Journal of Affective Disorders 213 (2017) 86–95

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Decreased Cingulate Cortex activation during cognitive control processing in bipolar disorder

Staci A. Gruber[a,b,*], M. Kathryn Dahlgren[a,c], Kelly A. Sagar[a,b], Atilla Gonenc[a,b], Lesley Norris[d], Bruce M. Cohen[b,e], Dost Ongur[b,d,e], Kathryn E. Lewandowski[b,d]

[a] Cognitive and Clinical Neuroimaging Core, McLean Imaging Center, McLean Hospital, 115 Mill Street, Belmont, MA 02478, United States
[b] Department of Psychiatry, Harvard Medical School, Boston, MA 02215, United States
[c] Department of Psychology, Tufts University, Medford, MA 02155, United States
[d] Schizophrenia and Bipolar Disorders Research Program, McLean Hospital, 115 Mill Street, Belmont, MA 02478, United States
[e] Program for Neuropsychiatric Research, McLean Hospital, 115 Mill Street, Belmont, MA 02478, United States

ARTICLE INFO

Keywords:
Bipolar disorder
fMRI
Cognitive control
Multi-Source Interference Task
MSIT
Executive function

ABSTRACT

Background: Cognitive deficits are well-documented in patients with bipolar disorder (BPD) and may impact the efficacy of psychotherapy. Cognitive control, a form of executive functioning, is often used therapeutically to shift patients' thoughts and behaviors from automatic, maladaptive responses to adaptive coping strategies. This study examined cognitive control processing in patients with BPD using the Multi-Source Interference Task (MSIT).

Method: Twenty-nine patients diagnosed with BPD and 21 healthy control (HC) subjects completed the MSIT with concurrent functional magnetic resonance imaging (fMRI).

Results: Patients with BPD generally performed worse on the MSIT relative to HC participants; the BPD group had significantly lower performance accuracy and made more omission errors. Further, fMRI analyses revealed differential patterns of activation between the groups during the MSIT. Region of interest (ROI) analyses revealed that relative to HC participants, patients with BPD activated significantly fewer voxels within the cingulate cortex (CC) and more voxels within prefrontal cortex (PFC), although the PFC findings did not survive more stringent significance thresholds.

Limitations: Patients and HCs were not matched for age, sex, and premorbid verbal IQ, however, these variables were controlled for statistically. Medication usage in the BPD group may have possibly impacted the results. Given a priori hypotheses, ROI analyses were utilized.

Conclusions: Decreased CC activation and increased PFC activation may be associated with impaired cognitive control, demonstrated by BPD patients when completing the MSIT. Identifying the neural mechanisms which underlie key cognitive abnormalities in BPD may aid in clarifying the pathophysiology of this disorder and inform selection of potential targets for cognition remediation in BPD.

1. Introduction

Bipolar disorder (BPD) affects approximately 2.6% of adults in the United States and is associated with a debilitating remitting, relapsing course and high rates of disability (Kessler et al., 2005). In addition to the severe changes in mood, which characterize BPD, neurocognitive deficits are well-documented in BPD patients, and are often apparent in both depressive and manic states and in euthymia, when alleviation of clinical symptoms has occurred (Lewandowski et al., 2013; Robinson et al., 2006).

Patients with BPD experience cognitive dysfunction in multiple cognitive domains; two meta-analyses have identified impairments in attention, verbal memory, and executive function as characteristic of BPD patients (Bourne et al., 2013; Robinson and Ferrier, 2006), findings which are among the most consistently reported in the literature (Arts et al., 2008; Robinson and Ferrier, 2006). Deficits in other cognitive domains including working memory, visuospatial learning and memory, verbal fluency, and processing speed are also commonly reported (Bourne et al., 2013; Balanzá-Martínez et al., 2005; Glahn et al., 2007; Lim et al., 2013).

Additionally, cognitive impairment is strongly associated with functional outcomes in patients with BPD (Green, 2006; Barch, 2009), highlighting the need for careful identification of the pathophy-

* Correspondence to: McLean Hospital, 115 Mill Street, Belmont, MA 02478, United States.
E-mail address: gruber@mclean.harvard.edu (S.A. Gruber).

http://dx.doi.org/10.1016/j.jad.2017.02.003
Received 20 December 2016; Accepted 5 February 2017
Available online 07 February 2017

siological processes underpinning key cognitive deficits. In fact, Lewandowski and colleagues (2013) reported that baseline neurocognitive functioning was the only significant predictor of community functioning after a six-month follow-up in patients with BPD. In addition, Gruber and colleagues reported that neuropsychological performance, particularly on the Stroop Color Word Test, a measure of frontal function and behavioral inhibition, predicted clinical recovery in BPD patients (Gruber et al., 2008), suggesting that cognitive function may be closely tied to clinical outcomes. Further, studies of cognitive remediation – behavioral interventions aimed at targeting cognitive dysfunction – suggest that training produces neurobiological changes in patients with psychosis, typically in frontal regions (Popov et al., 2011; Wykes et al., 2012; Bor et al., 2011; Wexler et al., 2000; Subramaniam et al., 2012; Eack et al., 2010; Penadés et al., 2016). While the exact association between training domain and neurobiological effect is unclear, indirect evidence supports some degree of domain specificity. Sensory gaiting was normalized in schizophrenia after auditory-focused cognitive training but not after general cognitive training (Popov et al., 2011), and a frontal/executive training program found greatest effects in frontal, parietal and precuneus activation using the n-back task (Penadés et al., 2013). Clarification of the neurobiological underpinnings of key cognitive functions such as attentional control in patients with BP will aid in the development of interventions to target these cognitive processes.

Cognitive control is an aspect of executive function that involves inhibition of an automatic response tendency in favor of a less automatic response. In psychotherapy, this skill is useful in order to shift patients' thoughts and behaviors from maladaptive responses that have become natural or automatic to more adaptive behaviors and coping strategies. Deficits in cognitive control have been reported in patients with BPD and their unaffected relatives (Bora et al., 2009; Stefanopoulou et al., 2009). Further, several studies using cognitive control tasks (e.g. the Stroop Color Word Task) in adult patients with BPD have reported abnormal brain activation relative to healthy control participants in the prefrontal cortex (PFC), especially the medial frontal gyrus and ventrolateral and dorsolateral PFC, and the cingulate cortex (CC), particularly the anterior (ACC; Gruber et al., 2004; Kronhaus et al., 2006; Roth et al., 2006; Pompei et al., 2011; Strakowski et al., 2005).

Interestingly, the exact nature of dysfunctional activation of the PFC and CC during cognitive control processing in patients with BPD remains unclear. Some evidence has suggested decreased PFC activation in BPD participants relative to healthy control participants, particularly when the two groups performed the Stroop task equally well (Pompei et al., 2011; Roth et al., 2006) or when the patients with BPD exhibited lower performance accuracy (Strakowski et al., 2005). However, in one study, when patients with BPD performed the interference condition of the Stroop task more slowly but with the same accuracy as healthy control participants, the patient group demonstrated increased dorsolateral PFC activation (Gruber et al., 2004). Medication may also play a role in dysfunctional activation of these areas, as medicated BPD participants have been shown to display increased PFC (particularly dorsolateral PFC) and ACC activation during the Stroop compared to unmedicated BPD participants (Strakowski et al., 2005).

In the current study, we utilized the Multi-Source Interference Task (MSIT) to assess the potential impact of BPD on cognitive control. The MSIT assesses cognitive control processing using two different types of cognitive interference (spatial and flanker), and has been shown to robustly and reliably activate regions of interest associated with attention, particularly the ACC (Bush et al., 2003). This task has been employed in studies assessing a variety of psychiatric conditions, including anxiety-based disorders such as obsessive compulsive disorder (OCD; Cocchi et al., 2012; Fitzgerald et al., 2010, 2013; Yucel et al., 2007a), generalized anxiety disorder (GAD; Fitzgerald et al., 2013), and posttraumatic stress disorder (PTSD; Shin et al., 2011); major depression (Davey et al., 2012); schizophrenia (Harrison et al., 2007; Heckers et al., 2004; Ikuta et al., 2012, 2014; Stern et al., 2009); attention-deficit/hyperactivity disorder (ADHD; Bush et al., 2008, 2013); and substance use disorders (Gruber et al., 2012; Harding et al., 2012; Yucel et al., 2007b). Studies utilizing the MSIT in those with anxiety and mood disorders generally indicate hyperactivation of frontal regions of interest within attention networks, particularly the ACC (Fitzgerald et al., 2010; Shin et al., 2011; Yucel et al., 2007a), and abnormal internetwork connectivity (Cocchi et al., 2012; Davey et al., 2012; Fitzgerald et al., 2010) during cognitive control processing. Interestingly, these differences in activation patterns have been observed despite similar task performance between healthy control and clinical participants. Although trends have been noted for slower response times in PTSD (Shin et al., 2011) and poorer performance accuracy in OCD (Yucel et al., 2007a), these findings were not statistically significant. The current interpretation of hyperactivation of attentional networks without concurrent performance differences is that it reflects neurocompensation; increased activation is necessary in clinical patients in order to achieve the same level of task performance as healthy control participants.

To date, however, no studies have utilized the MSIT to examine cognitive control in those diagnosed with BPD. Therefore, the aim of the current study was to examine behavioral performance as well as functional patterns of brain activation, using functional magnetic resonance imaging (fMRI), during completion of the MSIT in a sample of patients diagnosed with BPD as well as a sample of healthy control (HC) participants. In light of mounting evidence that patients with BPD experience cognitive deficits including difficulty with attention and executive functioning, we hypothesized that individuals with BPD may perform more poorly than HCs on the MSIT, reflected by lower percent accuracy and slower response times. In addition, given previous neuroimaging investigations, we expected that during the performance of the MSIT task, patients with BPD would exhibit hyperactivation of the attention network regions of interest (PFC and CC) relative to HC participants.

2. Materials and methods

2.1. Participants

Twenty-nine patients diagnosed with BPD and a history of psychotic symptoms, as well as 21 well-matched, non-psychiatric, healthy control subjects from previous investigations were recruited from the greater Boston area. Patients with BPD were recruited as part of a study of cognitive remediation; all scans included in the present study were acquired at baseline, prior to randomization to treatment or control groups. BPD diagnosis was determined by trained clinicians and research staff, through our cognitive remediation study or as part of a larger study on genotype and phenotype in psychotic disorders, using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-IV; First et al., 1994) in conjunction with all available collateral information from medical records and treatment providers. Interrater reliability exercises conducted regularly showed perfect rates of agreement (kappa=1.0) for primary SCID diagnoses (Öngür et al., 2009). In order to be considered for inclusion in this study, patients with BPD were required to have a current diagnosis of bipolar I disorder, and HC participants could not have any Axis I disorders. Exclusion criteria also included MRI contraindications; neurologic, tic, tremor, or movement disorders; delirium secondary to medical illness; history of head trauma or seizure disorders; and diagnosis of current substance abuse (past month) or substance dependence (past year). Further, in order to qualify for study entry, patients had to be euthymic at the time of study enrollment. Although all patients had a history of psychosis, to ensure that patients were not acutely symptomatic, total score on the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987), a measure of symptom severity for positive (e.g., hallucinations and delusions) and

negative (e.g., blunted affect, emotional withdrawal) symptoms could not exceed 75, scores on the psychosis items of the PANSS could not exceed 3 ("mild"), and ratings of current mania, as assessed by the Young Mania Rating Scale (YMRS; Young et al., 1978) could not exceed 6. Given this requirement, patients with current inpatient status were also excluded from the current study. All participants were required to have an estimated verbal IQ of 75 or higher, as assessed by either the North American Adult Reading Test (NAART; Blair and Spreen, 1989) or the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999). This criterion was applied in order to ensure that participants had the cognitive capacity to complete the MSIT, and that they would be able to participate in the cognitive training paradigm.

This research was approved by the Institution Review Board (IRB) of the Partners Healthcare System, which reviews research studies conducted at McLean Hospital and other sites. In accordance with IRB policy, prior to study participation, each individual was required to review and sign an IRB-approved informed consent form, which explained participants' rights, as well as the risks and benefits associated with participation in the current study. All study procedures were fully explained, and participants were explicitly informed of the voluntary nature of the study. Participants who demonstrated legal incompetence (defined by person or treatment guardianship) or mental incompetence (failure to understand the informed consent process) were not enrolled in the current investigation.

2.2. Demographic information and clinical state assessment

Demographic information including age and education level was obtained during the SCID. Additionally, socioeconomic information was collected using the Hollingshead Four-Factor Index of Socioeconomic Status (Hollingshead, 1975), and verbal IQ was measured with the NAART or WAIS. Current clinical state was measured using Montgomery Asberg Depression Rating Scale (MADRS; Montgomery and Asberg, 1979) as well as the YMRS and PANSS, which were also used to evaluate inclusion criteria for the study. Only the BPD group completed the PANSS, while both the HC and BPD groups completed the MADRS and YMRS.

Additionally, current psychiatric medication status information was collected for BPD patients during the clinical interview. All BPD participants reported current psychiatric medication use, and 27 of the 29 BPD participants (93.10%) were currently taking mood stabilizers. Further, eight (27.59%) were taking antidepressants, six (20.69%) were taking benzodiazepines, and three (10.35%) were taking stimulants. Additionally, a total of 19 (65.52%) BPD participants reported current treatment with antipsychotic medications, with most participants (18 or 62.07%) taking atypical antipsychotics and only two (6.90%) taking typical antipsychotics.

2.3. Multi-Source Interference Task (MSIT) procedures

All participants completed the Multi-Source Interference Task (MSIT) with concurrent fMRI. The MSIT incorporates aspects of well-established measures of cognitive interference (e.g. Stroop, Simon, and Eriksen Flanker tasks), and uses two different types of cognitive interference (spatial and flanker) to measure cognitive control (Fig. 1; Bush et al., 2003; Bush and Shin, 2006). During the MSIT, three-digit stimuli sets (comprised using the numbers 0, 1, 2, or 3) are presented briefly on a screen. Each set contains two identical distractor numbers and a target number that differed from the distractors. Participants report via a button press the *identity* of the target number that differs from the two distractor numbers. The task consists of two conditions presented in separate alternating blocks. During the control condition, distractor numbers are always zeros, and the identity of the target number always corresponds to its position on the button response pad (i.e. 100, 020, 003). However, during the interference condition, distractors numbers are always numbers other than 0, and the identity of the target number is always incongruent with its position on the button response pad (e.g. 211, 232, 331, etc.). The entire task is comprised of four blocks of control trials alternating with four blocks of interference trials; each stimulus is presented for 1750 ms, and each block contained 24 trials each of control and interference stimuli (48 total). The task begins and ends with a fixation period (30 s), making the total run time 6 min and 36 s.

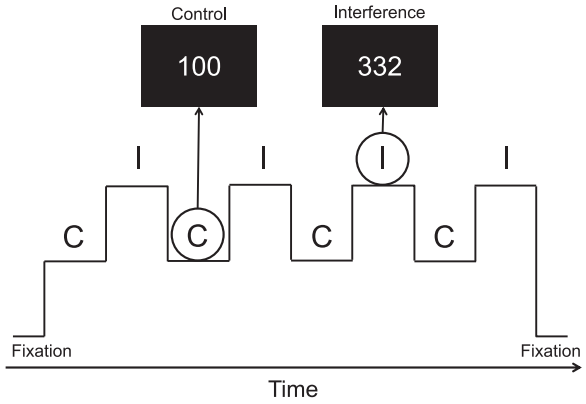

Fig. 1. Schematic of the Multi-Source Interference Task (MSIT). The MSIT begins and ends with a fixation period, and is comprised of four blocks of control trials alternating with four blocks of interference trials. Abbreviations: C = control condition; I = interference condition.

Once inside the scanner and prior to active scanning, subjects were given a practice session of the task to familiarize them with the response equipment and ensure that all individuals understood task instructions adequately. Performance on the MSIT was quantified by percent accuracy, number of errors, and response time (ms). A derived contrast score (interference-control) was also calculated in order to determine the effect of cognitive control without the influence of psychomotor speed. Errors were subdivided into two types: omission errors, which occur when no response is given before the next stimulus appears, and errors of commission, which reflect incorrect responses. Finally, as several studies have shown that BPD patients exhibit increased intra-subject variability of response times (ISV-RT; Adleman et al., 2014; Bora et al., 2006; Brotman et al., 2009; Gallagher et al., 2015), we also examined within-subject patterns of performance. ISV-RT, defined as the average variability in the time an individual participant takes to respond to task stimuli, was calculated for each of the task conditions (control and interference).

2.4. Statistical analyses

Demographic data were compared using two-tailed, univariate analyses of variance (ANOVAs) for scale variables (e.g., age) and Chi-Squared analyses for frequency variables (e.g., sex). Given our *a priori* hypotheses, one-tailed univariate ANOVAs were employed to assess differences in clinical state and MSIT performance between the HC and BPD groups. MSIT performance was assessed for each individual task condition as well as for the interference-control contrast. In addition, because statistically significant differences were detected between the groups for age, sex, and verbal IQ, univariate analyses of covariance (ANCOVAs) controlling for each of these potentially confounding variables were also conducted. However, the ANCOVAs yielded similar results as the ANOVAs; all main effects remained significant or trends. Therefore, for ease of interpretation, only the ANOVA results are presented in this publication; however, ANCOVA results are provided in the Supplemental material (Supplemental Table 1). Additionally, MSIT performance data for one BPD participant were lost due to equipment malfunction, but this individual's data were included in the fMRI analyses.

2.5. Neuroimaging methods

Imaging was performed on a Siemens Trio whole body 3T MRI scanner (Siemens Corporation, Erlangen, Germany) using a quadrature RF head coil. A T1-weighted anatomical image was acquired using a magnetization-prepared gradient echo sequence (TR=2100 ms; TE=2.25 ms; flip angle=12 degrees; 128 slices; FOV=256×256 mm^2; acquisition voxel size=1.0×1.0×1.3 mm^3). During the MSIT, 40 contiguous coronal slices were acquired from each subject, providing whole brain coverage (5 mm, 0 mm skip), and images were collected every 3 s using a single shot, gradient pulse echo sequence (TR=3000 ms; TE =30 ms, flip angle =90, with a 20 cm field of view and a 64×64 acquisition matrix; in plane resolution 3.125×3.125×3.125 mm^3). A total of 132 images per slice were collected in accordance with the original MSIT scanning parameters in order to allow for comparability of data from the current study to previous findings (Bush et al., 2003; Bush and Shin, 2006).

2.6. Image processing and analysis

Functional MRI images were analyzed using SPM8 (version 4667, Wellcome Department of Imaging Neuroscience, University College, London, UK) software package running in Matlab (version R2010b, MathWorks, Natick, MA, USA). First, blood oxygen level dependent (BOLD) fMRI data were corrected for motion in SPM8 using a 2-step intra-run realignment algorithm that uses the mean image created after the first realignment as a reference (a least squares approach and a 6 parameter rigid body spatial transformation). A criterion of 3 mm of head motion in any direction was used as an exclusionary criterion. The realigned images were then normalized to an EPI template in Montreal Neurological Institute (MNI) stereotactic space. Normalized images were re-sampled into 3 mm cubic voxels and then spatially smoothed using an isotropic Gaussian kernel with 6 mm full width at half maximum (FWHM). Global scaling was not used, high-pass temporal filtering with a cut-off of 128 s was applied, and serial autocorrelations were modeled with an AR(1) model in SPM8. Individual movement parameters were entered as regressors into the design. Using a general linear model, statistical parametric images were calculated individually for each subject examining the MSIT interference > control condition contrast.

These images were subsequently entered into second level model, subjected to a voxel-wise *t*-tests to assess for statistical significance. Using two sample *t*-tests, we made direct comparisons between the HC and the BPD groups. The region of interest (ROI) masks were defined using the Wake Forest University Pickatlas utility (Maldjian et al., 2003), which were further defined by Brodmann areas. Given our hypotheses, we examined two ROIs 1) frontal, which included the superior frontal, mid frontal and inferior frontal regions, and 2) cingulate, which included the mid and anterior CC. Contrast analyses consisted of the subtraction of one map from the other; for example, the cingulate activity of the BPD patients was subtracted from cingulate activity of the HC subjects in each condition to determine which areas showed increased activity in control relative to BPD subjects. The statistical threshold was originally set at $p < .05$ uncorrected and a minimum cluster extent (k) of 10 contiguous voxels. However, in order to ensure adequate statistical power, a Monte Carlo simulation was conducted and yielded a new threshold of k=54 which was applied to the current analyses. These simulations were completed in the AlphaSim module in AFNI (Ward, 2000) to compute the minimum voxel cluster size required to correct for Type I error in our statistical analysis.

Table 1
Demographic and clinical state data.

Demographic Variable	**HC**(n=21)	**BPD**(n=29)	***Statistic***	***Significance***
Frequency Variables			***X^2***	***p (2-tailed)***
Sex[a]	7M, 14F	18M, 11F	**4.023**	**.045**
Handedness[a]	20R, 1L	28R, 1L	.055	.815
Scale Variables			***F***	***p (2-tailed)***
Age[b]	23.95 *(4.90)*	29.83 *(8.82)*	**7.585**	**.008**
Education[*,b]	5.43 *(1.50)*	4.97 *(1.38)*	1.278	.264
SES[**,c]	52.55 (*11.39*)	49.33 (*12.62*)	.719	.402
Verbal IQ[***,d]	**127.81 (*5.89*)**	**111.57 (*22.86*)**	**10.045**	**.003**
Clinical State Variable			***F***	***p (1-tailed)***
YMRS[b]	**.76 (*1.14*)**	**5.67 (*4.81*)**	**20.887**	**< .001**
MADRS[b]	**1.33 (*1.28*)**	**11.72 (*8.56*)**	**30.283**	**< .001**
PANSS	–	48.53 (*11.06*)	NA	NA

[*] Education scores were based on the Structured Clinical Interview for DSM-IV (SCID): 1=Grade 6 or less, 2=Grade 7–12 (without graduation), 3=high school/high school equivalent, 4=part college, 5=graduated 2-year college, 6=graduated 4-year college, 7=part graduate/professional school, 8=completed graduate/professional school.
[**] Socioeconomic status (SES) was measured by the Hollingshead Four-Factor Index of Socioeconomic Status.
[***] IQ was assessed using either the North American Adult Reading Test (NAART) or the Wechsler Abbreviated Scale of Intelligence (WASI).
[a] df=1.
[b] df=1,48.
[c] df=1,38.
[d] df=1,47.

3. Results

3.1. Demographics and clinical state

As reported in Table 1, participants (aged 18–48) were well matched for years of education and socioeconomic status. The BPD participants were, on average, older than the HC participants (F(1,48) =7.585, p=.008), although the majority of individuals for both groups were in their twenties. The BPD participants also had significantly lower estimated verbal IQ scores than HC participants (F(1,47) =10.045, p=.003). Further, significantly more males were present in the BPD group relative to the HC group (X^2(1, N=50)=4.023, p=.045). However, as previously mentioned, ANCOVAs controlling for these potentially confounding variables were conducted and revealed that age, sex, and verbal IQ between-group differences did not significantly impact results. Fifteen of 29 BPD subjects endorsed comorbid anxiety or substance use disorders. Four subjects were diagnosed with current anxiety disorders (i.e., OCD, panic disorder, Generalized Anxiety Disorder), while four had a history of a past anxiety disorder. As previously mentioned, although current substance abuse (past month) or substance dependence (past year) were both exclusionary criteria for study entry, 10 BPD patients reported past alcohol abuse or dependence, and 12 had past drug abuse or dependence.

Although all patients were stable outpatients at the time of assessment, as expected, the BPD participants reported higher levels of clinical symptomatology than the HC participants. The BPD group had significantly higher ratings of depression on the MADRS (F(1,48) =30.283, $p < .001$) and mania on the YMRS (F(1,48)=20.887, $p < .001$) relative to the HC group. In the BPD group, the average MADRS score (M=11.72) indicated mild depression (range 7–19), whereas the HC group mean (M=1.33) was in the normal/symptoms absent range (range 0–6). Further, the average YMRS score for both the BPD

Table 2
Multi-Source Interference Task (MSIT) Performance: Healthy Controls (HC) vs Bipolar (BPD) Participants.

	HC Mean (SD)	BPD Mean (SD)	ANOVA[a]	
			F	*p* (η^2)
Control Trials				
Percent Accuracy	98.21 (2.93)	97.14 (3.04)	1.561	.109 (.032)
Response Time (ms)	**609.63 (97.63)**	**671.07 (80.67)**	**5.811**	**.010 (.110)**
# Commission Errors	**.19 (.51)**	**.64 (.87)**	**4.497**	**.020 (.087)**
# Omission Errors	1.52 (2.84)	2.11 (2.59)	.561	.229 (.012)
ISV-Response Time	128.32 (35.91)	130.57 (32.13)	.053	.409 (.001)
Interference Trials				
Percent Accuracy	**87.60 (12.68)**	**80.58 (11.99)**	**3.915**	**.027 (.077)**
Response Time (ms)	**868.97 (78.26)**	**930.51 (64.53)**	**9.092**	**.002 (.162)**
# Commission Errors	*3.62 (3.54)*	*5.18 (4.07)*	*1.962*	*.084 (.040)*
# Omission Errors	**8.29 (10.62)**	**13.46 (10.19)**	**2.991**	**.045 (.060)**
ISV-Response Time	*145.23 (20.75)*	*155.33 (26.82)*	*2.053*	*.080 (.042)*
Interference - Control Contrast				
Percent Accuracy	**−10.62 (10.78)**	**−16.56 (10.41)**	**3.788**	**.029 (.075)**
Response Time (ms)	259.34 (50.41)	259.44 (57.74)	< .001	.498 (< .001)
# Commission Errors	3.42 (3.37)	4.54 (3.77)	1.133	.147 (.024)
# Omission Errors	**6.76 (8.79)**	**11.38 (8.77)**	**3.288**	**.038 (.065)**
ISV-Response Time	16.91 (39.16)	24.76 (36.20)	.559	.229 (.012)

Bolded results are significant at α≤.05 (1-tailed) and *italicized* results are significant at α≤.10 (1-tailed).
Abbreviations: Analysis of Variance (ANOVA); Intra-Subject Variability (ISV).
[a] df=1,47.

Table 3
Multi-Source Interference Task Interference-Control Condition Activation Local Maxima within Cingulate Cortex (CC) and Frontal Cortex Regions of Interest (ROI).[a]

Group Region	Cluster Size (Voxels)	x	y	z	SPM {t}	Voxel *p* Uncorrected
Cingulate Cortex (CC)						
Healthy Controls						
Right middle cingulate cortex (BA32)	139	9	21	39	3.98	< .001
BPD Patients						
Right middle cingulate cortex (BA32)	114	9	21	39	4.25	< .001
Healthy Controls > BPD Patients						
Right middle cingulate cortex (BA24)	73	6	−3	30	2.94	.003
BPD Patients > Healthy Controls						
No activation *k*≥54	–	–	–	–	–	–
Frontal						
Healthy Controls						
Right superior frontal gyrus (BA6)	364	24	6	57	6.40	< .001
Left inferior frontal gyrus (BA45)	395	−45	27	27	5.45	< .001
Left superior frontal gyrus (BA6)	172	−24	−6	57	4.61	< .001
Right inferior frontal gyrus (BA45)	220	45	36	24	3.99	< .001
BPD Patients						
Left inferior frontal gyrus (BA44)	898	−36	12	24	5.57	< .001
Right superior frontal gyrus (BA6)	329	27	−3	60	4.69	< .001
Right middle frontal gyrus (BA45)	352	45	42	21	4.44	< .001
Healthy Controls > BPD Patients						
No activation *k*≥54	–	–	–	–	–	–
BPD Patients > Healthy Controls						
No activation *k*≥54	–	–	–	–	–	–

[a] Results reflect a significance threshold of k≥54.

(*M*=5.67) and HC (*M*=.76) groups were below the clinical threshold for hypomania/mania (severity threshold score =25+; Lukasiewicz et al., 2013) Additionally, the BPD group had an average score of 48.53 on the PANSS, which falls into the upper range of 'mildly ill' psychopathology (range 0–58) according to Leucht et al. (2005). Given that the clinical scale ratings from our BPD group were within the 'mildly ill' or 'symptom absent' range, we can confirm that this group was not acutely symptomatic during the study procedures (a requirement for inclusion in the study).

3.2. Multi-Source Interference Task (MSIT) data

Results suggest that all participants understood the task; each achieved percent accuracy scores significantly higher than chance would allow. Overall, the BPD patients performed more poorly on the MSIT relative to HC participants (Table 2). During the control condition, BPD patients exhibited slower response times ($F(1,47)=5.811$, $p=.010$) and higher rates of commission errors ($F(1,47)=4.497$, $p=.020$) compared to the HC participants. During the interference condition, BPD patients demonstrated lower percent accuracy ($F(1,47)=3.915$, $p=.027$), slower response times ($F(1,47)=9.092$,

p=.002), and higher rates of omission errors (F(1,47)=2.991, p=.045) relative to HC participants. BPD participants also demonstrated a trend for larger ISV-RT values relative to the HC participants during the interference condition (F(1,47)=2.053, p=.080). Additionally, the derived contrast (interference-control) revealed that in comparison to the HC group, the BPD group exhibited a significantly greater difference in percent accuracy between the control and the interference conditions (poorer performance during the interference condition vs the control condition; F(1,47)=3.788; p=.029), as well as increased omission errors (F(1,47)=3.288, p=.038) relative to HC participants. With regard to response time, significant differences were observed during both the control and interference conditions indicating slower response time in BPD compared to HC participants. However, no significant between-group differences in response time were detected for the interference-control contrast.

3.3. Functional neuroimaging data

As reported in Table 3, analysis of the fMRI data collected during completion of the MSIT revealed that the BPD and HC groups demonstrated generally similar patterns of activation for the interference-control contrast, yet also exhibited several notable differences in terms of both magnitude and localization of activation within the ROIs. Specifically, for the one-sample analyses within the CC ROI, qualitative assessments of both the HC and BPD groups exhibited activation in the right middle CC; however, the BPD group appeared to demonstrate relative hypoactivation in this region (k=114 vs. 139 voxels activated; Fig. 2A). Between-group contrast analyses (HC > BPD) also confirmed additional activation of the mid CC for the HC group that was not present in the BPD group (Fig. 2B); results indicate that the BPD group activated fewer overall voxels within the CC ROI relative to the HC group (0 vs 73 voxels). Within the frontal cortex ROI, one-sample analyses revealed that both the HC (k=1151) and BPD (k=1579) groups demonstrated robust bilateral activation within the superior and inferior frontal gyrus (Fig. 2A). Additionally, the BPD patients evidenced increased activation within the left inferior frontal gyrus relative to HCs (k=898 vs. 395), and also exhibited activation in the middle frontal gyrus, a region that did not appear to be activated by the HC group. Although the BPD patients exhibited increased activation in the frontal ROI relative to the HC group, these differences did not survive the minimum cluster threshold generated from the Monte Carlo simulation, and are therefore not reported.

4. Discussion

To our knowledge, this is the first study to utilize the MSIT to examine cognitive control processing and its associated attention network activation patterns in patients with BPD. As hypothesized, results indicate that patients with BPD performed worse on the MSIT, a task of cognitive control function, relative to HC participants. Specifically, once psychomotor speed was accounted for using the derived contrast, the BPD group demonstrated significantly poorer performance accuracy and made more omission errors than the HC group. Further, fMRI analyses revealed differential patterns of activation between the groups during the MSIT. Relative to HC participants, patients with BPD activated significantly fewer voxels within the CC ROI and more voxels within the frontal ROI (although the frontal ROI differences did not survive the minimum cluster threshold), and also demonstrated some qualitative differences in specific regions activated within these regions.

Findings from the current study are consistent with previous investigations demonstrating cognitive impairment in patients with BPD; specifically our results support previous work, which has also reported cognitive control deficits in BPD patients (e.g., Strakowski et al., 2005; Gruber et al., 2004). However, surprisingly few studies using the MSIT in clinical samples have found significant behavioral differences. Researchers using the MSIT in major depressive disorder (Davey et al., 2012) and substance abuse disorders (Gruber et al., 2012; Harding et al., 2012; Yucel et al., 2007b) did not detect significant performance differences between these populations and healthy control participants. Additionally, studies of anxiety-based disorders have not observed significant MSIT performance differences (Cocchi et al., 2012; Fitzgerald et al., 2010, 2013); however two studies have reported non-significant trends in MSIT performance. Shin et al. (2011) noted a trend for individuals with PTSD (and their trauma-unexposed identical twins) to have slower MSIT response times when compared to trauma-exposed participants without PTSD (and their trauma-unexposed identical twins; main effect of PTSD twin pair, p=.07). Yucel and collaborators (2007a) reported a trend for individuals with OCD to have worse performance accuracy compared to HC participants (p=.09). The MSIT literature in schizophrenia is highly inconsistent. While there is some evidence for increased commission errors in patients with schizophrenia relative to HC participants (Stern et al., 2009), and impaired performance accuracy in schizophrenia with concurrent antipsychotic medication use (Ikuta et al., 2014), others have not found significant MSIT performance differences (Heckers et al., 2004; Harrison et al., 2007).

In the current study, BPD participants exhibited slower response times relative to the HCs during both the control and interference conditions of the MSIT, but not on the interference-control derived contrast, which controls for psychomotor speed. However, for the derived contrast, BPD participants demonstrated impairment of performance accuracy, driven by significantly more omission errors in the BPD group relative to the control group. Interestingly, omission errors are suggestive of slowed cognitive control processing. Thus, even though differences in response time were not significant when psychomotor speed was accounted for, the fact that BPD subjects made significantly more omission errors than HC subjects suggests that cognitive control processing speed may be slower in individuals with BPD. Additionally, during the control condition, BPD participants made significantly more *commission* errors, reflective of a more impulsive response style, than HC participants. During the interference condition, the BPD group made more *omission* errors than the HC group. Taken together, these results suggest that individuals with BPD may be more impulsive during easy tasks, but during more difficult tasks requiring greater cognitive resource, impaired performance may instead be driven by slower processing.

Research on attentional processing in mood disorders has recently recognized the importance of assessing ISV-RT on tasks that require sustained attention. Increased ISV-RT has been observed in adults (Bora et al., 2006; Gallagher et al., 2015) and children with BPD and their unaffected first-degree relatives (Adleman et al., 2014; Brotman et al., 2009). These findings suggest that increased ISV-RT may be a characteristic of BPD as well as a potential familial risk marker for unaffected relatives. In the current study, we report some evidence of increased ISV-RT values for BPD participants during the MSIT interference condition; however, this finding only trended towards significance (p=.080). It is important to note that the majority of previous studies reporting significantly larger ISV-RT values in BPD used Continuous Performance Tests (Bora et al., 2006; Brotman et al., 2009; Gallagher et al., 2015) which assess sustained attention over longer periods of time. As the MSIT is a more complex measure of attention and executive function, as well as a shorter task, inherent differences in these measures may have contributed to the differences between previous findings and our own.

In addition, neuroimaging results revealed some degree of hypoactivation of the CC (particularly in the anterior and middle CC) and hyperactivation of the PFC (particularly the dorsolateral PFC) in patients with BPD relative to HC participants during cognitive control processing. This is consistent with previous studies examining cognitive control processing in BPD using the Stroop. For example, Gruber and colleagues (2004) reported increased dorsolateral PFC activation with some evidence for decreased ACC activation in BPD participants

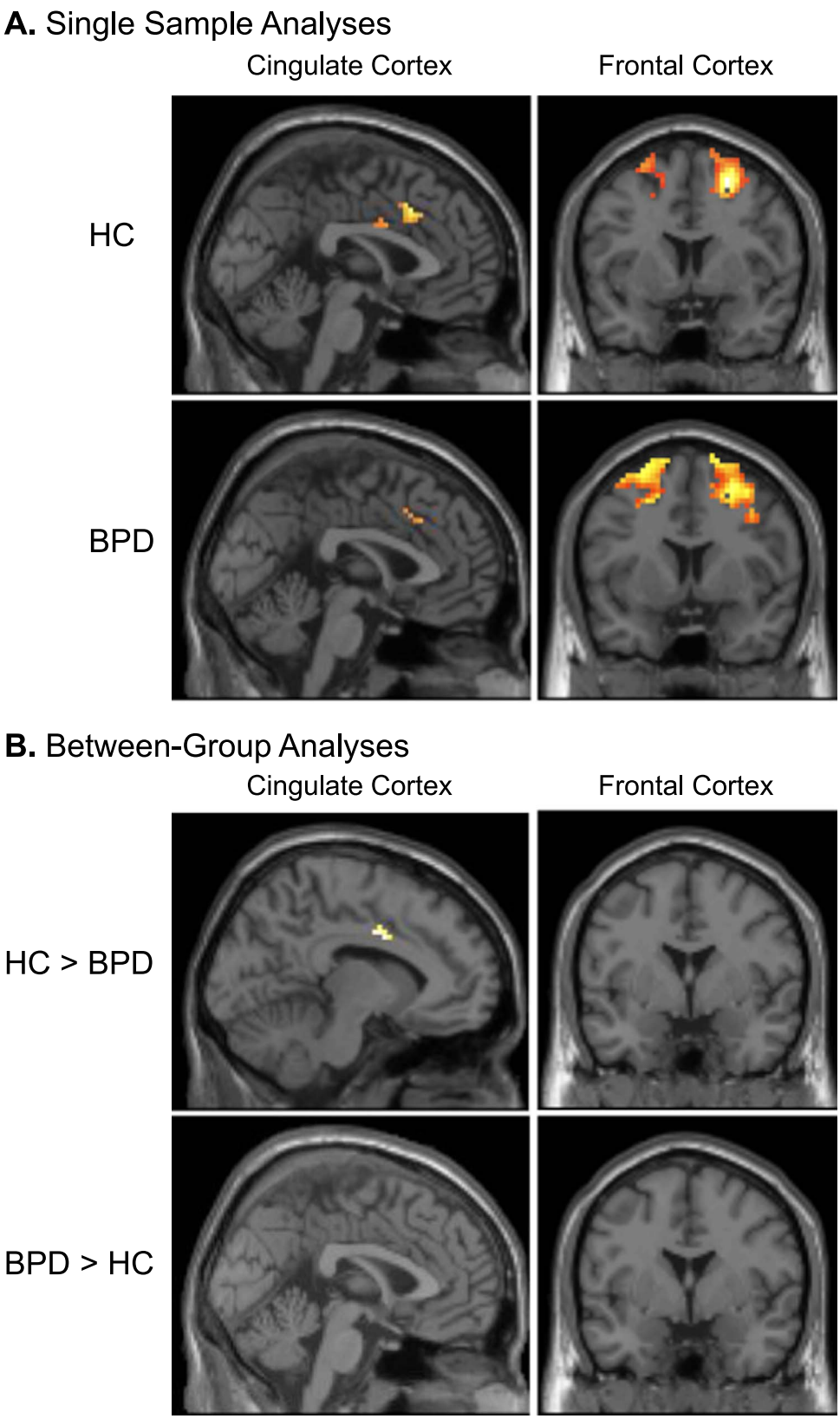

Fig. 2. Multi-Source Interference Task Interference-Control Condition Activation Images within Cingulate Cortex (CC) and Frontal Cortex Regions of Interest (ROI). Relative to HC participants, patients with BPD activated significantly fewer voxels within the cingulate cortex (CC) and more voxels within prefrontal cortex (PFC), although the PFC findings did not survive more stringent significance thresholds. (Please note: results used a significance threshold of $k \geq 54$ voxels).

compared to HC subjects during completion of the Stroop Color Word Test. Importantly, the authors also observed slower interference processing in the BPD group relative to the HC group. Although other researchers have witnessed decreased PFC activation in BPD compared to HC groups during the Stroop (Pompei et al., 2011; Roth et al., 2006; Strakowski et al., 2005), concurrent slower interference processing in

the BPD group was not observed.

Similar to the current study, hyperactivation of the PFC during the MSIT has also previously been reported in one study of patients with OCD (Fitzgerald et al., 2010). In contrast, however, Yucel and colleagues (2007a) observed decreased PFC activation in OCD. Additionally, while the current study demonstrated that BPD patients exhibited hypoactivation of the CC during the MSIT, most studies of anxiety disorders have reported increased CC (especially dorsal ACC) activation (Fitzgerald et al., 2010; Shin et al., 2011; Yucel et al., 2007a). Davey et al. (2012) examined MSIT performance in patients with major depression. Although results revealed task-related deactivation in the ventral and dorsal posterior CC, caudate and ventromedial PFC in both depressed individuals and healthy control participants, no significant between-group differences emerged. However, functional connectivity analyses revealed that among depressed patients, task engagement was associated with decreased connectivity between the ACC and ventromedial PFC. The extent of this reduction positively correlated with greater activation of the dorsolateral PFC (Davey et al., 2012). These differences in attentional network abnormalities may be due to distinct differences in clinical presentation or the unique clinical characteristics that differentiate BPD from affective, anxiety and other disorders. However, it is important to consider that previous MSIT literature in depression and anxiety disorders also reported CC and PFC dysfunction *without* concurrent performance deficits, whereas the current study observed *both* impaired MSIT performance and altered attentional network activation in BPD relative to HC participants. Abnormal attentional network activation in clinical populations without co-occurring performance differences is considered to be reflective of neurocompensatory or neuromodulatory effects; altered CC and PFC activation may be necessary in order for clinical patients to achieve the same level of task performance as HC participants. In contrast, our findings of decreased CC activation and increased PFC activation may be related to significant differences in task performance, notably, slower processing in the BPD sample. It is therefore possible that the combination of both altered patterns of activation and differences in task performance exhibited by the BPD sample relative to the HC group reflects a disruption in the neural circuitry underlying cognitive control, rather than a neurocompensation.

4.1. Limitations

While interesting, study findings should be interpreted in the context of several limitations. Patients and controls were not matched on several demographic variables (age, sex, and premorbid verbal IQ), which were subsequently controlled for in the statistical analyses. While the results of our ANCOVAs suggested that these potential confounding variables did not significantly impact task performance, these variables may still influence cognitive control processing, as they may mediate underlying processing strategies. Further, given that the covariates did not significantly impact task performance, we did not covary for these variables within the fMRI analyses. It remains possible, however, that activation patterns may have been affected by these variables, and findings should therefore be interpreted in the context of this potential limitation.

Additionally, medication may have an effect on both MSIT performance as well as attention network activation. For example, one of the few studies to report significant between-group performance differences on the MSIT reported that schizophrenic participants with current antipsychotic medication use had impaired performance accuracy compared to HC participants (Ikuta et al., 2014). Further, Strakowski et al. (2005) demonstrated that medicated BPD participants have altered attention network activation during cognitive control processing compared to unmedicated BPD participants, with increased dorsolateral PFC and anterior CC activation in the medicated group. Given that acutely symptomatic presentation in the BPD group was exclusionary for the current study, it is perhaps not surprising that all BPD participants reported current use of psychotropic medication, most commonly mood stabilizers (93.10%) and/or antipsychotic medications (65.52%). As our medicated BPD participants were compared to unmedicated HC participants, results demonstrating impaired MSIT performance and altered attention network activation in the BPD group may be affected by medication use. Interestingly, previous studies have reported attenuated activation in medicated patient groups (Arce et al., 2008; Bell et al., 2005; Del-Ben et al., 2005; Murphy et al., 2009; Paulus et al., 2005), which was not demonstrated in both ROIs in the current study. While research studies using unmedicated BPD participants may help to address this issue, unmedicated BPD participants are likely to be more symptomatic. It can therefore be difficult to differentiate the impact of acute symptomatology versus the impact of psychiatric medication. In the current study, three patients also reported use of stimulant medication. BPD patients are often prescribed stimulant medications to treat specific aspects of bipolar illness, particularly resistant depression, sedation, and racing thoughts. It is of note that the use of stimulants has previously been shown to increase brain activity as measured by blood oxygenation level dependent (BOLD) signal and other measures (i.e. PET, rCBF). Previous studies examining the impact of stimulants have noted increased signal change as measured by BOLD techniques in both human and animal studies (Easton et al., 2007; Rubia et al., 2011a, 2011b). In addition, two studies have also specifically shown increased activation during the MSIT after treatment with stimulants in individuals diagnosed with ADHD (Bush et al., 2008, 2013). For this reason, we completed a supplemental set of analyses to determine whether excluding the three patients on stimulant medication would impact study findings. Results remained largely unchanged, with groups demonstrating similar patterns of activation across both ROIs. However, the HC > BPD contrast analyses within the CC ROI, while identical in location, only trended towards significance (p=.06) after removing these three patients, likely as a result of loss of statistical power. Given that the data remained largely unchanged, the original analyses are presented in this report, as use of stimulant medications did not appear to impact study findings in a meaningful way.Finally, the current investigation may appear to be limited by modest sample sizes in each of the subject groups. It is of note, however, that the groups are well-characterized and of similar size relative to comparable neuroimaging studies (Gruber et al., 2012; Sagar et al., 2013).

4.2. Future directions

Given the potential impact that impaired cognitive control and attention network dysfunction may have on BPD treatment, especially psychotherapy, future studies should aim to assess whether cognitive control performance and CC and PFC activation change with successful treatment of BPD. As mentioned previously, the current study is part of a larger study examining the efficacy of cognitive remediation treatment. An important next step of this research will be to examine whether MSIT performance improves and attention network activation normalizes after completion of this psychotherapeutic regimen. More broadly, cognitive impairments may affect many psychotherapeutic and social rehabilitative treatments, and matching treatments to patient abilities may be improved by study and documentation of cognitive abilities and brain functional activities. Finally, it will be important for future studies to replicate the current findings which utilized only an ROI approach; this is currently underway with an additional sample of patients and will include both whole brain and ROI analyses.

5. Conclusions

The present findings support the use of the MSIT as a task of cognitive control processing in assessing participants with BPD. We found altered brain activation patterns during the MSIT in the neural

attention network, which has been associated with cognitive control processing; similar attention network abnormalities have been observed using other tasks of cognitive control (e.g. Stroop) in patients with BPD (Gruber et al., 2004) as well as using the MSIT in participants with anxiety disorders (Cocchi et al., 2012; Fitzgerald et al., 2010, 2013; Shin et al., 2011; Yucel et al., 2007a). Additionally, this particular pattern of dysfunction (decreased PFC and increased ACC activation) may be more typically observed with concurrent performance impairment. Pinpointing the neural mechanisms underlying key cognitive abnormalities may aid in the understanding of the pathophysiology of these disorders and may inform selection of potential targets for remediation efforts to improve cognition in BPD.

Acknowledgments

The authors wish to thank Sarah Sperry, Meredith Dreman, Megan Racine, and Rosemary Smith for their assistance with collecting the fMRI and MSIT data.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jad.2017.02.003.

References

Adleman, N.E., Yi, J.Y., Deveney, C.M., Guyer, A.E., Leibenluft, E., Brotman, M.A., 2014. Increased intrasubject variability in response time in unaffected preschoolers at familial risk for bipolar disorder. Psychiatry Res. 219 (3), 687–689. http://dx.doi.org/10.1016/j.psychres.2014.06.047.

Arce, E., Simmons, A.N., Lovero, K.L., Stein, M.B., Paulus, M.P., 2008. Escitalopram effects on insula and amygdala BOLD activation during emotional processing. Psychopharmacology 196, 661–672.

Arts, B., Jabben, N., Krabbendam, L., van Os, J., 2008. Meta-analysis of cognitive functioning in euthymic bipolar patients and their first-degree relatives. Psychol. Med. 38, 771–785.

Balanzá-Martínez, V., Tabarés-Seisdedos, R., Selva-Vera, G., Martinzed-Aran, A., Torrent, C., Salazar-Fraile, J., Leal-Cercos, C., Vieta, E., Gomez-Beneyto, M., 2005. Persistent cognitive dysfunctions in bipolar I disorder and schizophrenic patients: a 3-year follow-up study. Psychother. Psychosom. 74, 113–119.

Barch, D.M., 2009. Neuropsychological abnormalities in schizophrenia and major mood disorders: similarities and differences. Curr. Psychiatry Rep. 11 (4), 313–319.

Bell, E.C., Willson, M.C., Wilman, A.H., Dave, S., Silverstone, P.H., 2005. Differential effects of chronic lithium and valproate on brain activation in healthy volunteers. Hum. Psychopharmacol. 20, 415–424.

Blair, J.R., Spreen, O., 1989. Predicting premorbid IQ: a revision of the National Adult Reading Test. Clin. Neuropsychol. 3, 129–136.

Bor, J., Brunelin, J., d'Amato, T., Costes, N., Suaud-Chhagny, M.F., Saoud, M., Poulet, E., 2011. How can cognitive remediation therapy modulate brain activations in schizophrenia? An fMRI study. Psychiatry Res. 192, 160–166.

Bora, E., Yucel, M., Pantelis, C., 2009. Cognitive endophenotypes of bipolar disorder: a meta-analysis of neuropsychological deficits in euthymic patients and their first-degree relatives. J. Affect. Disord. 113 (1–2), 1–20.

Bora, E., Vahip, S., Akdeniz, F., 2006. Sustained attention deficits in manic and euthymic patients with bipolar disorder. Prog. Neuropsychopharmacol. Biol. Psychiatry 30, 1097–1102.

Bourne, C., Aydemir, O., Balanza-Martinez, V., Bora, E., Brissos, S., Cavanagh, J.T., Goodwin, G.M., 2013. Neuropsychological testing of cognitive impairment in euthymic bipolar disorder: an individual patient data meta-analysis. Acta Psychiatr. Scand. 129 (3), 149–162.

Brotman, M., Rooney, M.H., Skup, M., Pine, D.S., Leibenluft, E., 2009. Increased intrasubject variability in response time in youths with bipolar disorder and at-risk family members. J. Am. Acad. Child Adolesc. Psychiatry 48 (6), 628–635. http://dx.doi.org/10.1097/CHI.0b013e3181a27527.

Bush, G., Holmes, J., Shin, L.M., Surman, C., Makris, N., Mick, E., Seidman, L.J., Biederman, J., 2013. Atomoxetine increases fronto-parietal functional MRI activation in attention-deficit/hyperactivity disorder: a pilot study. Psychiatry Res. 211 (1), 88–91.

Bush, G., Shin, L.M., 2006. The multi-source interference task: an fMRI task that reliably activates the cingulo-frontal-parietal cognitive/attention network. Nat. Protoc. 1, 208–213.

Bush, G., Shin, L.M., Holmes, J., Rosen, B.R., Vogt, B.A., 2003. The multi-source interference task: validation study with fMRI in individual subjects. Mol. Psychiatry 8, 60–70.

Bush, G., Spencer, T.J., Holmes, J., Shin, L.M., Valera, E.M., Seidman, L.J., Makris, N., Surman, C., Aleardi, M., Mick, E., Biederman, J., 2008. Functional magnetic resonance imaging of methylphenidate and placebo in attention-deficit/hyperactivity disorder during the multi-source interference task. Arch. Gen. Psychiatry 65 (1), 102–114.

Cocchi, L., Harrison, B.J., Pujol, J., Harding, I.H., Fornito, A., Pantelis, C., Yücel, M., 2012. Functional alterations of large scale brain networks related to cognitive control in obsessive compulsive disorder. Hum. Brain Mapp. 33 (5), 1089–1106.

Davey, C.G., Yucel, M., Allen, N.B., Harrison, B.J., 2012. Task-related deactivation and functional connectivity of the subgenual cingulate cortex in major depressive disorder. Front. Psychiatry 3 (14), (eCollection 2012).

Del-Ben, C.M., Deakin, J.F.W., Mckie, S., Delvai, N.A., Williams, S.R., Anderson, I.M., 2005. The effect of citalopram pretreatment on neuronal responses to neuropsychological tasks in normal volunteers: an fMRI study. Neuropsychopharmacology 30, 1724–1734.

Eack, S.M., Hogarty, G.E., Cho, R.Y., Prasad, K.M., Greenwald, D.P., Hogarty, S.S., Keshavan, M.S., 2010. Neuroprotective effects of cognitive enhancement therapy against gray matter loss in early schizophrenia: results from a 2-year randomized controlled trial. Arch. Gen. Psychiatry 67, 674–682.

Easton, N., Marshall, F., Fone, K.C., Mardsen, C.A., 2007. Differential effects of the d- and l- isomers of amphetamine on pharmacological MRI BOLD contrast in the rat. Psychoparhamcology 193, 11–30.

First, M.B., Spitzer, R.L., Gibbon, M., Williams, B.W., 1994. Structured Clinical Interview for Axis I DSM IV Disorder, Patient Edition (SCID–I/P). Version 2.0. Biometric Research Department, NY State Psychiatric Institute, New York, NY.

Fitzgerald, K.D., Liu, Y., Stern, E.R., Welsh, R.C., Hanna, G.L., Monk, C.S., Phan, K.L., Taylor, S.F., 2013. Reduced error-related activation of dorsolateral prefrontal cortex across pediatric anxiety disorders. J. Am. Acad. Child Adolesc. Psychiatry 52, 1183–1191.

Fitzgerald, K.D., Stern, E.R., Angstadt, M., Nicholson-Muth, K.C., Maynor, M.R., Welsh, R.C., Hanna, G.L., Taylor, S.F., 2010. Altered function and connectivity of the medial frontal cortex in pediatric obsessive-compulsive disorder. Biol. Psychiatry 68 (11), 1039–1047.

Gallagher, P., Nilsson, J., Finkelmeyer, A., Goshawk, M., Macritchie, K.A., Lloyd, A.J., Watson, S., 2015. Neurocognitive intra-individual variability in mood disorders: effects on attentional response time distributions. Psychol. Med. 45 (14), 2985. http://dx.doi.org/10.1017/S0033291715000926.

Glahn, D.C., Bearden, C.E., Barguil, M., Barrett, J., Reichenberg, A., Bowden, C.L., Soares, J.C., Velligan, D.I., 2007. The neurocognitive signature of psychotic bipolar disorder. Biol. Psychiatry 62 (8), 910–916.

Green, M.F., 2006. Cognitive impairment and functional outcome in schizophrenia and bipolar disorder. J. Clin. Psychiatry 67 (10), e12.

Gruber, S.A., Dahlgren, M.K., Sagar, K.A., Gonenc, A., Killgore, W.D., 2012. Age of onset of marijuana use impacts inhibitory processing. Neurosci. Lett. 511 (2), 89–94.

Gruber, S.A., Rogowska, J., Yurgelun-Todd, D.A., 2004. Decreased activation of the anterior cingulate in bipolar patients: an fMRI study. J. Affect. Disord. 82 (2), 191–201.

Gruber, S.A., Rosso, I.M., Yurgelun-Todd, D.A., 2008. Neuropsychological performance predicts clinical recovery in bipolar patients. J. Affect. Disord. 105, 253–260.

Harding, I.H., Solowij, N., Harrison, B.J., Takagi, M., Lorenzetti, V., Lubman, D.I., Seal, M.L., Pantelis, C., Yucel, M., 2012. Functional connectivity in brain networks underlying cognitive control in chronic cannabis users. Neuropsychopharmacology 37, 1923–1933.

Harrison, B.J., Yucel, M., Fornito, A., Wood, S.J., Seal, M.L., Clarke, K., Pantelis, C., 2007. Characterizing anterior cingulate activation in chronic schizophrenia: a group and single-subject fMRI study. Acta Psychiatr. Scand. 116, 271–279.

Heckers, S., Weiss, A.P., Deckersbach, T., Goff, D.C., Morecraft, R.J., Bush, G., 2004. Anterior cingulate cortex activation during cognitive interference in schizophrenia. Am. J. Psychiatry 161, 707–715.

Hollingshead, A., 1975. Four Factor Index of Social Status. Yale University, New Haven, CT.

Ikuta, T., Robinson, D.G., Gallego, J.A., Peters, B.D., Gruner, P., Kane, J., John, M., Sevy, S., Malhotra, A.K., Szeszko, P.R., 2014. Subcortical modulation of attentional control by second-generation antipsychotics in first-episode psychosis. Psychiatry Res. 221 (2), 127–134.

Ikuta, T., Szeszko, P.R., Gruner, P., DeRosse, P., Gallego, J., Malhotra, A.K., 2012. Abnormal anterior cingulate cortex activity predicts functional disability in schizophrenia. Schizophr. Res. 137 (1–3), 267–268.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13 (2), 261–276.

Kessler, R.C., Chiu, W.T., Demler, O., Walters, E.E., 2005. Prevalence, severity, and comorbidity of twelve-month DSM-IV disorders in the National Comorbidity Survey Replication (NCS-R). Arch. Gen. Psychiatry 62 (6), 617–627.

Kronhaus, D.M., Lawrence, N.S., Williams, A.M., Frangou, S., Brammer, M.J., Williams, S.C., Andrew, C.M., Phillips, M.L., 2006. Stroop performance in bipolar disorder: further evidence for abnormalities in the ventral prefrontal cortex. Bipolar Disord. 8 (1), 28–39.

Leucht, S., Kane, J.M., Kissling, W., Hamann, J., Etschel, E., Engel, R.R., 2005. What does the PANSS mean? Schizophr. Res. 79 (2), 231–238.

Lewandowski, K.E., Cohen, B.M., Keshavan, M.S., Sperry, S.H., Ongur, D., 2013. Neuropsychological functioning predicts community outcomes in affective and non-affective psychoses: a 6-month follow-up. Schizophr. Res. 148 (1–3), 34–37.

Lim, C.S., Baldessarini, R.J., Vieta, E., Yucel, M., Bora, E., Sim, K., 2013. Longitudinal neuroimaging and neuropsychological changes in bipolar disorder patients: review of the evidence. Neurosci. Biobehav. Rev. 37, 418–435.

Lukasiewicz, M., Gerard, S., Besnard, A., Falissard, B., Perrin, E., Sapin, H., Tohen, M., Reed, C., Azorin, J.M., EMBLEM Study Group, 2013. Young Mania Rating Scale: how to interpret the numbers? Determination of a severity threshold and of the minimal clinically significant difference in the EMBLEM cohort. Int. J. Methods

Psychiatr. Res. 22 (1), 46–58.
Maldjian, J.A., Laurienti, P.J., Kraft, R.A., Burdette, J.H., 2003. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. Neuroimage 19 (3), 1233–1239.
Montgomery, S.A., Asberg, M.A., 1979. A new depression scale designed to be sensitive to change. Br. J. Psychiatry 134 (4), 561–571.
Murphy, S.E., Norbury, R., O'Sullivan, U., Cowen, P.J., Harmer, C.J., 2009. Effect of a single dose of citalopram on amygdala response to emotional faces. Br. J. Psychiatry 194, 535–540.
Öngür, D., Lin, L., Cohen, B.M., 2009. Clinical characteristics influencing age at onset in psychotic disorders. Compr. Psychiatry 50, 13–19.
Paulus, M.P., Feinstein, J.S., Castillo, G., Simmons, A.N., Stein, M.B., 2005. Dose-dependent decrease of activation in bilateral amygdala and insula by lorazepam during emotion processing. Arch. Gen. Psychiatry 62, 282–288.
Penadés, R., Pujol, N., Catalán, R., Massana, G., Rametti, G., García-Rizo, C., Junqué, C., 2013. Brain effects of cognitive remediation therapy in schizophrenia: A structural and functional neuroimaging study. Biol. Psychiatry 73 (10), 1015–1023. http://dx.doi.org/10.1016/j.biopsych.2013.01.017.
Penadés, R., Pujol, N., Catalán, R., Masana, G., García-Rizo, C., Bargalló, N., Junqué, C., 2016. Cortical thickness in regions of frontal and temporal lobes is associated with responsiveness to cognitive remediation therapy in schizophrenia. Schizophr. Res. 171, 110–116.
Pompei, F., Jogia, J., Tatarelli, R., Girardi, P., Rubia, K., Kumari, V., Frangou, S., 2011. Familial and disease specific abnormalities in the neural correlates of the stroop task in bipolar disorder. Neuroimage 56 (3), 1677–1684.
Popov, T., Jordanov, T., Rockstroh, B., Elbert, T., Merzenich, M.M., Miller, G.A., 2011. Specific cognitive training normalizes auditory sensory gating in schizophrenia: a randomized trial. Biol. Psychiatry 69, 465–471.
Robinson, L.J., Ferrier, I.N., 2006. Evolution of cognitive impairment in bipolar disorder: a systematic review of cross-sectional evidence. Bipolar Disord. 8, 103–116.
Robinson, L.J., Thompson, J.M., Gallagher, P., Goswami, U., Young, A.H., Ferrier, I.N., Moore, P.B., 2006. A meta-analysis of cognitive deficits in euthymic patients with bipolar disorder. J. Affect. Disord. 93, 105–115.
Roth, R.M., Koven, N.S., Randolph, J.J., Flashman, L.A., Pixley, H.S., Ricketts, S.M., Wishart, H.A., Saykin, A.J., 2006. Functional magnetic resonance imaging of executive control in bipolar disorder. Neuroreport 17 (11), 1085–1089.
Rubia, K., Halari, R., Cubillo, A., Smith, A.B., Mohammad, A.M., Brammer, M., Taylor, E., 2011a. Methylphenidate normalizes fronto-striatal underactivation during interference inhibition in medication-naïve boys with attention-deficit hyperactivity disorder. Neuropsychopharmacology 36, 1575–1586.
Rubia, K., Halari, R., Mohammad, A.M., Taylor, E., Brammer, M., 2011b. Methylphenidate normalizes frontocingulate underactivation during error processing in attention-deficit/hyperactivity disorder. Biol. Psyhicatry 70, 255–262.
Sagar, K.A., Dahlgren, M.K., Gonenc, A., Gruber, S.A., 2013. Altered affective processing in bipolar disorder: an fMRI study. J. Affect. Disord. 150, 1192–1196.
Shin, L.M., Bush, G., Milad, M.R., Lasko, N.B., Brohawn, K.H., Hughes, K.C., Macklin, M.L., Gold, A.L., Karpf, R.D., Orr, S.P., Rauch, S.L., Pitman, R.K., 2011. Exaggerated activation of dorsal anterior cingulate cortex during cognitive interference: a monozygotic twin study of posttraumatic stress disorder. Am. J. Psychiatry 168, 978–985.
Stefanopoulou, E., Manoharan, A., Landau, S., Geddes, J.R., Goodwin, G., Frangou, S., 2009. Cognitive functioning in patients with affective disorders and schizophrenia: a meta-analysis. Int. Rev. Psychiatry 21 (4), 336–356.
Stern, E.R., Welsh, R.C., Fitzgerald, K.D., Taylor, S.F., 2009. Topographic analysis of individual activation patterns in medial frontal cortex in schizophrenia. Hum. Brain Mapp. 30 (7), 2146–2156.
Strakowski, S.M., Adler, C.M., Holland, S.K., Mills, N.P., DelBello, M.P., Eliassen, J.C., 2005. Abnormal FMRI brain activation in euthymic bipolar disorder patients during a counting stroop interference task. Am. J. Psychiatry 162 (9), 1697–1705.
Subramaniam, K., Luks, T.L., Fisher, M., Simpson, G.V., Nagarajan, S., Vinogradov, S., 2012. Computerized cognitive training restores neural activity within the reality monitoring network in schizophrenia. Neuron 73, 842–853.
Ward, B.D., 2000. Simultaneous inference for fMRI data, Retrieved February 7, 2017, from https://afni.nimh.nih.gov/pub/dist/doc/manual/AlphaSim.pdf.
Wechsler, D., 1999. Wechsler Abbreviated Scale of Intelligence. The Psychological Corporation, New York, NY.
Wexler, B.E., Anderson, M., Fulbright, R.K., Gore, J.C., 2000. Preliminary evidence of improved verbal working memory performance and normalization of task-related frontal lobe activation in schizophrenia following cognitive exercises. Am. J. Psychiatry 157, 1694–1697.
Wykes, T., Reeder, C., Huddy, V., Taylor, R., Wood, H., Ghirasim, N., Landau, S., 2012. Developing models of how cognitive improvements change functioning: mediation, moderation and moderated mediation. Schizophr. Res. 138, 88–93.
Young, R.C., Biggs, J.T., Ziegler, V.E., Meyer, D.A., 1978. A rating scale for mania: reliability, validity and sensitivity. Br. J. Psychiatry 133 (5), 429–435.
Yucel, M., Harrison, B.J., Wood, S.J., Fornito, A., Wellard, R.M., Pujol, J., Clarke, K., Phillips, M.L., Kyrios, M., Velakoulis, D., Pantelis, C., 2007a. Functional and biochemical alterations of the medial frontal cortex in obsessive-compulsive disorder. Arch. Gen. Psychiatry 64, 946–955.
Yucel, M., Lubman, D., Harrison, B., Fornito, A., Allen, N., Wellard, R., Roffel, K., Clarke, K., Wood, S.J., Forman, S.D., Pantelis, C., 2007b. A combined spectroscopic and functional MRI investigation of the dorsal anterior cingulate region in opiate addiction. Mol. Psychiatry 12 (7), 691–702.