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Connectome signatures of neurocognitive abnormalities in euthymic bipolar I disorder

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ABSTRACT

Objectives: Connectomics have allowed researchers 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 hemisphere) and its nodal clustering coefficient (right hemisphere).

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.

1. 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

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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., 2014). 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.

2. Materials and methods

2.1. 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 et al., 2014; Leow et al., 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.

2.2. 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 .61 for processing speed, .79 for verbal memory, .74 for working memory, and .53 for cognitive flexibility.

2.3. 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.

2.4. 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 = 2500 ms, TE = 25 ms, flip angle = 78°, Matrix 64 × 64, FOV = 192 mm, in-plane voxel size = 3 mm isotropic, slice thickness = 3 mm, .75 mm gap, and 30 total interleaved slices. The total sequence time was 4 min and 48 s, 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 = 5000 ms, TE = 34 ms, flip angle = 90°, Matrix 128 × 128, FOV = 192 mm, in-plane voxel size 1.5 × 1.5 × 3.0 mm, slice thickness = 3 mm, and 30 total slices.

2.5. 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 = 1000 s/mm^2) and 1 non-diffusion weighted scan; field of view (FOV) 190 mm by 190 mm; voxel size 2 × 2 × 2 mm; TR = 8400 ms; TE = 93 ms. High-resolution structural images were acquired using T1-weighted magnetization-prepared rapid-acquisition gradient echo (MPRAGE; FOV 250 mm by 250 mm; voxel size: 1 × 1 × 1 mm; TR = 1900 ms, TE = 2.26 ms, flip angle = 9°, matrix = 256 × 256, and total sequence time 6 min and 50 s). Further details on the FA analysis and structural brain network construction are provided in Supplementary materials.

2.6. 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 $P < .05$ 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.

2.7. 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.

2.8. Statistical analysis

2.8.1. 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 $\alpha = .05$. 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.

2.8.2. 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., 2015) 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.

2.8.3. 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.

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)	.8 (1.1)	–	–	3.7 (2.4)	.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)	.7 (1.2)	–	–	1.9 (2.1)	.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	–

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

3. Results

3.1. 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.

3.1.1. Cognitive performance

3.1.1.1. 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) (Fig. 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.

3.1.2. Structural connectivity

3.1.2.1. 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 et al., 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

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	**−0.70 (0.67)**	**0 (1)**	**0.04**
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)	$p = .273$
NoGo Condition	98.7 (1.4)	98.5 (3.3)	$p = .156$
Mean Reaction Time (s)			
Go Condition	**0.56 (0.16)**	**0.44 (0.07)**	**P = .016**
NoGo Condition	**0.59 (0.12)**	**0.50 (0.07)**	**P = .021**

Standard deviations are provided in parentheses. Significant differences are indicated in boldface (p < .05).

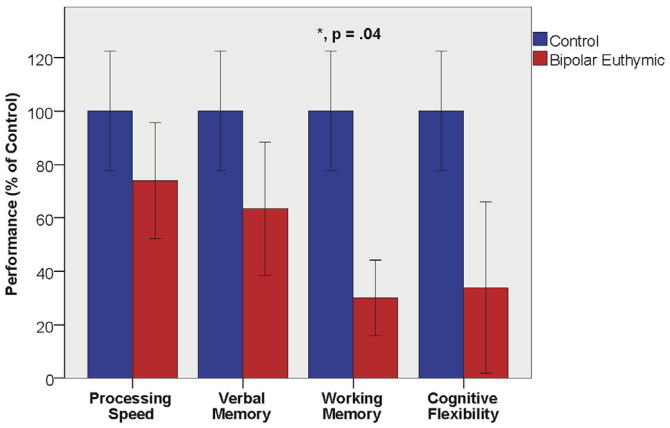

Fig. 1. Cognitive domain performance z-scores for health control and bipolar subjects. While bipolar subjects demonstrated reduced performance across all domains, only working memory was significantly different (F = 4.6, p = .04, df = 1). Data are presented as a percentage of the mean performance for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

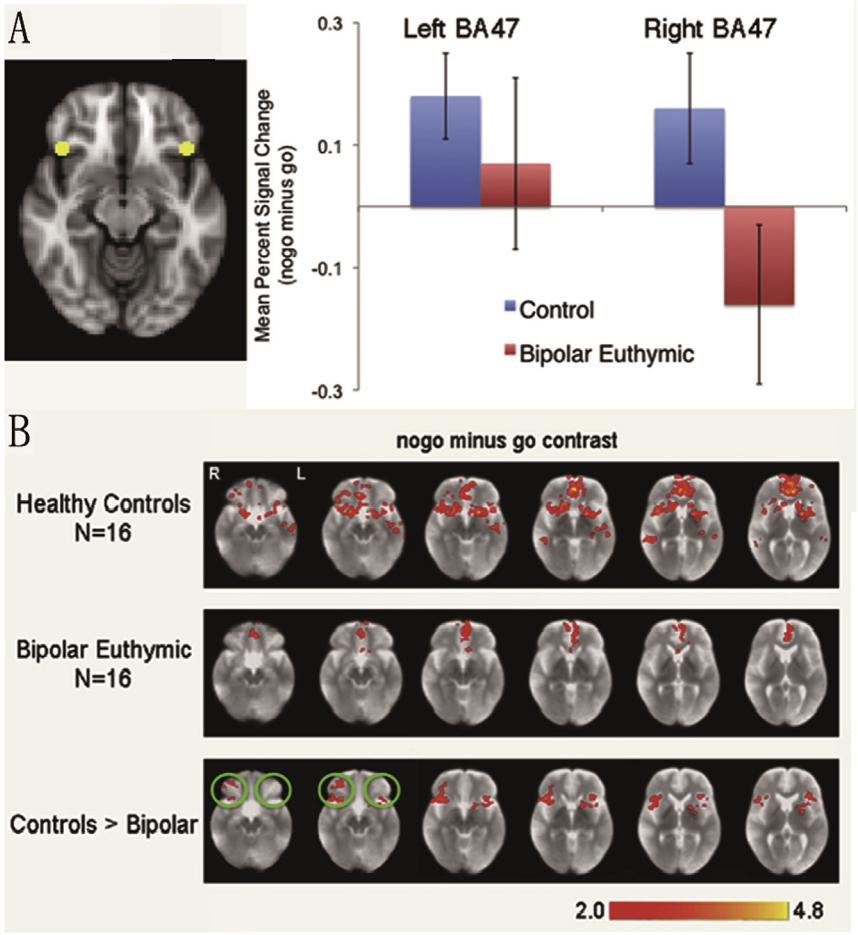

Fig. 2. BA47 GoNoGo Activation Differences. A. Spherical BA47 regions of interest (yellow) were defined by the nogo minus go contrast and are depicted on a representative high-resolution anatomical image. Error bars denote standard error of the mean. **B**. Between-group whole-brain results display significantly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

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.

3.1.3. Functional connectivity

3.1.3.1. 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: $.241 \pm .117$ vs. bipolar: $-.241 \pm .117$, $p = .013$) versus the left (control: $.267 \pm .123$ vs. bipolar: $-.017 \pm .123$, $p = .146$) (Fig. 2A). Results of the whole-brain analysis (Fig. 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 ($Z > 2.0$, $p < .05$ 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).

3.1.4. Connectome analyses

3.1.4.1. 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 ($r = .54$, $p = .012$, $q = .068$, $df = 20$) (Fig. 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 (Fig. 4a).

3.1.4.2. fMRI associations with orbitofrontal local connectome properties. Linear regression analyses for determining significant predictors of BA47 activation during the Go/NoGo task revealed that

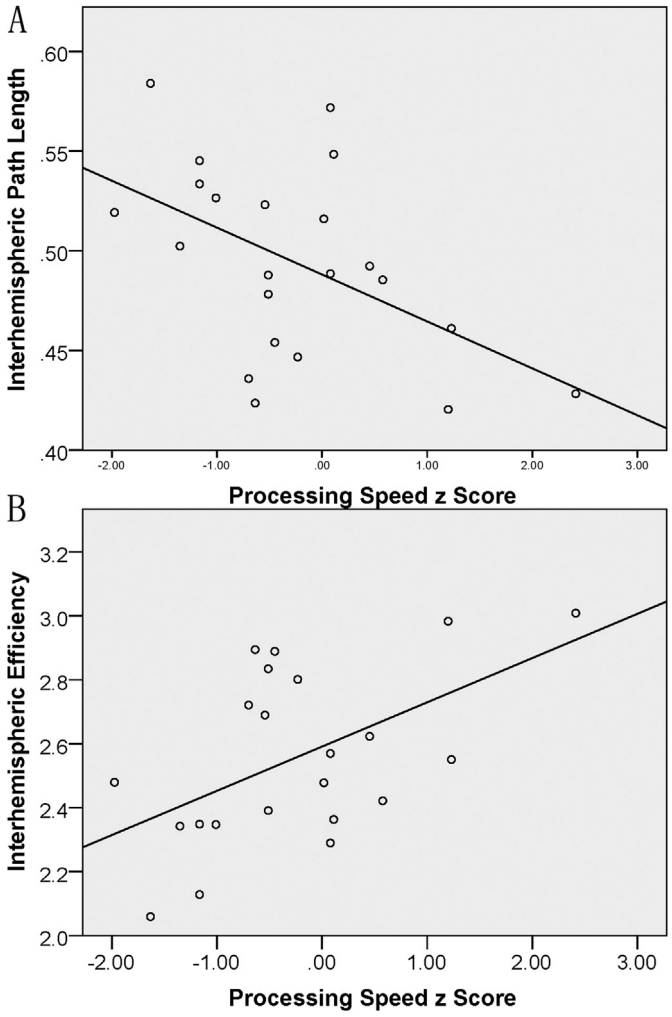

Fig. 3. Processing speed significantly correlates with network measures of interhemispheric integration in bipolar participants. **A**. Interhemispheric path length negatively correlates with processing speed ($r = -.50$, $p = .017$, $q = .068$, $df = 20$). **B**. Interhemispheric efficiency positively correlates processing speed ($r = .54$, $p = .012$, $q = .068$, $df = 20$).

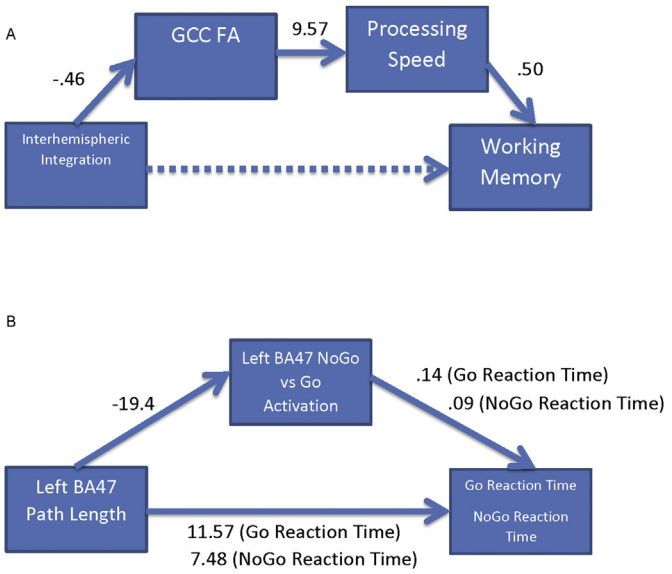

Fig. 4. Mediation Models: **A**. FA in the genu of the corpus callosum (GCC FA) is a significant mediator of the relationship between interhemispheric integration (measured by "graph distance" or path length between two hemispheres) and processing speed, which in turn mediates the association of FA and 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.

left BA47 activation was associated with lateral OFC path length ($\beta = -.40$, $p = .03$) and right BA47 activation was significantly predicted by right lateral OFC clustering coefficient ($\beta = -.50$, $p = .004$) (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 (Fig. 4b).

4. 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 the structural connectome property of path length is associated with neurocognitive performance during a Go/NoGo task. More specifically, our results indicate that the structural connectome alterations of longer BA47 path length may underlie neurocognitive and fMRI activation abnormalities in euthymic bipolar subjects.

This study builds on our previous study (Leow et al., 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., 2014; Thompson et al., 2007; Torres et al., 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 et al., 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. 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 et al., 2011), and c) other studies support BA47 hypoactivation 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.

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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.

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.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jpsychires.2015.05.017.

References

Altman S, Haeri S, Cohen LJ, Ten A, Barron E, Galynker II , et al. Predictors of relapse in bipolar disorder: a review. J psychiatric Pract 2006;12:269–82.

Altshuler LL, Bookheimer SY, Townsend J, Proenza MA, Eisenberger N, Sabb F, et al. Blunted activation in orbitofrontal cortex during mania: a functional magnetic resonance imaging study. Biol Psychiatry 2005;58:763–9.

Altshuler LL, Ventura J, van Gorp WG, Green MF, Theberge DC, Mintz J. Neurocognitive function in clinically stable men with bipolar I disorder or schizophrenia and normal control subjects. Biol Psychiatry 2004;56:560–9.

Bearden CE, van Erp TG, Dutton RA, Boyle C, Madsen S, Luders E, et al. Mapping corpus callosum morphology in twin pairs discordant for bipolar disorder. Cereb cortex (New York, N. Y : 1991) 2011;21:2415–24.

Beckmann CF, Jenkinson M, Smith SM. General multilevel linear modeling for group analysis in FMRI. Neuroimage 2003;20:1052–63.

Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc Ser B Methodol 1995;57:289–300.

Blumberg HP, Leung HC, Skudlarski P, Lacadie CM, Fredericks CA, Harris BC, et al. A functional magnetic resonance imaging study of bipolar disorder–state–and trait-related dysfunction in ventral prefrontal cortices. Archives Gen Psychiatry 2003;60:601–9.

Cassidy F, Ahearn EP, Carroll BJ. Substance abuse in bipolar disorder. Bipolar Disord 2001;3:181–8.

Cerullo MA, Adler CM, Delbello MP, Strakowski SM. The functional neuroanatomy of bipolar disorder. Int Rev psychiatry (Abingdon, England) 2009;21:314–22.

Chen CH, Suckling J, Lennox BR, Ooi C, Bullmore ET. A quantitative meta-analysis of fMRI studies in bipolar disorder. Bipolar Disord 2011;13:1–15.

Cremaschi L, Penzo B, Palazzo M, Dobrea C, Cristoffanini M, Dell'Osso B, et al. Assessing working memory via N-back task in euthymic bipolar I disorder patients: a review of functional magnetic resonance imaging studies. Neuropsychobiology 2013;68:63–70.

Delis DC, Kramer JH, Kaplan E. California verbal Learning test. 2nd ed. San Antonio, TX: Psychological Corporation; 2000.

Delis DC, Kramer JH, Kaplan E. The Delis-Kaplan executive function System. San Antonio, TX: Psychological Corporation; 2001.

Dunlop BW, Binder EB, Cubells JF, Goodman MM, Kelley ME, Kinkead B, et al. Predictors of remission in depression to individual and combined treatments (PReDICT): study protocol for a randomized controlled trial. Trials 2012;13:106.

Gadelkarim JJ, Ajilore O, Schonfeld D, Zhan L, Thompson PM, Feusner JD, et al. Investigating brain community structure abnormalities in bipolar disorder using path length associated community estimation. Hum Brain Mapp 2014;35(5):2253–64.

Goldberg JF, Chengappa KN. Identifying and treating cognitive impairment in bipolar disorder. Bipolar Disord 2009;11(Suppl 2):123–37.

Hafeman DM, Chang KD, Garrett AS, Sanders EM, Phillips ML. Effects of medication on neuroimaging findings in bipolar disorder: an updated review. Bipolar Disord 2012;14:375–410.

Hajek T, Alda M, Hajek E, Ivanoff J. Functional neuroanatomy of response inhibition in bipolar disorders–combined voxel based and cognitive performance meta-analysis. J psychiatric Res 2013a;47:1955–66.

Hajek T, Alda M, Hajek E, Ivanoff J. Functional neuroanatomy of response inhibition in bipolar disorders - combined voxel based and cognitive performance meta-analysis. J Psychiatr Res 2013b;47:1955–66.

Hajek T, Cullis J, Novak T, Kopecek M, Blagdon R, Propper L, et al. Brain structural signature of familial predisposition for bipolar disorder: replicable evidence for involvement of the right inferior frontal gyrus. Biol Psychiatry 2013c;73:144–52.

Hamilton M. Rating depressive patients. J Clin psychiatry 1980;41:21–4.

Hayes AF. PROCESS: a versatile computational tool for observed variable mediation, moderation, and conditional process modeling. 2012.

Kozicky JM, Ha TH, Torres IJ, Bond DJ, Honer WG, Lam RW, et al. Relationship between frontostriatal morphology and executive function deficits in bipolar I disorder following a first manic episode: data from the systematic treatment optimization program for early mania (STOP-EM). Bipolar Disord 2013;15:657–68.

Kriegeskorte N, Simmons WK, Bellgowan PS, Baker CI. Circular analysis in systems neuroscience: the dangers of double dipping. Nat Neurosci 2009;12:535–40.

Lee RS, Hermens DF, Scott J, Redoblado-Hodge MA, Naismith SL, Lagopoulos J, et al. A meta-analysis of neuropsychological functioning in first-episode bipolar disorders. J Psychiatr Res 2014;57:1–11.

Leow A, Ajilore O, Zhan L, Arienzo D, Gadelkarim J, Zhang A, et al. Impaired inter-hemispheric integration in bipolar disorder revealed with brain network analyses. BiolPsychiatry 2013;73:183–93.

Linke J, King AV, Poupon C, Hennerici MG, Gass A, Wessa M. Impaired anatomical connectivity and related executive functions: differentiating vulnerability and disease marker in bipolar disorder. Biol Psychiatry 2013;74:908–16.

Mann-Wrobel MC, Carreno JT, Dickinson D. Meta-analysis of neuropsychological functioning in euthymic bipolar disorder: an update and investigation of moderator variables. Bipolar Disord 2011;13:334–42.

Martínez-Arán A, Vieta E, Colom F, Torrent C, Sánchez-Moreno J, Reinares M, et al. Cognitive impairment in euthymic bipolar patients: implications for clinical and functional outcome. Bipolar Disord 2004;6:224–32.

Mazzola-Pomietto P, Kaladjian A, Azorin JM, Anton JL, Jeanningros R. Bilateral decrease in ventrolateral prefrontal cortex activation during motor response inhibition in mania. J Psychiatr Res 2009;43:432–41.

McKenna BS, Sutherland AN, Legenkaya AP, Eyler LT. Abnormalities of brain response during encoding into verbal working memory among euthymic patients with bipolar disorder. Bipolar Disord 2014;16(3):289–99.

Menon V, Adleman NE, White CD, Glover GH, Reiss AL. Error-related brain activation during a Go/NoGo response inhibition task. Hum Brain Mapp 2001;12:131–43.

Mettenburg JM, Benzinger TL, Shimony JS, Snyder AZ, Sheline YI. Diminished performance on neuropsychological testing in late life depression is correlated with microstructural white matter abnormalities. Neuroimage 2012;60:2182–90.

Nakata H, Sakamoto K, Ferretti A, Gianni Perrucci M, Del Gratta C, Kakigi R, et al. Executive functions with different motor outputs in somatosensory Go/Nogo tasks: an event-related functional MRI study. Brain Res Bull 2008;77:197–205.

Oertel-Knochel V, Reinke B, Alves G, Jurcoane A, Wenzler S, Prvulovic D, et al. Frontal white matter alterations are associated with executive cognitive function in euthymic bipolar patients. J Affect Disord 2014;155:223–33.

Penfold C, Vizueta N, Townsend JD, Bookheimer SY, Altshuler LL. Frontal lobe hypoactivation in medication-free adults with bipolar II depression during response inhibition. Psychiatry Res 2015;231(3):202–9.

Pettigrew JD, Miller SM. A 'sticky' interhemispheric switch in bipolar disorder? Proc Biol sciences/The R Soc 1998;265:2141–8.

Pompei F, Jogia J, Tatarelli R, Girardi P, Rubia K, Kumari V, et al. Familial and disease specific abnormalities in the neural correlates of the stroop task in bipolar Disorder. NeuroImage 2011;56:1677–84.

Rubinov M, Sporns O. Complex network measures of brain connectivity: uses and interpretations. Neuroimage 2010;52:1059–69.

Sarrazin S, Poupon C, Linke J, Wessa M, Phillips M, Delavest M, et al. A multicenter tractography study of deep white matter tracts in bipolar I disorder: psychotic features and interhemispheric disconnectivity. JAMA psychiatry 2014;71:388–96.

Sepede G, De Berardis D, Campanella D, Perrucci MG, Ferretti A, Serroni N, et al. Impaired sustained attention in euthymic bipolar disorder patients and non-affected relatives: an fMRI study. Bipolar Disord 2012;14:764–79.

Shimony JS, Sheline YI, D'Angelo G, Epstein AA, Benzinger TL, Mintun MA, et al. Diffuse microstructural abnormalities of normal-appearing white matter in late life depression: a diffusion tensor imaging study. BiolPsychiatry 2009;66:245–52.

Spitzer RL, Williams JB, Gibbon M, First MB. The structured clinical interview for DSM-III-r (SCID). I: history, rationale, and description. ArchGenPsychiatry 1992;49:624–9.

Strakowski SM, Adler CM, Holland SK, Mills N, DelBello MP. A preliminary FMRI study of sustained attention in euthymic, unmedicated bipolar disorder. Neuropsychopharmacology 2004;29:1734–40.

Strakowski SM, Adler CM, Holland SK, Mills NP, DelBello MP, Eliassen JC. Abnormal fMRI brain activation in euthymic bipolar disorder patients during a counting stroop interference task. Am J Psychiatry 2005;162:1697–705.

Thompson JM, Gray JM, Hughes JH, Watson S, Young AH, Ferrier IN. Impaired working memory monitoring in euthymic bipolar patients. Bipolar Disord 2007;9:478–89.

Torres IJ, Boudreau VG, Yatham LN. Neuropsychological functioning in euthymic bipolar disorder: a meta-analysis. Acta Psychiatr Scand 2007;116:17–26.

Townsend JD, Bookheimer SY, Foland-Ross LC, Moody TD, Eisenberger NI, Fischer JS, et al. Deficits in inferior frontal cortex activation in euthymic bipolar disorder patients during a response inhibition task. Bipolar Disord 2012;14:442–50.

Wechsler D. Wechsler Adult Intelligence scale. 3rd ed. San Antonio, TX: Psychological Corporation; 1997.

Woolrich M. Robust group analysis using outlier inference. Neuroimage 2008;41:286–301.

Woolrich MW, Behrens TE, Beckmann CF, Jenkinson M, Smith SM. Multilevel linear modelling for FMRI group analysis using bayesian inference. Neuroimage 2004;21:1732–47.

Worsley KJ. Statistical analysis of activation images. Ch 14. In: Jezzard P, Matthews PM, Smith SM, editors. Functional MRI: an Introduction to methods. New York: Oxford University Press; 2001. p. 251–70.

Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. Br J psychiatry : J Ment Sci 1978;133:429–35.

Zimmerman ME, DelBello MP, Getz GE, Shear PK, Strakowski SM. Anterior cingulate subregion volumes and executive function in bipolar disorder. Bipolar Disord 2006;8:281–8.