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AN FMRI STUDY OF WORKING MEMORY IN PERSONS WITH BIPOLAR DISORDER OR AT GENETIC RISK FOR BIPOLAR DISORDER

Heidi W. Thermenos[1,2], **Jill M. Goldstein**[1,2,3,4,5], **Snezana M. Milanovic**[1,2,3], **Susan W. Gabrieli**[6], **Nikos Makris**[2,3,7], **Peter LaViolette**[2], **Jennifer K. Koch**[1], **Stephen V. Faraone**[8], **Ming T. Tsuang**[1,3,4,9], **Stephen L. Buka**[10], and **Larry J. Seidman**[1,2,3,4]

[1]Harvard Medical School Department of Psychiatry, Beth Israel Deaconess Medical Center, Massachusetts Mental Health Center Division of Public Psychiatry, Boston, MA 02115

[2]Massachusetts General Hospital/Martinos Center for Biomedical Imaging (Massachusetts Institute of Technology, Harvard Medical School and Massachusetts General Hospital), Charlestown, MA 02129

[3]Harvard Medical School, Department of Psychiatry, Massachusetts General Hospital, Boston, MA 02114

[4]Harvard Institute of Psychiatric Epidemiology and Genetics, Boston, MA 02115

[5]Harvard Medical School, Departments of Medicine, Division of Women's Health, Connor's Center for Women's Health & Gender Biology, & Department of Psychiatry, Brigham and Women's Hospital, Boston, MA 02115

[6]Massachusetts Institute of Technology, Department of Brain and Cognitive Sciences, Harvard-MIT Division of Health Sciences and Technology, Boston, MA 02139

[7]Athinoula A. Martinos Center, Harvard Medical School Departments of Neurology and Radiology Services, Center for Morphometric Analysis, Massachusetts General Hospital, Boston, MA 02129

[8]Medical Genetics Research Program and Department of Psychiatry, SUNY Upstate Medical University, Syracuse, NY 13210

[9]University of California, San Diego, Department of Psychiatry, Center for Behavioral Genomics, La Jolla, CA 92093

[10]Department of Community Health, Brown University, Providence, RI 02912

Abstract

BACKGROUND—First-degree relatives of persons with bipolar disorders (BD) carry elevated risk for the illness, and manifest deficits in attention and memory (possible "endophenotypes"). However, there is only one published fMRI study of candidate endophenotypes in BD. We used functional magnetic resonance imaging (fMRI) to examine brain function in BD and in first-degree relatives performing a 2-back working memory (WM) task, and correlated brain activity with mood measures taken at the scanning session.

METHODS—Subjects (age 32–46) were 19 persons with BD, 18 unmedicated, non-psychotic first-degree relatives (RELs) of persons with BD, and 19 matched controls, ascertained from a long-term follow-up of a prenatal cohort study in New England. fMRI signal during 2-back and 0-

Correspondence: Heidi W. Thermenos, Ph.D., Athinoula A. Martinos Center for Biomedical Imaging, Building 149, 2nd Floor (Room 2602E), 13th Street, Charlestown, MA 02129; Tel: 617-726-0265; Fax: 617-726-4078, hthermen@bidmc.harvard.edu.

back WM tasks was measured on a Siemens 1.5T MR scanner. fMRI data were analyzed using SPM-2.

RESULTS—Persons with BD and RELs failed to suppress activation in the left anterior insula (BA 13) during WM, whereas controls suppressed activation. Compared to controls, RELs also failed to suppress activation in the orbitofrontal cortex (OFC) and superior parietal cortex. Controls and RELs exhibited greater activation than BD individuals in the left frontopolar cortex (BA10) during WM. Results remained significant after controlling for confounders except for mild attenuation of OFC findings. Significant correlations between brain activity, mood and WM suggest that activity in WM circuits is affected by activity in emotion-regulatory circuits.

CONCLUSIONS—Persons with BD, and RELs exhibit altered activity in the frontopolar cortex and insula, which may represent biomarkers of genetic risk for BD.

Keywords

bipolar disorder; genetics; functional MRI; working memory; insula; frontopolar cortex

INTRODUCTION

Working memory (WM) deficits occur in many neuropsychiatric disorders, but may occur via different, disease-specific pathophysiology. In schizophrenia, WM deficits have been associated with dysfunction primarily in dorsal and lateral cortical WM regions (i.e., dorsolateral prefrontal [DLPFC] and parietal cortex). There is mounting evidence that WM deficits also occur in Bipolar Disorder (BD), even during euthymic periods, with largest effects when tasks involve verbal learning and the manipulation of information (Robinson *et al.* 2006)). However, the few neuroimaging studies of WM in BD have been inconsistent, and the physiological basis of WM deficits in BD remains unclear. In this study, to further clarify this issue, we examined not only the functional neuroanatomy of BD during WM, but we also studied brain activity in first-degree biological relatives of persons with BD. We evaluated this latter group to assess the possibility that altered neural substrates activated by WM tasks might be an endophenotype for BP.

A growing literature demonstrates that across cognitive and emotional tasks and clinical states, BD exhibits altered activity in frontal (Adler *et al.* 2004; Blumberg *et al.* 2003; Blumberg *et al.* 1999; Frangou 2005; Haldane *et al.* 2004; Kruger *et al.* 2006a; Kruger *et al.* 2003; Lagopoulos *et al.* 2007; Monks *et al.* 2004), limbic and paralimbic regions, including the orbitofrontal cortex (OFC) (Altshuler *et al.* 2005a; Altshuler *et al.* 2005b; Blumberg *et al.* 1999; Kruger *et al.* 2006b) and insula (Adler *et al.* 2004; Chang *et al.* 2004; Kruger *et al.* 2006a; Kruger *et al.* 2003). This suggests that WM and other cognitive deficits in BD could be substantially associated with abnormalities in mood regulatory networks. In behavioral studies, mood disturbances disrupt WM and other cognitive functions, and may do so via direct and indirect effects on the function of WM networks.

For example, Pochon et al 2002 demonstrated that OFC suppression plays a role in inhibiting adverse emotional signals in order to maximize the level of N-back performance (Pochon *et al.* 2002). Thus, impaired OFC suppression during WM could play a role in WM deficits in BD. In addition, high emotion-regulatory demands on the frontopolar cortex may supercede or interfere with its role in cognitive coordination and rule learning (Burgess *et al.* 2007; Koechlin *et al.* 1999; Owen *et al.* 2005; Strange *et al.* 2001) and thereby impair WM performance.

Here, we tested the hypothesis that WM deficits in BD are associated with core abnormalities in frontopolar and orbitofrontal regions associated with suppression of task-

induced negative emotion. These putative abnormalities may lead to hyperactivity in regions associated with emotional arousal during WM (e.g., anterior cingulate, amygdala, and anterior insula), and further interfere with WM by compromising other functions of the frontopolar cortex (cognitive coordination and task learning), and by drawing attention away from task-goals toward negative emotion (Wang *et al.* 2008).

Another important question is whether WM deficits in BD represent a core phenotypic feature of the disorder, or whether they are secondary to medication and other confounds that typically complicate the study of BD. To address this question, we studied WM in a sub-sample of BD participants and in unmedicated, non-bipolar, non-psychotic first-degree relatives (RELS) of persons with BD who are at elevated genetic risk (GR) for BD and expected to show similar, but milder WM deficits (Brambilla *et al.* 2005). Cognitive or neurobiological phenotypes ("endophenotypes") identified in RELs may reflect the expression of important susceptibility genes for BD, and may improve the power of future genetic studies of BD to detect risk loci.

To date, there is a relative paucity of studies measuring cognition or brain structure and function in RELs of BD. There is some evidence of verbal learning and memory and WM (Antila *et al.* 2007a; Antila *et al.* 2007b; Christensen *et al.* 2006; Kieseppa *et al.* 2005; Zalla *et al.* 2004) deficits, and the majority of structural magnetic resonance imaging (MRI) studies have reported no structural abnormalities in RELs (with a few exceptions (Kieseppä *et al.* 2003; McDonald *et al.* 2004). To date, the strongest evidence of a BD endophenotype from studies of BD or RELs implicates the frontal lobe in disease vulnerability (Chang *et al.* 2004; Haldane *et al.* 2004; Lagopoulos *et al.* 2007; McDonald *et al.* 2004; Monks *et al.* 2004); in particular, ventral prefrontal (Monkul *et al.* 2005) and frontopolar regions (Adler *et al.* 2004) involved in control of cognitive, emotional and hedonic functions (Burgess *et al.* 2007; Daselaar *et al.* 2008; Koechlin *et al.* 1999; Lévesque *et al.* 2004; Masaki *et al.* 2006; Owen *et al.* 2005; Rolls 1999; Strange *et al.* 2001). Somewhat consistent with this, the only published functional MRI (fMRI) study in RELs demonstrated hyperactivation in left frontal pole/ventrolateral gyrus during WM performance (Drapier *et al.* 2008), while the only PET study of an emotional challenge task found hyperactivation in the insula and medial frontal cortex in RELs (Kruger *et al.* 2006a).

We used fMRI to study brain activity using a visual N-back WM task in BD, unmedicated RELs and controls. Based on the literature summarized above on BD performing WM and other cognitive and emotional tasks we predicted that: 1) WM deficits in BD would be associated with altered activity in frontopolar and orbitofrontal regions, and hyperactivity in emotional and autonomic arousal brain regions (i.e., anterior cingulate, amygdala, and anterior insula); 2) abnormal brain activity in all regions would be associated with mood state scores, and frontopolar abnormalities, with reduced 2-back task performance; 3) RELs would exhibit frontopolar hyperactivity, reflecting their genetic risk for the illness; and 4) WM performance would be significantly correlated with mood state scores.

MATERIALS AND METHODS

Subjects

Subjects were 19 stabilized outpatients with bipolar illness (including a sub-sample of 10 who were unmedicated at the time of scanning), 18 unmedicated, non-psychotic, non-bipolar first-degree relatives of persons with BD, and 19 healthy controls. All subjects were adult offspring (age 32 to 46) of women enrolled in the National Collaborative Perinatal Project (NCPP), a prospective study of pregnant women and their offspring (followed from pregnancy through age seven) that included participants with other psychoses, and a standard neuroimaging protocol (recruitment procedures and schizophrenia data previously

described)(Thermenos *et al.* 2005). Recruitment from a birth cohort sample ascertains participants from a constrained population, helping to control for sociodemographic factors in the families of origin.

Exclusion criteria in the adult sample were: a history of neurological disease, traumatic brain injury, medical illness with documented cognitive sequelae, sensory impairments, IQ less than 70, fewer than eight years of formal education, substance abuse within the past six months, or contraindications for MRI. RELs were included if they had no history of psychotic illness, and controls were included if they were without any lifetime psychiatric diagnosis or a family history of psychotic illness. The nine BD subjects who were on psychotropic medications (of the total sample of 19), remained on medication for neuroimaging (8 on antipsychotics, 6 on mood stabilizers, 2 on antidepressants, and 1 on anxiolytic medication). The study was approved by the Human Research Committees at Harvard University, the Massachusetts Mental Health Center and Massachusetts General Hospital (MGH). All subjects gave informed consent.

Psychiatric Assessment

Subjects were interviewed by a trained diagnostic interviewer using the Structured Clinical Interview for DSM-IV (SCID) and the Scales for the Assessment of Negative and Positive Symptoms (SANS/SAPS)(Andreasen 1983; Andreasen 1984). Interviews were conducted by Master's level clinicians (supervised by JMG and LJS). Expert diagnosticians made best-estimate consensus diagnoses according to the Diagnostic and Statistical Manual of Mental Disorders-4th edition (DSM-IV) criteria, based on all available data. Family history of Axis I psychiatric disorders was based on direct interviews of the probands using the Diagnostic Interview Schedule for DSM-IV (Robins *et al.* 1995), the SCID, and the Family Interview for Genetic Studies (FIGS) (Maxwell 1996) (for clinical diagnostic details, see (Goldstein *et al.* (submitted))). Approximately ½ hour before scanning, subjects took the Profile of Mood States (POMS) (McNair *et al.* 1992) to determine their mood at that time and during the week prior to scanning.

Based on the SCID, none of the relatives of BD had current major depressive, manic or hypomanic episodes in the past month prior to interview. Two RELs had past major depressive episodes, with an average age of onset of 25.9. None had past episodes of hypomanic or manic symptoms (by design of the study). For the BD patients, none at the time of interview were currently manic (i.e., none had a manic episode in the past month prior to SCID interview) and one had been considered hypomanic in the month prior to the interview. The average age of onset of manic symptoms was 22.9. Their average age of onset of major depressive episodes was 23.3. All were outpatients and considered to be stable at the time of brain imaging. When subsequently contacted for neuroimaging, all participants were able to be scanned and none were observed to be manic or hypomanic during the imaging session.

Neuropsychological Testing

General intellectual ability ("IQ") was assessed using the Vocabulary and Block Design subtests of the WAIS-R (Brooker *et al.* 1986; Wechsler 1981). The Reading subtest of the WRAT-R (Jastak *et al.* 1985) was used as an estimate of premorbid intellectual potential. Handedness was assessed with the Annett scale.

FMRI: Two-Back Working Memory Task and Control CPT-X Task

We used a sequential letter, visual "N-back" (2-back) WM task and a simple vigilance task (the Continuous Performance Test "X" Task, or "0-back") as a control task, as previously described (Thermenos *et al.* 2005). The two tasks were presented in a blocked design, with

three 32-second blocks of the 0-back task, alternating with three 32-second blocks of the 2-back WM task (sixteen 1800 msec trials per block, with a 200 msec interstimulus interval). Each block of task was preceded by a 20 second block of fixation. Accuracy (hit rate) and reaction times (RT) were dependent variables.

Neuroimaging

Imaging was conducted on a Siemens Sonata 1.5 Tesla full-body MR scanner at the MGH Martinos Center for Biomedical Imaging. A sagittal localizer scan was performed for placement of slices, followed by a coronal T2-weighted sequence, collected to rule out unexpected neuropathology. Two sagittal 3D MP-RAGE (T1-weighted, non-selective inversion-prepared spoiled gradient echo pulse) sequences were collected (TR/TE/T1/flip = 2.73 s/3.39 ms/1.0 s/7 degrees, bandwidth =190 Hz/pixel, sampling matrix = 256 × 192 pixels, FOV = 256 × 256 mm, effective slice thickness = 1.33 mm on a 170 mm slab of 128 partitions). Two whole-brain gradient echo EPI pulse sequences, 21 contiguous axial slices parallel to the anterior commissure-posterior commissure line, (5 mm, 1 mm skip, TR/TE/flip= 2000/40/90; voxel size 3.1 × 3.1 × 5 mm; FOV = 200 mm), were collected while subjects performed tasks.

Statistical Analyses

The Statistical Package for the Social Sciences (SPSS) (Standard Version 11.0.1, 2002, SPSS Inc., Chicago IL) was used for statistical analyses of demographic, neuropsychiatric and behavioral variables. fMRI data were analyzed using SPM-2 software (Wellcome Department of Cognitive Neurology, London, UK) and in-house software (http://web.mit.edu/swg/software.htm) running in MATLAB (Mathworks, Inc., Sherborn, MA). For each subject, functional images were realigned and normalized to the Montreal Neurological Institute template supplied with SPM-2. For individual analyses, functional data were smoothed with an 8-mm Gaussian kernel.

Statistical analyses were performed at the single subject level using SPM-2. Each block was modeled using a boxcar function convolved with a canonical hemodynamic response function. Estimated motion correction parameters were included as confounding covariates in order to increase sensitivity and further reduce the possibility of motion artifacts. A linear contrast was used to test the relative effect of the 2-back compared to the 0-back task. Contrasts were created for each subject for the 2-back > 0-back comparison and then submitted to a second level, random-effects analysis, using one-sample t tests for within-group and two-sample t tests for between-group comparisons. A two-sample analysis of covariance (ANCOVA) was used to assess the effect of potentially confounding variables (age, IQ, education, parental education, 2-back accuracy, POMS mood scores, and lifetime alcohol and drug use) on between-group activation differences.

Statistical maps for the whole group (N = 56) and individual, within-group analyses were thresholded at $p < .05$ corrected for multiple comparisons across the entire brain volume. Statistical maps for between-group comparisons were thresholded at $p < 0.005$ (uncorrected) with a minimal spatial extent of 5 voxels (different thresholds were selected for within and between group analyses as these analyses are differentially powered). Regions of interest (ROIs) used in the small volume correction were 10 mm spheres built around coordinates from previous fMRI studies of WM in BD or controls, or were anatomically-defined masks of hypothesized regions of interest, generated using the Wake Forest University-PickAtlas tool (V1.04): http://www.fmri.wfubmc.edu; (Maldjian *et al.* 2003)) or using anatomical masks created via manual segmentation and parcellation of the MNI template under the supervision of our neuroanatomist (NM), an expert in these techniques. These were the frontopolar cortex (x, y, z: +/−34, 56, 19: +/−26, 64, 14)(Adler *et al.* 2004); inferior frontal

cortex (x, y, z: +/−36, 31, 13)(Wager *et al.* 2003)); the OFC (BA 47), anterior cingulate, anterior insula, amygdala and superior parietal cortex (anatomical masks).

In regions showing between-group differences in activation, the measure of activation response (the first eigenvalue) was extracted from each subject's data, and the effect size (Cohen's *d*) was calculated. Group differences in activation could have arisen from activation differences during 0-back, 2-back, or both. To address this question, for each subject, beta values were extracted from 10 mm, common ROIs separately for each condition. Average beta values for each task were calculated for all of the groups and compared using ANOVAS (for 3-groups) or t-tests (for 2-groups); average beta values for each condition were compared within groups using t-tests. To assess the effect of emotion on WM and associated physiology, we calculated bivariate Pearson correlations of natural log-transformed POMS scores to WM performance (accuracy and reaction time) and brain activity in the four 10 mm regions of interest that differentiated the groups.

RESULTS

Demographic Matching Characteristics

BD and controls were statistically similar in sex, ethnicity, handedness, parental education, and reading ability, but BD were slightly older (39 vs. 41 years). RELs and controls were statistically similar on sex, ethnicity, handedness, and reading ability, but RELs were slightly younger (36 vs. 39 years) and had significantly less parental education (Table 1). Compared to RELs, BD patients were significantly older (mean = 41 vs. 36 years) but statistically comparable on the other five matching variables. Moreover, it should be noted that the age range was narrow and similar for all groups (controls: 34–44; BD: 36–46; RELs: 32–43) owing to ascertainment from the NCPP.

Neuropsychological and Achievement Characteristics

BD had significantly less education and lower IQ scores than controls whereas RELs had significantly less education than controls. There were no significant differences between BD and RELS (Table 1).

Substance Abuse, Mood and Psychiatric Symptoms

BD had significantly greater lifetime drug and alcohol use, and used more alcohol on the day prior to scanning than controls (Table 1). RELs had significantly greater lifetime drug and alcohol use than controls. RELS and BD patients did not differ on these variables.

On the POMS, BD had higher scores than controls and RELs on Depression, Tension/Anxiety and Confusion scales ($p<0.05$)(Table 1). There were no differences between RELs and controls.

Task Performance During fMRI

Groups performed similarly on the 0-back task (but BD patients had marginally slower RT than controls) (Table 1). On the 2-back, compared to controls, BD had significantly lower WM accuracy and marginally longer RT. RELs had marginally lower accuracy than controls on the 2-back, but RTs were comparable. BD and RELs did not differ significantly on the 2-back variables (Table 1).

Neuroimaging

In a single group of all 56 participants, there was greater activation during 2-back than the 0-back task in cortical regions typically associated with WM, including middle frontal gyrus

(bilaterally), right inferior frontal gyrus, left inferior parietal lobule and right middle temporal gyrus ($p < 0.0001$, corrected across the whole brain for multiple comparisons).

When activation during WM was compared between groups, differences were observed in insular, frontopolar, orbitofrontal and parietal cortices (Figures 1–3, Table 2). BD and RELs exhibited significantly increased activity in the left anterior insula (BA 13) compared to controls (Figure 1, Table 2). BD exhibited significantly reduced activity in the left frontopolar cortex (BA 10) compared to controls, while RELs exhibited significantly greater activity in this region (Figure 2, Table 2). RELs also exhibited significantly greater activity than controls in the left orbitofrontal cortex (BA 47) and at the boundary of the right superior parietal lobule and the postcentral gyrus (Figure 3, Table 2).

When beta values were extracted from common regions of interest, an ANOVA revealed significant differences among CON, BD and RELs in the insula ($F [2, 53] = 3.62$, $p = 0.03$) and frontopolar cortex ($F [2, 53] = 3.96$, $p = 0.02$), and between CON and RELs in the OFC ($t = 2.54$, $p = 0.02$) and parietal region ($t = 2.26$, $p = 0.03$) during WM (see bar graphs, Figures 1–3). There were no significant differences between the groups during 0-back. Only the controls exhibited a significant modulation (reduction) of activation in the insula ($p= 0.001$), OFC ($p = 0.01$) and parietal region ($p = 0.05$) during WM compared to 0-back (Figures 1 and 3). In the frontopolar cortex, BD did not exhibit the significant modulation (enhancement) activity during WM compared to 0-back seen in controls ($p= 0.01$) and RELs ($p= 0.02$) (Figure 2).

Sub-sample analysis to assess the effect of medication on the results

As a preliminary analysis to assess whether psychiatric medication affected the results in BD patients, we selected the 10 BD (from our original sample of 19) who were unmedicated, and compared them to the original control sample. The sub-group of 10 unmedicated BD was slightly older (39 vs. 42 years), and had significantly less education, greater lifetime alcohol use, more alcohol use on the day prior to scanning than controls, higher POMS Confusion scores, and lower WM accuracy than controls (Table 3). Compared to RELs, unmedicated BD were significantly older. Like the full sample of BD and RELs, the subgroup of 10 unmedicated BD exhibited significantly increased activity in the left anterior insula (BA 13) compared to controls (Figure 4, Table 3). Also like the full sample of BD, the sub-sample of unmedicated BD exhibited a significant trend toward reduced activity in the left frontopolar cortex (BA 10) compared to controls and RELs, with effect sizes > 1.0 (Figure 4, Table 3).

Relationship of POMS scores to WM performance

There were several significant correlations between mood scores and WM performance ($p<.05$), all in the expected direction (worse performance or slower RT and more symptoms). Accuracy: Fatigue was negatively correlated with accuracy across all participants ($r= -.41$) and in BD ($r= -.66$). Vigor was also correlated with accuracy ($r=.33$) across all participants. In RELs, Tension/Anxiety ($r= -.70$), Confusion ($r= -.55$) and Depression ($r= -.53$) were negatively correlated with accuracy. Reaction time (RT): Confusion was correlated with RT across all participants ($r= .42$) and in controls ($r=.46$). Depression was correlated with RT across all participants ($r= .40$) and in BD ($r=.46$). RT was also correlated with both Anger/Hostility ($r= .35$) and Tension/Anxiety ($r=.32$) across all participants.

Relationship of POMS scores to brain activity

OFC activity was significantly correlated with Depression ($r = .48$) in controls. In RELs, frontopolar activity was correlated with Confusion ($r = .72$), Tension/Anxiety ($r = .51$) and

Depression (r = .60); parietal activity was correlated with Confusion (r = .73) and insula activity was correlated with Confusion (r = .45) and Tension-Anxiety (r = .49)(all ps<.05).

Covariance analyses to assess the effects of potential confounders on the results

Group differences in fMRI activity remained significant after controlling for age, IQ, education, parental education, POMS mood scores and alcohol use on the day prior to scanning (Table 2). When education was used as a covariate, effect sizes in the insula, parietal lobe and OFC were increased to over 1.70 (for RELs vs. controls). However, the difference between RELs and controls in the OFC was not significant after controlling for lifetime alcohol use, and was marginal (p = 0.1) after controlling for lifetime drug use. Lifetime alcohol use also had a small impact on the difference between RELs and controls in the insula (the p-value was reduced to 0.07, though the effect size remained large, d=1.32). Controlling for lifetime drug use, on the other hand, increased the effect size in the parietal cortex to 1.85. Thus of all the potential confounders a history of substance abuse had the only significant effects and theses were on analyses between RELS and controls.

Finally, the difference between BD and controls in the frontopolar cortex was reduced to a marginally significant level (p = 0.06) after controlling for group differences in 2-back accuracy, although the effect size remained large, d = 1.05.

DISCUSSION

During WM, BD patients and RELs exhibited altered activity in the anterior insula and frontopolar cortex compared to controls. RELs also showed alterations in the OFC and a parietal region at the boundary of the superior parietal lobule and post-central gyrus. Most results remained significant when potentially confounding variables were covaried, and were observed despite no statistical differences between controls and RELs on a majority of variables suggesting that the findings may be associated with genetic risk for BD, rather than disease-associated confounders. The OFC findings between RELS and controls must be considered tentative, as the results were attenuated after covariance with substance abuse. Overall, results are consistent with a growing literature demonstrating that BD exhibit altered activity in frontal, orbitofrontal and insular regions (independent of the task used and clinical state), and are strikingly similar to results of imaging studies of emotional tasks in BD (Chang *et al.* 2004; Kruger *et al.* 2006a) and their siblings (Kruger *et al.* 2006a), and those probing negative emotion processing in controls. Significant correlations between brain activity, mood state and WM performance observed here further suggest that activity in WM circuits is affected by activity in emotion regulation circuits (even in non-depressed control subjects). Together, data suggest that frontopolar and orbitofrontal deficits are involved in failure to suppress emotional arousal during WM. High emotional arousal appears to draw attention away from task-stimuli (toward negative emotion and arousal), and further interferes with cognitive functions of the frontopolar cortex that are important in WM.

Frontopolar cortex

Controls and RELs exhibited greater activation than BD in the left frontopolar cortex (BA10), a region engaged when subjects must coordinate multiple cognitive functions, goals and sub-goals (as during rule-learning, but not simple WM or dual-task activities)(Burgess *et al.* 2007; Koechlin *et al.* 1999; Owen *et al.* 2005; Strange *et al.* 2001) and during regulation of emotion (Daselaar *et al.* 2008; Lévesque *et al.* 2004; Masaki *et al.* 2006)). Our finding of increased frontopolar activity in RELs is consistent with the one previous fMRI study of BD and RELs (which demonstrated hyperactivity in left frontal pole/ventrolateral gyrus during 2-back performance, and a similar trend in BD during 1-back performance

(Drapier *et al.* 2008), and with results of two fMRI studies of WM in BD (Adler *et al.* 2004; Chang *et al.* 2004), and one PET study of unaffected siblings (Kruger *et al.* 2006a). In RELs, the correlation of three negative emotion scores with frontopolar activity (r's > .5) and reduced WM accuracy (r's >−.5) suggests that high negative emotion-regulatory demands on the frontopolar cortex may interfere with its other functions (i.e., cognitive coordination/ rule learning), leading to decrements in task performance. When 2-back accuracy was controlled, the significance of the difference between BD and controls in this region was reduced to a marginal level (p = 0.06), further suggesting a role for frontopolar cortex in 2-back task performance (the between-group effect size remained large, d = 1.05).

Anterior insula

BD and RELs failed to suppress activation in the left anterior insula, (whereas controls suppressed activation in this region), and insula activity was correlated with POMS Confusion and Tension/Anxiety in RELs. The anterior insula plays a key role in regulation of emotion and hedonic function (functions disrupted in BD), and insula activity has been observed during negative emotion processing (Phillips *et al.* 1997), poor response inhibition (Ramautar *et al.* 2006) and autonomic hyperarousal (Nagai *et al.* 2004) in controls. Increased insula activation has been previously observed in BD during WM (Adler *et al.* 2004) and in RELs after emotional challenge (Kruger *et al.* 2006a). While lifetime alcohol use had a small impact on the difference between RELs and controls in the insula (p = 0.07), the effect size remained large, d=1.32.

Orbitofrontal cortex

RELs failed to suppress activation in the OFC (whereas controls suppressed activation), and failed to show the significant OFC-Depression correlation seen in controls, suggesting faulty modulation of emotion by the OFC during WM in RELs. Indeed, the OFC is implicated in regulation of affective responses (Kimbrell *et al.* 1999) (Pochon *et al.* 2002), autonomic arousal (Nagai *et al.* 2004) and goal-directed behavior (Rolls 1999), and OFC suppression has been shown to play a role in inhibiting adverse emotional signals in order to maximize the level of N-back performance (Pochon *et al.* 2002). While the group difference in the OFC was not robust when using lifetime alcohol use as a covariate (and was marginal using lifetime drug use), it is likely that OFC activity and substance abuse each represent meaningful parts of the genetic risk for BD associated with reward circuitry dysfunctions that cannot be meaningfully separated. Most imaging studies of BD and one study of BD siblings (Kruger *et al.* 2006b) demonstrate reduced (rather than increased) OFC activity relative controls, but, as here, suggest that aberrant OFC activity may be a marker of genetic risk for BD (Blumberg *et al.* 1999; Drevets 1999).

Parietal/postcentral region

RELs failed to suppress activity in a region at the boundary of the superior parietal lobule and postcentral gyrus, and activity in this region was correlated with Confusion across all subjects and in RELs. The superior parietal lobule has been implicated in attention to emotion (Compton *et al.* 2003) and WM (Wager *et al.* 2003), and altered parietal activity during WM has previously been reported in BD (Adler *et al.* 2004; Monks *et al.* 2004). The postcentral gyrus, implicated in somatosensory reactivity, exhibits structural abnormalities in BD (Lyoo *et al.* 2006), and activity in this region was associated with negative affect in one study of euthymic BD (Malhi *et al.* 2007). Failure to suppress parietal activity in RELs, and the correlation of this activity with Confusion across all subjects and RELs, suggests high autonomic and somatosensory reactivity (and diversion of attention from task to these sensations) may contribute to cognitive deficits in this group.

Limitations

The sample size was modest, especially in unmedicated BD subjects, thus, all results should be viewed as preliminary. While there were significant differences between the groups in age and on other potentially confounding variables such as lifetime substance abuse, differences remained largely significant when these variables were covaried except for the OFC. While the problem of substance abuse is inherent to studies of BD, all subjects in this study were free of a substance abuse or dependence disorder within the past 6 months. While there were significant age differences, the age range was quite narrow and similar in all groups, and all subjects were in the NCPP and thus drawn from a comparable population of origin. The age differences are largely an effect of very small standard deviations, as the means and ranges are very comparable across groups. Groups also differed on several variables known to be effects of psychiatric illness (education, IQ, WM performance) (Kremen *et al.* 1995), however, the groups were similar on a measure of pre-morbid intellectual function (WRAT-3 Reading). None of these variables had a significant effect on the results. Moreover, the consistency of findings in RELs and unmedicated BD participants suggests that defects of hedonic circuitry are likely a meaningful part of BD genetic risk.

Conclusions

While preliminary, results of this study suggest that frontopolar and insula (and possibly OFC) regions are involved in failure to suppress emotional arousal during WM in BD and RELs. High emotional arousal may interfere with the role of frontopolar cortex in cognitive coordination and task learning, and draw attention away from WM task goals and toward negative emotional sensations. The results are largely consistent with a small literature on brain function in persons at genetic risk for BD, suggesting that these abnormalities are related substantially to genetic risk for the disorder. Future work should explicitly probe interactions between brain regions, task interactions between cognitive and emotional information processing, and investigate the suitability of frontopolar and insular abnormalities as markers of genetic risk for BD.

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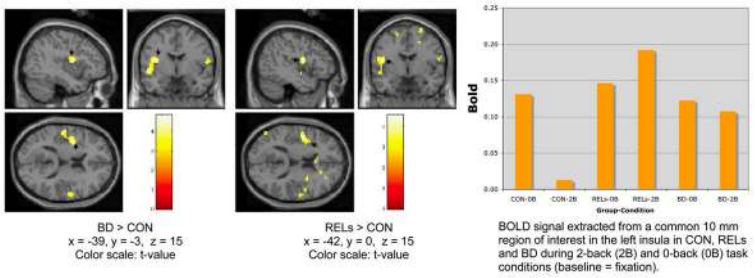

Figure 1.

SPM(t) maps showing exaggerated blood-oxygen-dependent (BOLD) signal in the left anterior insula (BA 13) in bipolar disorder (BD) and first-degree relatives of persons with bipolar disorder (RELs) compared to controls (CON) during fMRI (2-back WM > 0-back task contrast)

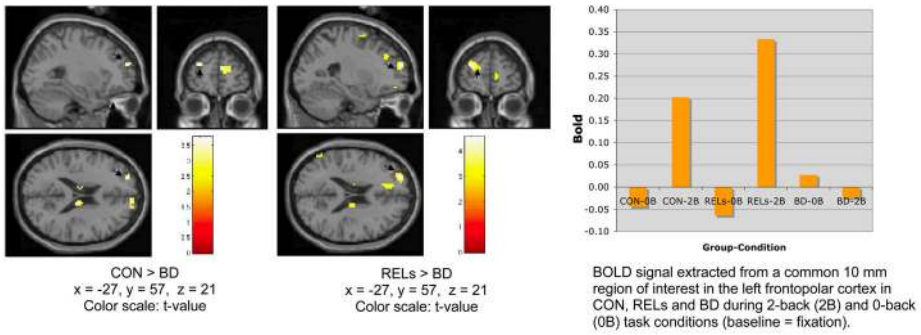

Figure 2.

SPM(t) maps showing reduced BOLD signal in the left frontopolar cortex (BA 10) in BD compared to CON and RELs during fMRI (2-back WM > 0-back task contrast)

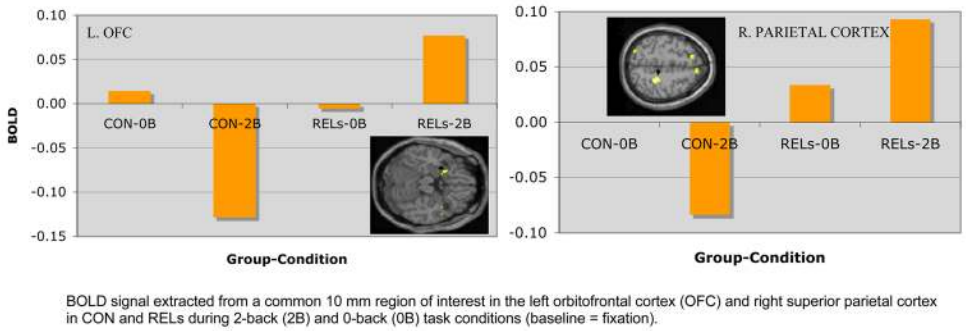

Figure 3.

Exaggerated BOLD signal in the left orbitofrontal cortex (OFC, BA 47) and right superior parietal cortex (at the boundary of the superior parietal lobule and superior postcentral gyrus) in RELs compared to CON during fMRI (2-back WM > 0-back task contrast).

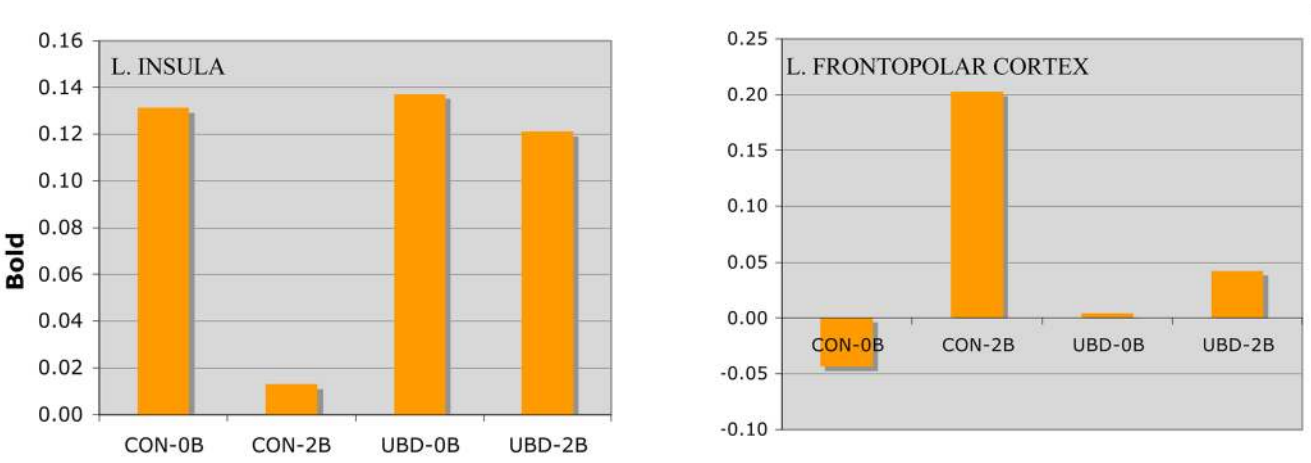

Figure 4.

BOLD signal extracted from a common 10 mm region of interest in the left insula and frontopolar cortex in CON and a sub-sample of 10 unmedicated BD (UBD) during 2-back (2B) and 0-back (0B) task conditions (baseline = fixation).

Table 1

Demographic, neuropsychological and other characteristics of controls (CON), first-degree relatives of persons with bipolar disorder (RELs), and persons with bipolar disorder (BD).

Variable	Con (n=19)	RELS (n=18)	BD (n=19)	*Con v. RELS*	*Con v. BD*	*RELS v. BD*
Matching variables	Mean *(SD) or %*	Mean *(SD) or %*	Mean *(SD) or %*	*t (p) or X^2 (p)*	*t (p) or X^2 (p)*	*t (p) or X^2 (p)*
Age at MRI	39.2 *(2.7)*	36.3 *(2.6)*	41.1 *(3.1)*	3.21 *(.003)**	2.05 *(.05)**	5.07 *(.0001)**
Gender (% Male)	47.4%	44.4%	57.8%	.67 *(.41)*	2.01 *(.37)*	. 67 *(.41)*
Ethnicity (% Cauc.)	94.7%	94.1%	68.4%	.00 *(1.0)*	4.53 *(.10)*	7.24 *(.07)*
Handedness (% R)	84.2%	82.4%	73.7%	1.21 *(.55)*	.54 *(.76)*	1.90 *(.39)*
Parental Education yrs	14.2 *(3.0)*	11.8 *(1.9)*	13.0 *(2.6)*	2.83 *(.008)**	1.29 *(.21)*	1.52 *(.14)*
WRAT-3[a] Reading	103.5 *(8.7)*	98.9 *(10.4)*	97.8 *(11.5)*	1.42 *(.16)*	1.70 *(.10)*	.30 *(.77)*
Education & IQ						
Education (years)	15.3 *(2.5)*	13.3 *(2.1)*	12.6 *(2.2)*	2.45 *(.02)**	3.38 *(.002)**	.92 *(.37)*
IQ estimate[b]	110.6 *(13.3)*	103.3 *(11.5)*	100.1 *(10.3)*	1.72 *(.10)*	2.67 *(.01)**	.88 *(.39)*
In Scanner tasks	Mean *(SD)*	Mean *(SD)*	Mean *(SD)*	*t (p)*	*t (p)*	*t (p)*
0-back % correct	98.7 *(1.7)*	96.6 *(8.1)*	93.0 *(17.2)*	1.02 *(.32)*	1.39 *(.18)*	.80 *(.43)*
0-back reaction time[c]	560 *(60)*	590 *(80)*	620 *(120)*	1.21 *(.23)*	1.96 *(.06)*	.92 *(.36)*
2-back % correct	89.9 *(6.2)*	84.3 *(10.3)*	78.9 *(14.7)*	1.98 *(.06)*	2.95 *(.006)**	1.25 *(.22)*
2-back reaction time[c]	810 *(130)*	840 *(120)*	910 *(170)*	.79 *(.44)*	1.96 *(.06)*	1.29 *(.21)*
POMS Mood scores						
Tension/Anxiety	33.2 *(6.0)*	32.9 *(5.5)*	39.4 *(8.3)*	0.17 *(0.86)*	2.56 *(0.02)**	2.79 *(0.009)**
Depression	37.9 *(6.6)*	37.1 *(4.0)*	43.4 *(9.3)*	0.49 *(0.63)*	2.03 *(0.05)**	2.66 *(0.01)**
Anger/Hostility	44.2 *(7.7)*	42.2 *(5.0)*	47.2 *(8.5)*	0.90 *(0.37)*	1.13 *(0.27)*	2.15 *(0.04)**
Vigor	63.2 *(10.3)*	60.8 *(10.2)*	57.6 *(12.0)*	0.72 *(0.48)*	1.52 *(0.14)*	0.87 *(0.39)*
Fatigue	44.8 *(7.1)*	43.1 *(5.2)*	49.6 *(12.0)*	0.83 *(0.41)*	1.48 *(0.15)*	2.15 *(0.04)**
Confusion	34.4 *(5.4)*	34.4 *(3.4)*	40.2 *(7.6)*	0.04 *(0.97)*	2.63 *(0.01)**	2.91 *(0.008)**

Am J Med Genet B Neuropsychiatr Genet. Author manuscript; available in PMC 2013 September 04.

Variable	Con (n=19)	RELS (n=18)	BD (n=19)	*Con v. RELS*	*Con v. BD*	*RELS v. BD*
Substance use						
Recent alcohol use[d,e]	.16 *(.37)*	.59 *(1.0)*	1.26 *(2.28)*	1.61 *(.12)*	2.08 *(.05)**	1.24 *(.23)*
Lifetime alcohol use[f]	.95 *(.78)*	1.89 *(1.08)*	2.21 *(1.13)*	3.03 *(.005)**	4.00*(.0004)**	.88 *(.38)*
Lifetime drug use[f]	.74 *(.87)*	1.94 *(1.39)*	2.00 *(1.67)*	3.14 *(.004)**	2.93 *(.007)**	.11 *(.91)*

[a] WRAT-R, Wide Range Achievement Test-Revised (Jastak & Jastak, 1985).

[b] IQ estimate derived from vocabulary and block design age-scaled scores of the Wechsler Adult Intelligence Scale-Revised (Wechsler, 1981).

[c] milliseconds

[d] Number of alcoholic beverages consumed on the day prior to scanning.

[e] Levene's Test for Equality of Variances was significant, therefore equality of variances was not assumed.

[f] Interviewer ratings from the Structured Clinical Interview for DSM-IV (SCID) (First et al. 1996) which assesses abuse and/or dependence on both illicit drugs and prescribed medications (when not being used as prescribed). Examples of drugs assessed include cannabis, sedatives/hyponotics/anxiolytics, stimulants, opiods, cocaine, and hallucinogens/PCP).

* Significance level, p< .05.

Am J Med Genet B Neuropsychiatr Genet. Author manuscript; available in PMC 2013 September 04.

Table 2

Normalized fMRI signal change differences in controls, first-degree relatives of persons with bipolar disorder (RELs), and persons with bipolar disorder (BD) during fMRI (2-back WM > 0- back task contrast) and analyses of covariance for potential confounders.

Regions of Interest	L/R	Cluster extent	Coordinates (MNI)[a]	Difference in fMRI Response Between Groups				fMRI Response Difference using ANCOVA	
		(voxels)	(x, y, z)	Comparison	t^b	Effect Size (*d*)	*p*-value	Effect Size (*d*)	*p*-value
Anterior insula (BA 13)	L	49	−39, −3, 15	BD > Con	4.84	1.61	.040[c]	1.33 (Alc-r) 1.34 (IQ) 1.51 (Drg-l) 1.60 (Age) 1.67 (2b) 1.70 (Edu) 1.70 (Alc-l) 1.28 (Drg-l) 1.32 (Alc-l) 1.35 (Age) 1.70 (Edu)	.052[c] (Alc-r) .050[e] (IQ) .010[e] (Drg-l) .049[d] (Age) .003[e] (2b) .037[c] (Edu) .002[e] (Alc-l) .036[e] (Drg-l) .070[e] (Alc-l) .06[c] (Age) .007[d] (Edu)
	L	15	−42, 0, 15	Rels> Con	4.05	1.37	.034[e]		
Frontopolar cortex (BA 10)	L	7	−27, 57, 21	Con > BD	3.72	1.24	.05[d]	1.05 (2b) 1.06 (Edu) 1.11 (Alc-l) 1.14 (IQ) 1.16 (Alc-r) 1.29 (Age) 1.34 (Drg-l) N/A	.060[d] (2b) .050[d] (Edu) .040[e] (Alc-l) .033[e](IQ) .030[e] (Alc-r) .038[d] (Age) .008[e] (Drg-l) N/A
	L	20	−27, 57, 21	Rels > BD	4.57	1.54	.035[d]		
Orbitofrontal cortex (BA 47)	L	7	−24, 12, −18	Rels > Con	3.82	1.29	.05[e]	NS (Alc-l) 1.16 (Age) 1.26 (Drg-l) 1.73 (Edu)	NS (Alc-l) .070[e] (Age) .10[e] (Drg-l) .004[e] (Edu)
Superior parietal region (bordering superior parietal lobule and superior postcentral gyrus)	R	14	27, −42 57	Rels > Con	3.94	1.33	.02[d]	1.34 (Age) 1.58 (Alc-l) 1.71 (Edu) 1.85 (Drg-l)	037[d] (Age) .010[d] (Alc-l) .033[c] (Edu) .0001[c] (Drg-l)

[a]MNI: Montreal Neurological Institute Coordinate System.

[b]Maximum voxel-wise t-value within the cluster of interest.

[c] Cluster-wise statistic was corrected across the entire brain (p< .05).

[d] Small volume correction method was used to correct the cluster-wise statistic (p < .05).

[e] Small volume correction method was used to correct the voxel-wise (family-wise error) statistic (p < .05).

Abbreviations: Edu = education, 2b = 2-back task accuracy, Alc-r = Recent alcohol use (last 24 hours), Alc-l = Lifetime alcohol use-lifetime, Drg-l = Lifetime Drug use, IQ= Intelligence Quotient.

Am J Med Genet B Neuropsychiatr Genet. Author manuscript; available in PMC 2013 September 04.

Table 3

Comparison of demographic, neuropsychological variables and normalized fMRI signal change (2-back WM > 0- back task contrast) in controls (CON) vs. a sub-sample of 10 unmedicated persons with bipolar disorder (BD) who were part of the original sample of BD (n=19).

Variable	Con (n=19)	Unmed BD (n=10)	*Con v. Unmed BD*
Matching variables	Mean *(SD) or %*	Mean *(SD) or %*	*t (p) or X^2 (p)*
Age at MRI	39.2 *(2.7)*	41.7 *(2.9)*	2.20 *(.04)**
Gender (% Male)	47.4%	60.0%	*.42 (.7)*
Ethnicity (% Cauc.)	94.7%	70.0%	*3.93 (.08)*
Handedness (% R)	84.2%	80.0%	*.97 (.62)*
Parental Education yrs	14.2 *(3.0)*	13.3 *(3.0)*	.59 *(.56)*
WRAT-3[a] Reading	103.5 *(8.7)*	97.7 *(11.8)*	1.30 *(.20)*
Education & IQ			
Education (years)	15.3 *(2.5)*	13.2 *(1.4)*	2.28 *(.03)**
IQ estimate[b]	110.6 *(13.3)*	101.4 *(10.9)*	1.53 *(.13)*
In Scanner tasks			
0-back % correct	98.7 *(1.7)*	96.8 *(4.9)*	1.47 *(.15)*
0-back reaction time[c]	560 *(60)*	570 *(80)*	.56 *(.58)*
2-back % correct	89.9 *(6.2)*	81.3 *(9.5)*	2.94 *(.007)**
2-back reaction time[c]	810 *(130)*	850 *(160)*	.93 *(.36)*
POMS Mood scores			
Tension/Anxiety	33.2 *(6.0)*	37.8 *(7.7)*	1.69 *(0.10)*
Depression	37.9 *(6.6)*	40.4 *(6.9)*	0.92 *(0.37)*
Anger/Hostility	44.2 *(7.7)*	46.6 *(7.2)*	0.78 *(0.44)*
Vigor	63.2 *(10.3)*	60.2 *(6.6)*	0.80 *(0.43)*
Fatigue	44.8 *(7.1)*	47.3 *(5.3)*	0.95 *(0.35)*
Confusion	34.4 *(5.4)*	39.7 *(6.1)*	2.31 *(0.03)**
Substance use			
Recent alcohol use[d,e]	.16 *(.37)*	2.30 *(2.79)*	2.42*(.04)**

Am J Med Genet B Neuropsychiatr Genet. Author manuscript; available in PMC 2013 September 04.

Variable	Con (n=19)	Unmed BD (n=10)	*Con v. Unmed BD*
Lifetime alcohol use[f]	.95 *(.78)*	1.80 *(1.14)*	2.39*(.02)*[*]
Lifetime drug use[f]	.74 *(.87)*	1.20 *(1.40)*	1.10 *(.28)*
fMRI signal change	(x, y, z)[g]	Effect size	*t*[h] *(p-value)*
Anterior Insula (BA 13)			
Unmed BD > Con	−36, 0, 15	2.00	5.20 (.045)[i]
Frontopolar Cx. (BA 10)			
Con > Unmed BD	−27, 57, 21	1.07	2.77 (.13)[i]
Rel > Unmed BD	−27, 57, 21	1.21	3.15 (.08)[i]

[a]WRAT-R, Wide Range Achievement Test-Revised (Jastak & Jastak, 1985).

[b]IQ estimate derived from vocabulary and block design age-scaled scores of the Wechsler Adult Intelligence Scale-Revised (Wechsler, 1981).

[c]milliseconds

[d]Number of alcoholic beverages consumed on the day prior to scanning.

[e]Levene's Test for Equality of Variances was significant, therefore equality of variances was not assumed.

[f]Interviewer ratings from the Structured Clinical Interview for DSM-IV (SCID) (First et al. 1996) which assesses the abuse and/or dependence on both illicit drugs and prescribed medications (when not being used as prescribed). Examples of drugs assessed include cannabis, sedatives/hyponotics/anxiolytics, stimulants, opiods, cocaine, and hallucinogens/PCP).

[g]MNI: Montreal Neurological Institute Coordinate System.

[h]Maximum voxel-wise t-value within the cluster of interest.

[i]Small volume correction method was used to correct the cluster-wise statistic ($p < .05$).

[*]Significance level, $p < .05$.