memory, working memory and cognitive flexibility. Consistent with the literature (Cremaschi et al. , 2013, McKenna et al. , 2013, Thompson et al. , 2007, Torres, Boudreau, 2007), we found that euthymic bipolar subjects performed worse on working memory tasks. Additionally, both working memory and processing speed domain scores were significantly associated with corpus callosum white matter integrity (FA values) in the entire sample (the correlation was driven mostly by the bipolar subjects). Post-hoc mediation analyses further revealed that the relationship between interhemispheric integration/FA in the corpus callosum and working memory is mediated by processing speed. This finding is consistent with previous reports in the literature. Interestingly, almost two decades ago, Pettigrew and Miller identified an abnormal “sticky” interhemispheric switch in bipolar patients

(Pettigrew and Miller, 1998). More recently, a large multicenter diffusion imaging study revealed interhemispheric disconnectivity in bipolar patients, particularly in those with psychotic symptoms (Sarrazin et al. , 2014). In addition, white matter integrity has been associated with processing speed in a number of studies in bipolar disorder (Bearden et al. , 2011) and in late-life depression (Mettenburg et al. , 2012, Shimony et al. , 2009). The present study adds to this growing literature by providing a multimodal approach linking structural disconnectivity to cognitive deficits in euthymic bipolar disorder.

Additionally, we found abnormal hypoactivation in the right BA47 during a response inhibition Go/NoGo task in euthymic BPI. Previous fMRI studies of euthymic bipolar patients have used tasks that probe inferior frontal/orbitofrontal function (BA47) (Cerullo et al. , 2009, Chen et al. , 2011, Townsend, Bookheimer, 2012) to reveal frontal hypoactivation. A large meta-analysis study also supports right BA47 hypo-activation as a trait marker in bipolarity (Hajek, Alda, 2013a). Furthermore, it has been recently argued that structural changes in right BA47 reflect biological risk for bipolarity (Hajek et al. , 2013c), while another study reported a negative association between BA47 functional activation and the number of prior manic episodes (Pompei et al. , 2011). The present study adds to the literature by linking structure connectome to functional activation in this region, demonstrating that the more locally segregated and/or the less globally integrated BA47 is, the less activated it is during response inhibition, and are abnormal in euthymic bipolar disorder. As stronger local segregation/clustering and less global integration indicate less efficient information transfer, this may explain the

observed longer reaction times for both the Go and NoGo conditions for our bipolar subjects. Last, we conducted post-hoc mediation analyses to explore the relationship among the three (structural connectome, functional activation and cognitive performance), with results suggesting that structural connectome properties are associated with the relationship between BA47 activation and cognitive performance.

Taken these findings as a whole, we thus hypothesize that structural connectome properties in BA47 may potentially serve as an imaging marker for neurocognitive abnormalities associated with mood disorders as supported by: a) structure connectome abnormalities are predictors for functional activation and neurocognitive deficits seen in BPI, b) there is a negative association between functional activation and the number of prior manic episodes (Pompei, Jogia, 2011), and c) other studies support BA47 hypo-activation as a trait marker of bipolarity (Altshuler et al. , 2005, Hajek, Alda, 2013a). Such a hypothesis is most relevant when one considers that there have been virtually no imaging or neuropsychological predictors of recurrence in bipolar disorder, except for clinical presentations themselves (e.g., a review article concluded that stressful events, higher numbers of prior episodes, shorter between-episode intervals, and persistence of affective symptoms predict relapse) (Altman et al. , 2006). Additionally, there are also no practical prospective predictors for the nature of the next acute mood episode (mania vs depression). Such major limitations not only exist in our understanding of bipolar disorder, but also in mood disorders in general (to address such limitations in MDD, e.g., the PReDICT trial is recently launched to identify predictors of treatment response and future recurrence) (Dunlop et al. , 2012). To this

end, in future studies we plan to determine if “connectome signatures” identified here may: a) when combined with other variables identify otherwise healthy subjects at risk and b) prospectively predict the disease course in bipolar patients.

Although this study examined a sample that is well balanced with a multitude of clinical, imaging and psychometric measurements, there are a few limitations. First, our findings should be interpreted in the context of a relatively small sample size as some subjects had missing neuropsychological measurements or fMRI data, and as a result may have decreased our power to detect more subtle group differences or correlations contributing to possible false negative findings. Second, while there have been substantial research interests in applying connectomics to imaging studies of the human brain, the exact interpretation of these sophisticated (and at times abstract) graph theory-based connectome metrics remains unclear. Third, limitations pertaining to our sample characteristics should be acknowledged. While we carefully screened all participants with a diagnostic interview and operationalized euthymic mood at time of scan, our bipolar participants were predominantly medicated and our control participants were not screened for psychiatric illnesses in their first-degree relatives. While medications reportedly have limited impact on fMRI and DTI findings in bipolar disorder (Hafeman et al. , 2012), future research should examine whether those on medication have different modularity than non-medicated bipolar subjects. In addition, a substantial number of bipolar subjects had a history of (but not current) substance use disorders so the impact of this common comorbidity on our results cannot be ruled out (Cassidy et al. , 2001). Lastly, data collection for this study was not designed to relate

specific white matter tracts to corresponding functional anatomic and NP regions. Future studies could more closely link NP cognitive domains in order to fully evaluate whether a white matter structural deficit directly correlates with a functional deficit in regions known to play a role in a particular NP task (e.g., an fMRI working memory task that probes dorsolateral prefrontal cortex).

Nevertheless, this represents the first connectome study to relate structural connectome properties to neurocognitive performances and fMRI activations during a well-validated executive function task in euthymic bipolar patients. Our findings further support the utility of brain connectomics in the study of mood disorders, and point to future directions in research that may help elucidate neuroanatomical abnormalities in bipolar disorder, and relate them to longitudinal disease course.

Table 1. Demographic and Clinical Characteristics of Bipolar I Euthymic Subjects and Healthy Controls

Characteristic	Total Sample (n=47)		NP Sample (n=42)		fMRI Sample (n=32)	
	Bipolar	Control	Bipolar	Control	Bipolar	Control
Age, mean (SD), years	43.0 (12.1)	43.2 (10.8)	42.6 (11.7)	43.6 (10.9)	46.7 (11.8)	40.4 (11.2)
Gender						
Female	11	12	9	11	7	9
Male	13	11	13	9	9	7
Education, mean (SD), years*	**14.1 (1.6)**	**15.7 (2.2)**	**14.2 (1.6)**	**15.5 (2.1)**	**13.8 (1.7)**	**16.1 (2.4)**
HAM-D[a] (21-item) score, mean (SD)	3.3 (2.3)	0.8 (1.1)	-	-	3.7 (2.4)	0.9 (1.2)
HAM-D (28-item) score, mean (SD)	4.6 (3.5)	1.1 (1.3)	-	-	4.8 (4.1)	1.2 (1.2)
YMRS[b] score, mean (SD)	1.8 (1.9)	0.7 (1.2)	-	-	1.9 (2.1)	0.8 (1.3)
Age of bipolar illness onset, mean (SD), years	21.2 (10.9)	-	22.0 (10.8)	-	23.3 (11.9)	-
Duration of bipolar illness, mean (SD), years	22.0 (14.3)	-	20.9 (12.3)	-	23.4 (15.8)	-
Duration of euthymic episode, mean (SD), weeks	104.9 (235.1)	-	108.5 (245.1)	-	82.8 (169.7)	-
Lifetime No. manic episodes, mean (SD)	9.4 (14.0)	-	7.6 (11.1)	-	11.4 (16.5)	-
Lifetime No. depressive episodes, mean (SD)	9.3 (14.5)	-	9.6 (15.1)	-	8.0 (10.0)	-
History of psychosis, count	3	-	2	-	3	-
Current Comorbidity		-		-		-
Panic Disorder Without Agoraphobia	1	-	1	-	1	-
Social Phobia	1	-	1	-	0	-
Specific Phobia	1	-	1	-	1	-
Posttraumatic stress disorder	1	-	1	-	1	-
Past Comorbidity		-		-		-
Panic Disorder Without Agoraphobia	2	-	2	-	1	-
Social Phobia	2	-	2	-	1	-
Posttraumatic stress disorder	1	-	1	-	1	-
Substance/alcohol use disorders	14	-	12	-	10	-

[a] HAM-D, Hamilton Depression Rating Scale; [b] YMRS, Young Mania Rating Scale.

, t = 2.9, df = 45, p = .006, Total Sample;, t = 2.1, df = 35, p = .04, NP Sample;*, t = 3.2, df = 30, p = .003, fMRI Sample

Table 2. Neuropsychological test and fMRI behavioral performance by group.

	Bipolar I Euthymic	Healthy Controls	P-value
Neuropsychological Tests (z-scores)			
Processing Speed	-.26 (1.02)	0 (1)	.75
Verbal Memory	-.36 (1.17)	0 (1)	.41
Working Memory	**-.70 (.67)**	**0 (1)**	**.04**
Cognitive Flexibility	-.66 (1.5)	0 (1)	.24
Go/NoGo fMRI Paradigm			
Mean Accuracy (% correct)			
Go Condition	94.4 (5.8)	94.5 (8.1)	$p = 0.273$
NoGo Condition	98.7 (1.4)	98.5 (3.3)	$p = 0.156$
Mean Reaction Time (s)			
Go Condition	**0.56 (0.16)**	**0.44 (0.07)**	**p = 0.016**
NoGo Condition	**0.59 (0.12)**	**0.50 (0.07)**	**p = 0.021**

Standard deviations are provided in parentheses. Significant differences in indicated in boldface.

Table 1. Demographic and Clinical Characteristics of Bipolar I Euthymic Subjects and Healthy Controls

Table 2. Neuropsychological test and fMRI behavioral performance by group.

Figure 1. Cognitive domain performance z-scores for health control and bipolar subjects. While bipolar subjects demonstrated reduced performance across all domains, only working memory was significantly different ($F = 4.6$, $p = .04$, $df = 1$). Error bars indicate the standard error of the mean.

Figure 2. BA47 GoNoGo Activation Differences. (A). Spherical BA47 regions of interest (yellow) were defined by the nogo minus go contrast and are depicted on a representative high-resolution anatomical image. Error bars denote standard error of the mean. (B). Between-group whole-brain results display significantly greater activation in BA 47 (highlighted in green circles) in control subjects as compared to euthymic bipolar subjects during response inhibition.

Figure 3. Processing speed significantly correlates with network measures of interhemispheric integration in bipolar participants

Figure 4. Mediation Models: .**A**. FA in the genu of the corpus callosum (GCC FA) is a significant mediator of the relationship between interhemispheric integration (measured by “graph distance” or path length between two hemispheres) and processing speed, which in turn mediates the association of FA and working memory. **B**. BA47 task activation mediates the relationship between BA47 nodal path lengths and performance

during the Go/NoGo task. Unstandardized beta weights for significant variables are displayed on the models.

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Contributors

Dr. Altshuler was the project PI and supervised the collection of neuroimaging data and the analysis of functional MRI data by Dr. Vizueta. Dr. Leow served as the corresponding and primary investigator for this study, overseeing the execution of all analyses and interpretation of all results. Dr. Ajilore completed the data analyses and wrote the paper with Dr. Leow. Dr. Zhan preprocessed the structural MRI data and participated in part of the data analysis. Drs. Altshuler and Vizueta reviewed and contributed to the first and final drafts of the manuscript.

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Conflict of Interest

Dr. Altshuler has received past funding from Takeda Pharmaceuticals North America, Inc., and H. Lundbeck A/S (advisory board honoraria, October 2012); and past and potential future funding from Sunovion Pharmaceuticals Inc. (advisory board honoraria, Jan 2013). The remaining authors report no financial relationships with commercial interests.

Highlights:

- The relationship between structural connectome properties and cognitive function was examined
- Integrity of the corpus callosum mediates the relationship between processing speed and interhemispheric integration
- Processing speed mediates the association between integrity of the corpus callosum and working memory
- Structural connectome properties of Brodmann area 47 underlie impaired response inhibition in euthymic bipolar subjects

Figure 1

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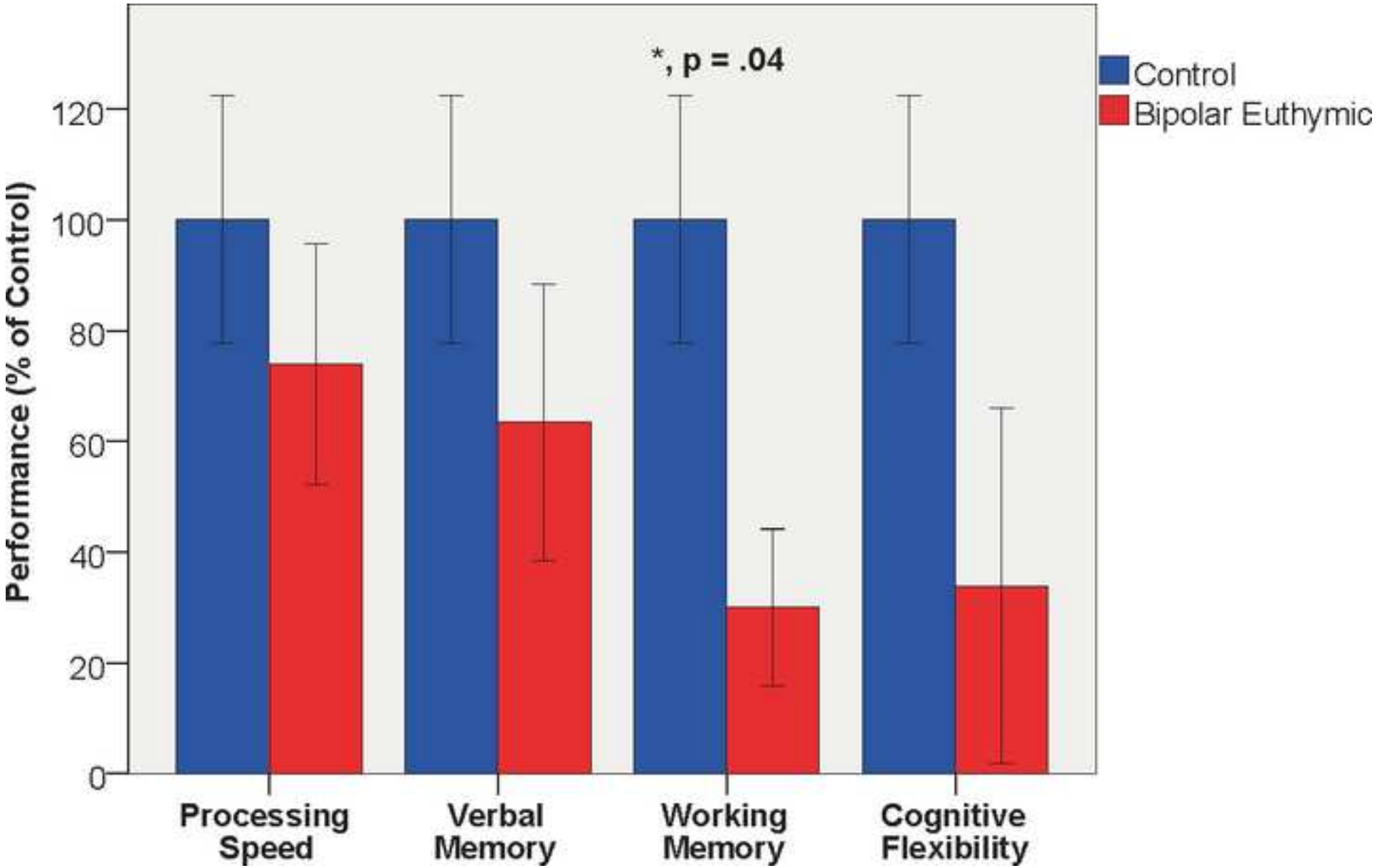

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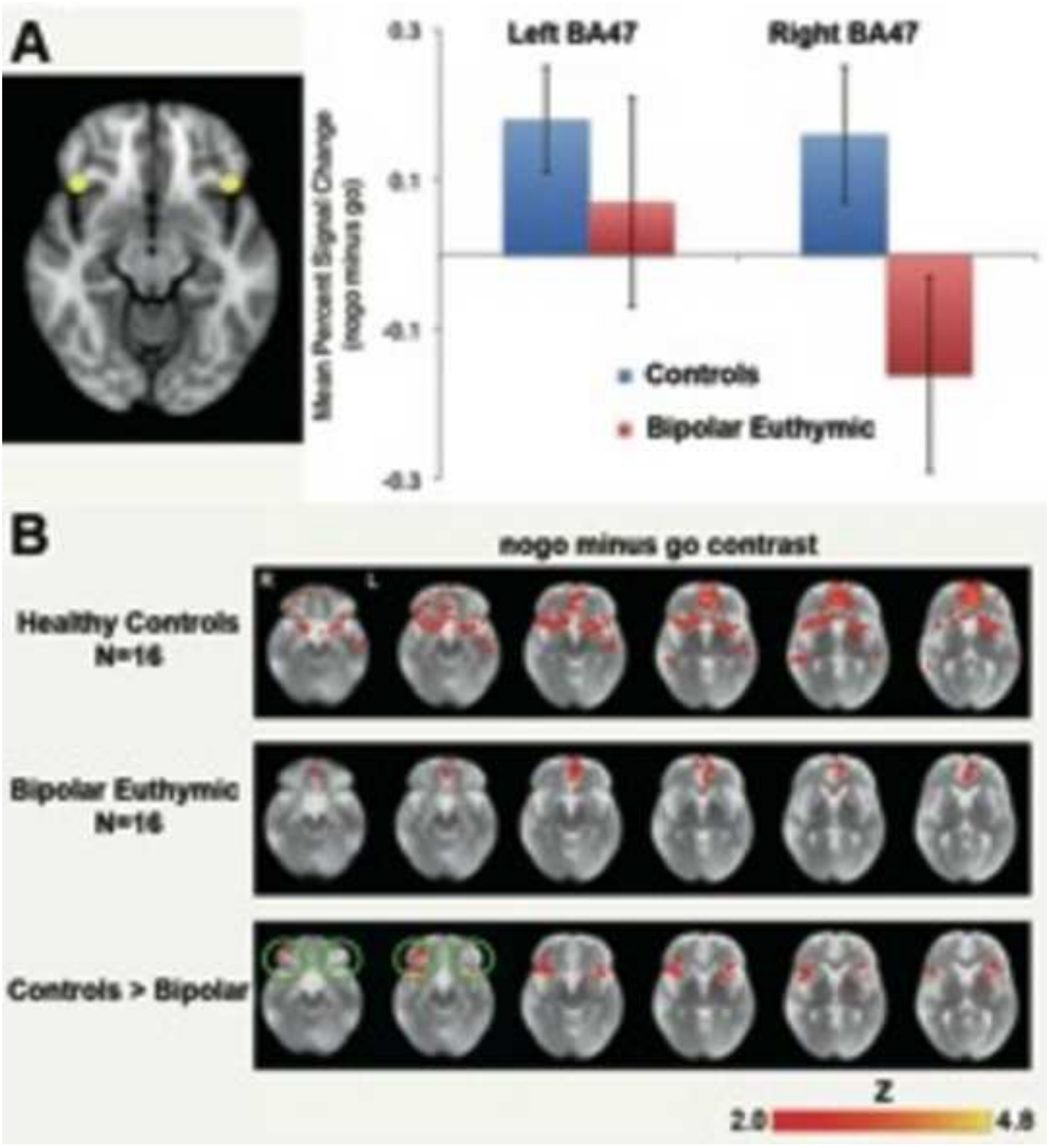

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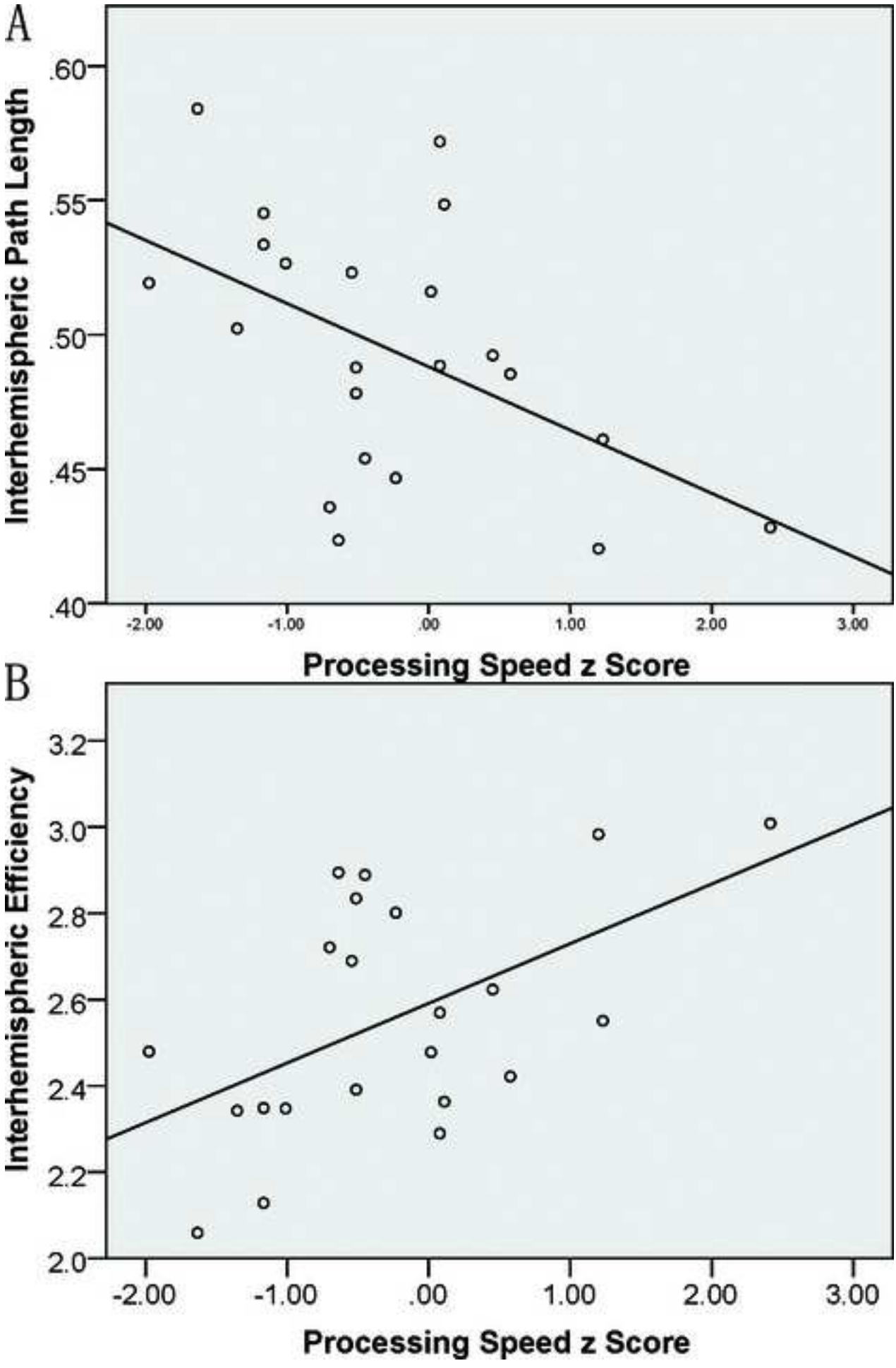

Figure 4

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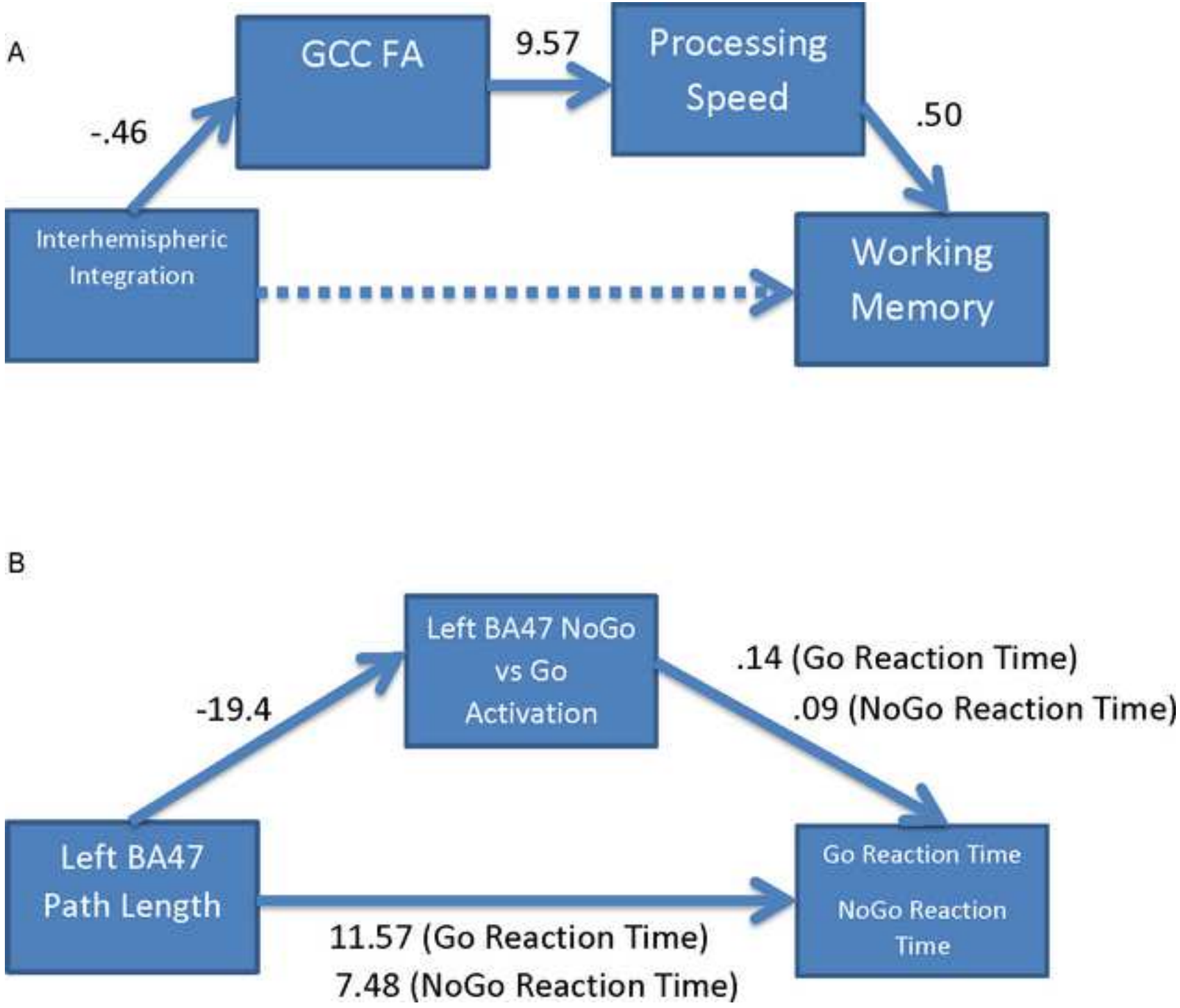

Supplementary Material

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