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A functional MRI study of working memory in adolescents and young adults at genetic risk for bipolar disorder: preliminary findings

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Abstract

Objectives—In this report, we seek to (i) identify a potential neuroimaging endophenotype for bipolar disorder (BD) in emotion regulatory and autonomic circuitry in young first-degree relatives of persons with BD; and (ii) replicate our previous work identifying the functional neuroanatomy of working memory (WM) in an older sample of relatives of persons with BD.

Methods—Ten adolescent and young adult (age 13–24) unmedicated, non-ill, first-degree relatives of persons with BD (RELS) and 10 demographically comparable healthy controls performed a 2-back WM task and a 0-back control task during functional magnetic resonance imaging (fMRI). fMRI data were collected on a 1.5 Tesla scanner and analyzed using SPM-2. Mood was assessed on the day of scanning.

Results—The groups did not differ on any demographic, neuropsychological, or in-scanner task performance variables. In contrast to controls, RELS showed (i) weak task-dependent modulation activity in the cerebellar vermis (CV), insula, and amygdala/parahippocampal region, and (ii) exaggerated modulation of activity in the frontopolar cortex and brainstem, even after controlling for potential confounders. Many of the group differences were driven by differences in activity in the low-level (0-back) baseline task.

Conclusions—Young, unmedicated RELS exhibited altered task-dependent modulation of frontopolar, CV, and insula activity during WM, especially during the low-level (0-back) baseline task. Results are largely consistent with our initial study of older adult RELS, suggesting these alterations may represent biomarkers of genetic risk for BD.

Keywords

autonomic nervous system; bipolar disorder; functional MRI; genetics; working memory

Deficits in executive function and verbal learning are present in bipolar disorder (BD) (1, 2), and to a lesser extent in their first-degree relatives (RELS) (3–7), suggesting that these deficits may be potential endophenotypes for BD. While cognitive measures are often used to probe brain activity in BD, a growing literature documents that BD patients and their RELS exhibit altered activity in insular, frontopolar, and orbitofrontal cortices [independent of the cognitive or emotional task used or clinical state, e.g., (8)], suggesting a trait-like, task-independent pattern of brain activity. This pattern of brain activity is remarkably similar to the activity seen in results of imaging studies of negative emotion and autonomic hyperarousal in healthy subjects (9–11), and is observed while subjects perform cognitive tasks not designed to probe emotion in BD or RELS (12–14). This suggests an important dysfunction in neural circuits underlying emotion and autonomic arousal, and is consistent with recent evidence of exaggerated frontal cortical and subcortical responses to emotional faces in RELS (15).

We previously suggested that this pattern of altered brain activity may be a biomarker of BD, reflecting expression of susceptibility genes for BD (13). We hypothesized that frontopolar and orbitofrontal (OFC) alterations in BD reflect reduced cognitive and emotional control during task performance (10, 16–21). Consistent with this hypothesis, we previously showed that negative emotion scores in adult RELS were positively correlated with frontopolar activity and reduced working memory (WM) accuracy (13). Behavioral studies also confirm that negative mood disrupts cognitive task performance in control and mood disordered samples (22, 23).

Indeed, the strongest evidence of a BD endophenotype from studies of BD or RELS implicates the frontal lobe in disease vulnerability (12, 24–28); in particular, the ventral prefrontal (29) and frontopolar regions (12, 13, 30). However, it is also noteworthy that two of the brain regions that most reliably emerge as altered in our and other imaging studies of BD (OFC, insula) are observed in imaging studies of autonomic arousal and pain [insula/prefrontal cortex (31, 32); OFC/insula (10)]. The autonomic nervous system (ANS) plays an important role in maintaining vigilance for task performance (33, 34), and there is preliminary evidence of altered ANS regulation in euthymic BD and RELS [including abnormalities in pain sensitivity (35, 36), cardiovascular and vagal function (37–40), the sleep/wake cycle (41–45), attention (46), and motivation (47)]. Based on these preliminary data, we speculated that altered regulation of ANS, by the OFC, insula, and other structures, may play a role in disrupting control of both cognition and emotion during task performance in BD and RELS (13).

Here, we used functional magnetic resonance imaging (fMRI) and the identical N-back WM task used in our previous work in older RELS (13) to examine brain activity in adolescent and young adult (non-psychotic and non-ill) RELS and controls, who are proximate to the peak age of risk for illness-onset and within the period in which critical illness-related neurodevelopmental changes are presumed to occur. Characterizing the phenotype in this developmental period may eventually help to clarify pathophysiological processes in BD and inform future targets for prevention (48).

Based on our previous work (13), we predicted that RELS would exhibit greater activity than controls during WM in frontopolar, insular, and orbitofrontal cortices, as well as a core region associated with emotion, the amygdala. We also predicted, based on our previous findings in adult RELS (13), that (i) negative emotion (specifically depression, confusion, and tension/anxiety) in RELS would be associated with reduced 2-back accuracy and slower reaction times; (ii) frontopolar activity during WM would be associated with greater negative emotion and reduced 2-back accuracy; (iii) insula activity would be associated with greater negative emotion; and (iv) RELS would show an absence of the negative emotion-OFC activity relationship seen in controls. Finally, on an exploratory basis, we predicted that altered activity in additional regions involved in the regulation of the ANS in RELS would correlate with negative emotion and reduced WM performance. This exploratory hypothesis was based on our previous work showing alterations in multiple regions involved in regulation of the ANS (insula, OFC), and is further suggested by the role of the ANS in task-vigilance and observations of autonomic disturbances in clinical BD.

Materials and methods

Subjects

Subjects were 10 non-psychotic, non-BD, and unmedicated first-degree RELS of persons with a DSM-IV diagnosis of BD (with psychotic features), and 10 healthy, unmedicated control subjects selected to be comparable ($p > 0.05$) on age (range 13-24), gender, education, socioeconomic status (SES), ethnicity, handedness, and reading achievement. Subjects were excluded if they had: any lifetime diagnosis of psychotic illness, substance dependence, neurological disease, history of head injury or medical illness with documented cognitive sequelae, sensory impairments, general intellectual ability (IQ) < 70 , contraindications for magnetic resonance imaging, or current psychotropic medication use. RELS also were excluded if they had any personal history of bipolar illness, and controls were excluded if they had any lifetime psychiatric diagnosis or a family history of psychotic illness. None of the 10 RELS had a lifetime or current diagnosis of any mood disorder. Control families with children in the same age range were recruited from the same geographic area (metropolitan Boston, MA, USA), with similar SES and ethnicity as the patient families. Controls were administered the same clinical procedures as RELS. The study was approved by the human research committees of the Massachusetts Mental Health Center, Massachusetts General Hospital, Harvard University, and other recruitment sites. Subjects aged 18 years and older gave informed consent. Parents of children < 18 years of age gave informed consent and the youth gave assent.

Psychiatric assessment

Bipolar-I disorder patients with psychotic features and control probands (clinically-ill BD or healthy persons respectively, with unaffected relatives < 25) were assessed using the Diagnostic Interview for Genetic Studies (49) and the Family Interview for Genetic Studies (50). Relatives of BD and control probands were screened for presence of other Axis-I disorders, psychosis, and substance use with the Washington University in St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia (51). We administered the psychosis, mood disorders, and substance abuse modules of the K-SADS and our Neurodevelopmental Questionnaire (52) to establish other inclusion and exclusion criteria. Subjects' mood during the past week was assessed with the Profile of Mood States (POMS) (53) approximately 30 min before scanning.

Neuropsychological testing

IQ was calculated by prorating scaled scores of eight subtests (four Verbal and Performance scales each) from the Wechsler Intelligence Scale for Children—third edition (54) (for

subjects < age 17) or the Weschler Adult Intelligence Scale—third edition (55) (for subjects 17 years and older) including: Vocabulary, Comprehension, Digit Span, Arithmetic, Block Design, Picture Arrangement, Digit Symbol/Coding, and Symbol Search. The Wide Range Achievement Test—third edition Reading subtest (56) was used to estimate general intellectual function (57). Handedness was assessed with the Annett Scale (58).

fMRI: working memory and control vigilance tasks

Subjects performed two runs of a sequential letter, block-designed visual N-back WM task with blocks of rest, of 0-back trials, and of 2-back trials, as previously described (59). Briefly, in each run, three 32-sec blocks of the 0-back task alternated with three 32-sec blocks of the 2-back task (16 200-msec trials per block, with a 1800-msec inter-stimulus interval), and each task block was preceded by a 20-sec block of fixation. Hit rate and reaction time were dependent variables.

Neuroimaging

Imaging was conducted on a Siemens Sonata 1.5 Tesla full-body magnetic resonance scanner at the Massachusetts General Hospital Martinos Center. A sagittal localizer scan was performed for placement of slices, followed by a coronal T2-weighted sequence to rule out unexpected neuropathology. Two sagittal 3D MP-RAGE (T1-weighted, nonselective inversion-prepared spoiled gradient echo pulse) sequences were collected (TR/TE/T1/flip = 2.73 sec/3.39 msec/1.0 sec/7, 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). Whole-brain gradient-echo echo planar imaging was acquired (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) while subjects performed two N-back task runs.

Statistical analysis

Demographic, neuropsychological, and clinical variables were compared using independent sample *t*-tests performed in the Statistical Package for the Social Sciences (SPSS) software (Standard Version 11.0.1, 2002, SPSS Inc., Chicago, IL, USA). fMRI data were analyzed using Statistical Parametric Mapping (SPM)-2 software (Wellcome Department of Cognitive Neurology, London, UK) and in-house software running under the MATLAB environment (Mathworks, Inc., Sherborn, MA, USA).

First-level analyses—For each participant, functional images were realigned, normalized to the Montreal Neurological Institute (MNI) template supplied with SPM-2, and smoothed with an 8-mm Gaussian kernel. Within-subject analyses employed a block-based general linear model. Each block (2-back and 0-back) was modeled using a boxcar function convolved with a canonical hemodynamic response function. Estimated motion correction parameters were included as additional covariates. A contrast was created for each subject for the 2-back > 0-back condition. Contrasts were then submitted to second level random-effects analyses.

Second-level analyses—Within-group effects for the 2-back > 0-back contrast were tested using one-sample *t*-tests on contrast images for the entire sample (*n* = 20) and each group separately. Between-group differences for the 2-back > 0-back contrast were tested using a two-sample *t*-test. Statistical maps were initially thresholded at *p* < 0.005 (uncorrected).

Whole-brain analysis—For unpredicted regions, cluster-wise inferences were family-wise error (FWE) corrected for multiple comparisons at $p < 0.05$.

Region-of-interest (ROI) analysis—For a priori defined ROIs based on our previous work studying activity in emotion-regulatory regions during WM in adult RELS (13), the cluster-wise [FWE-corrected ($p < 0.05$)] were reported using the small volume correction method with (i) anatomical masks created using the Wake Forest University PickAtlas Tool (bilateral insula and amygdala) (<http://www.fmri.wfubmc.edu>) (60), and (ii) 10 mm spherical masks of the left frontopolar cortex and left OFC (defined around a peak coordinate taken from the literature (13, 30), as we defined previously (13). Effect sizes corresponding to group differences were calculated using Cohen's d .

Group differences observed in the 2-back > 0-back contrast can be driven by group differences in the 2-back condition, the 0-back condition, or both. In order to further characterize differences in the 2-back > 0-back contrast, parameter estimates for the 2-back and the 0-back conditions (levels of task-related activation or suppression calculated relative to fixation baseline, i.e., 2-back > fixation, 0-back > fixation contrasts) were extracted from the significant functional clusters that differentiated the groups in the 2-back > 0-back contrast. These parameter estimates were subjected to within-group and between-groups post-hoc t -tests, and are depicted in graphs (Figs. 1–4). To address the possibility that group activation differences reflected group differences in potentially confounding variables, we performed ANCOVAs in which POMS vigor scores and IQ were included as covariates (group differences were marginal: vigor, $p = 0.06$; IQ, $p = 0.12$).

To test *a priori* hypotheses about relationships between emotion, task performance, and brain activity based on our previous research in adult RELS (13), bivariate Pearson correlations of WM performance (accuracy and reaction time), natural log-transformed POMS scores and fMRI parameter estimates (extracted from the functional clusters that differentiated the groups) were calculated using SPSS. An exploratory correlational analysis was also conducted in the cerebellar vermis (CV) and brainstem clusters that differentiated the groups. To control for false positives in bivariate correlations, correlations with false discovery rate (FDR)-corrected p -values < 0.05 were reported.

Results

Demographic, neuropsychological, and other characteristics

The groups were similar in age, gender, ethnicity, handedness, education, SES, reading achievement and IQ scores, history of substance use, and all but one of the POMS scores [POMS vigor scores marginally differed between groups ($p = 0.06$)] (Table 1). During fMRI scanning, RELS and controls had similar accuracy and reaction times on the 0-back and 2-back WM tasks.

Neuroimaging

In the total sample of 20 participants, there was greater activation during the 2-back (versus 0-back) task in cortical regions typically associated with WM, including the bilateral dorsolateral prefrontal cortex (BA 9/46) and inferior frontal cortex (BA 45), left superior parietal lobule and inferior frontal cortex (BA 39/40), left frontopolar cortex (BA 10) and bilateral cerebellum (all $p < 0.05$, cluster-level corrected). Regions of significant activation and deactivation for the 2-back > 0-back contrast in controls and RELS are described in Tables 2 and 3, respectively.

Between-group comparisons: whole-brain analysis—When activation during 2-back and 0-back was compared between groups (2-back > 0-back contrast), controls exhibited greater activation than RELS during WM in the CV (lobule IX) and hemispheric XIII regions, extending to the pons level ($p = 0.03$, cluster-level corrected) (Table 4, Fig. 1A). Further exploration of the parameter estimates (for the 0-back > fixation and 2-back > fixation contrasts) extracted from the CV cluster revealed that controls exhibited significant within-group modulation (enhancement) of activity from the 0-back to the 2-back condition ($p = 0.0001$). Compared to controls, RELS exhibited significantly greater activity in the CV cluster during the 0-back condition ($p = 0.05$), and did not exhibit significant within-group modulation of activity from 0-back to 2-back, as seen in controls ($p = 0.58$) (Fig. 1A, see graph). Group differences were due to significant between-group differences in both the 0-back ($p = 0.05$) and 2-back conditions ($p = 0.01$). This finding remained significant when POMS vigor scores ($p < 0.01$, Table 4) and IQ ($t = 5.32$, $d = 2.58$, $p = 0.022$) were covaried.

Controls also showed greater activity (specifically, less deactivation) than RELS in the brainstem [2-back > 0-back contrast; in the midbrain in the right reticular formation, extending to the pons level with activation in the dorsal raphe nucleus and extending to the ventral tegmental area (VTA)], which was statistically significant when POMS vigor scores were used as a covariate in the analysis ($p = 0.005$, cluster-level corrected) (Table 4, Fig. 1B). Parameter estimates (for the 0-back > fixation and 2-back > fixation contrasts) extracted from the brainstem cluster revealed greater modulation (deactivation) during the 0-back in controls than RELS ($p = 0.05$), with both groups showing significant deactivation in response to the 2-back task (controls: $p = 0.05$, RELS: $p = 0.02$), (Fig. 1B, graph). Group differences were driven by differences in only the 0-back ($p = 0.05$) and not the 2-back condition ($p = 0.48$). This finding was not robust when IQ was covaried, however, the t -value and effect size were still large ($t = 4.47$, $d = 2.17$).

Between-group comparisons: region-of-interest analysis—RELS exhibited significantly greater activation compared to controls in the left frontopolar cortex (2-back > 0-back contrast) (Table 4, Fig. 2, graph), in the same region which differentiated older adult controls and RELS from BD patients in our previous WM study (13). This finding was marginally significant when vigor scores ($p = 0.06$, Table 4) and IQ scores ($t = 3.42$, $d = 1.66$, $p = 0.09$) were covaried. Parameter estimates (for the 0-back > fixation and 2-back > fixation contrasts) extracted from the frontopolar cluster revealed lower 0-back activity in the RELS compared to controls ($p = 0.03$) and significant modulation (enhancement) of activity from 0-back to 2-back only in the RELS ($p = 0.02$) but not controls ($p = 0.90$) (Fig. 2, bar graph). Group differences were driven by differences in only the 0-back condition ($p = 0.03$) but not the 2-back condition ($p = 0.38$).

Findings in three *a priori* ROIs (the insula, amygdala, and OFC) emerged only in covariate analyses. In ANCOVA using POMS vigor score as a covariate, controls showed significantly greater activation than RELS in the left and right insula (BA 13) and the right amygdala/parahippocampal gyrus region (2-back > 0-back contrast) (Table 4, Fig. 3). Parameter estimates (for the 0-back > fixation and 2-back > fixation contrasts) extracted from the left insula cluster and a cluster which included the right insula, amygdala, and parahippocampus revealed a pattern similar to that seen in the CV: while controls significantly enhanced activation from 0-back to 2-back (L: $p = 0.0007$; R: $p = 0.00007$), RELS exhibited significantly higher activity in these regions during the 0-back condition than controls (L: $p = 0.003$; R: $p = 0.001$), with weak within-group modulation from 0-back to 2-back task (L: $p = 0.92$; R: $p = 0.84$) (Fig. 3, see graphs). Group differences were due to significant differences in only the 0-back condition (L: $p = 0.003$; R: $p = 0.001$) but not the 2-back condition (L: $p = 0.24$; R: $p = 0.22$).

In ANCOVA using IQ as a covariate, RELS also showed greater activation (specifically, less deactivation) in the left OFC (2-back > 0-back contrast) (Fig. 4), as we predicted based on our previous study of older adult RELS (13). However, this finding did not achieve significance at the FWE cluster-corrected level (BA 47; $t = 3.40$, $d = 1.65$, $p = 0.045$, using the voxel-wise FDR correction). Parameter estimates (for the 0-back > fixation and 2-back > fixation contrasts) extracted from the OFC cluster revealed that controls marginally suppressed OFC activation from 0-back to 2-back ($p = 0.06$) (Fig. 4, graph). RELS, by contrast, exhibited a trend toward greater deactivation than controls during 0-back ($p = 0.10$), and failed to modulate activity (with further deactivation) from 0-back to 2-back ($p = 0.75$).

Examination of parameter estimates suggested that patterns of weak or hyper-modulation of activity from 0-back during the 2-back in RELS may have been in part due to group differences in the low-level 0-back task. Indeed, a two-sample t -test reflecting the 0-back > fixation contrast revealed significantly greater activation in RELS (compared to controls) in the CV region, brainstem, insula (anterior and posterior regions, bilaterally), amygdala (bilaterally), and right inferior temporal gyrus (BA 20/21); and lower activity in the left frontopolar cortex. There were no statistically significant group differences in the OFC.

Predicted relationships of brain activity, task performance, and mood

In RELS, left frontopolar activity ($p = 0.04$) and insula activity (bilaterally; L: $p = 0.01$, R: $p = 0.02$) were related to depression. Suppression of OFC activity during 0-back was marginally related to confusion in both controls and RELS, and to tension/anxiety in controls (all $p = 0.06$). Also in RELS, tension/anxiety was negatively related to 2-back reaction time ($p = 0.05$), while frontopolar activity was marginally negatively related to 2-back reaction time ($p = 0.10$).

Exploratory relationships of brain activity, task performance, and mood

In RELS, CV activity was related to anger/hostility in RELS ($p = 0.04$), while brainstem activity was related to tension/anxiety and fatigue ($p = 0.05$). No other exploratory correlations between brain activity, mood, and task performance survived FDR-correction for multiple comparisons.

Relationships of brain activity, task performance, and mood across all subjects (RELS and controls)

Unexpectedly, in predicted regions, activity during the 0-back condition was primarily related to mood in the whole sample. Activity in the insula (bilaterally) during 0-back was significantly related to all six POMS scores [tension/anxiety, depression, anger/hostility, vigor, fatigue, and confusion (all FDR-corrected, $p < 0.05$)]. Frontopolar activity during 0-back was related to vigor and confusion, while OFC activity during 0-back was significantly related to tension/anxiety, vigor, fatigue, and confusion ($p < 0.05$). In exploratory correlations, CV activity during 0-back ($p = 0.05$) and 2-back ($p = 0.001$) was related to vigor. Brainstem activity was marginally related to tension/anxiety and fatigue ($p = 0.06$). No other correlations between brain activity, mood, and task performance survived FDR-correction for multiple comparisons.

Discussion

During performance of a WM task in which performance was comparable across groups, RELS showed (i) weak modulation (activation or deactivation from 0-back to 2-back condition) in the CV, insula, and amygdala/parahippocampal region, and (ii) exaggerated modulation in the frontopolar cortex and brainstem (from 0-back to 2-back) compared to

that seen in controls. In the CV, group differences were due to significant differences in both the 0-back and 2-back conditions, while group differences in other regions were driven by exaggerated activity (brainstem, insula, and amygdala) or reduced activity (frontopolar cortex) in the 0-back condition in RELS (as indicated by our examination of parameter estimates for 0-back and 2-back conditions, and by 2-group *t*-tests comparing 0-back and fixation conditions). In addition, RELS showed a nonsignificant trend toward reduced deactivation in the left OFC, slightly weaker than the significant finding in our previous study in adult RELS (13). Results were observed despite the absence of statistical differences between groups on all demographic, neuropsychological, in-scanner performance, and most clinical variables; and many results were robust to ANCOVAs using vigor and IQ as covariates. However, all results should be viewed as preliminary due to the small sample size.

Our results suggest altered neural reactivity to a low-load cognitive-challenge in RELS which affects modulation in response to a higher-load cognitive challenge, consistent with reports of altered low-level task response in mood disorder populations (14, 61, 62). The frontopolar findings largely replicate those of two BD studies of adult RELS (12, 13) and two fMRI studies of WM in BD (24, 30). Contrary to our hypotheses based on previous work (12), there was minimal evidence of a link between negative-emotion related brain activity and task performance in RELS. For example, while tension/anxiety was related to faster 2-back reaction time in RELS (FDR-corrected $p = 0.05$), activity in the frontopolar cortex was only marginally related to WM performance (FDR-corrected $p = 0.10$). However, activity in many of the regions that differentiated the groups (frontopolar, insular, CV, and brainstem) was significantly related to negative mood in RELS, despite the fact that both groups exhibited mood scores in the normal range and did not differ on average (with the exception of vigor level, $p = 0.06$). Further, insular, frontopolar, and orbitofrontal activity during the 0-back condition was significantly related to mood scores in the whole sample.

Alterations in the CV are consistent with a study showing CV volume is associated with resilience to BD in RELS (63), decreased CV signal during WM in BD (24), and abnormal spectroscopic (64) and structural findings in the CV in BD (65, 66). Altered CV activity may reflect homeostatic or compensatory adaptation in RELS which confers resilience to cognitive and emotional deficits seen in BD, consistent with the relationship of cerebellar volume and resilience to mood disorder in RELS (63). Indeed, the CV participates in regulation of the midbrain/VTA–amygdala/parahippocampal components of the Papez circuit (67–73), and plays a strong role in regulation of emotion (74–79), long-term fear conditioning (80, 81), and Pavlovian conditioned cardiac responses (82, 83), even independent of the amygdala (81). Further, CV transcranial magnetic stimulation (a putative treatment for mood disorders) directly affects amygdala/hippocampal activity (73). Here, CV activity was related to vigor in the whole sample and to anger/hostility in RELS. While speculative, altered CV modulation in RELS may reflect preserved capacity for vigor and externalizing emotions (anger), which confer protection against depression and mood disorder.

In addition, CV activity in RELS may reflect a compensatory adaptation that preserves task performance in the context of altered task-related frontopolar modulation. Notably, lesions of the CV are associated with both executive function deficits (attention, WM) as well as cognitive, emotional, and locomotor changes seen in BD (76–79). Thus, it is possible that inability to compensate for other abnormalities with CV activity may be one correlate of BD illness. Interestingly, the CV is sensitive to stress, glucocorticoids, and drugs of abuse (67, 84–87), which can be triggers to the onset of BD.

Many of the regions differentiating the groups (CV, insula, amygdala, raphe and other brainstem nuclei, and the VTA) participate in an extended visceromotor network modulating reward, fear, stress and autonomic/neuroendocrine responses, and motivation (10, 47, 64, 67–69, 72, 73, 75, 76, 81–86, 88–94). While pathophysiological mechanisms are unclear, abnormal modulation of this network could explain some of the abnormal cognitive, motivational, neuroendocrine, autonomic, and emotional symptoms in mood disorders (89). The reticular formation, for example, plays pivotal roles in the regulation of several domains affected in mood disorders (arousal, attention, autonomic reflexes, motor functions, the wake/sleep cycle, and pain) (94). The VTA (origin of the mesocortical and mesolimbic dopamine systems innervating several structures showing group differences here, such as the prefrontal, orbitofrontal, insular cortices, and amygdala) plays roles in the regulation of locomotor inhibition, arousal, affect, and drive (95). The raphe nuclei are implicated in antidepressant action (96) and pain inhibition, and are potentially relevant given genetic evidence of serotonergic abnormalities in BD (97, 98).

Finally, the findings of this study are also consistent with other recent findings of autonomic dysregulation in BD and other mood disorders, including (i) cardiovascular and vagal abnormalities (which pre-exist psychopharmacologic treatment) (37–40, 99); (ii) a relationship of maladaptive emotion regulation responses to lower vagal recovery in relatives of depressed persons (100); and (iii) vagus nerve stimulation as a putative treatment for severe mood disorders (101, 102).

Limitations

The findings of this study should be viewed as preliminary, due to the small sample size and exploratory nature of some of the results. Replication of the results in larger samples is needed. The result in the OFC, for example, did not meet our criteria for statistical significance. Though the resolution of fMRI is not sufficient to separate activations in small structures (i.e., in the pons and midbrain), the regions activated span multiple small structures and preliminary findings suggest a coherent network associated with regulation of autonomic arousal. In follow-up studies with larger samples, we will use ROIs derived from individual structural anatomy to look more precisely at the location of activations.

Conclusions

While preliminary, findings suggest altered modulation of the CV, frontopolar cortex, and insula during WM in familial risk for BD. If replicated in larger samples, these findings may represent biomarkers of genetic risk for BD.

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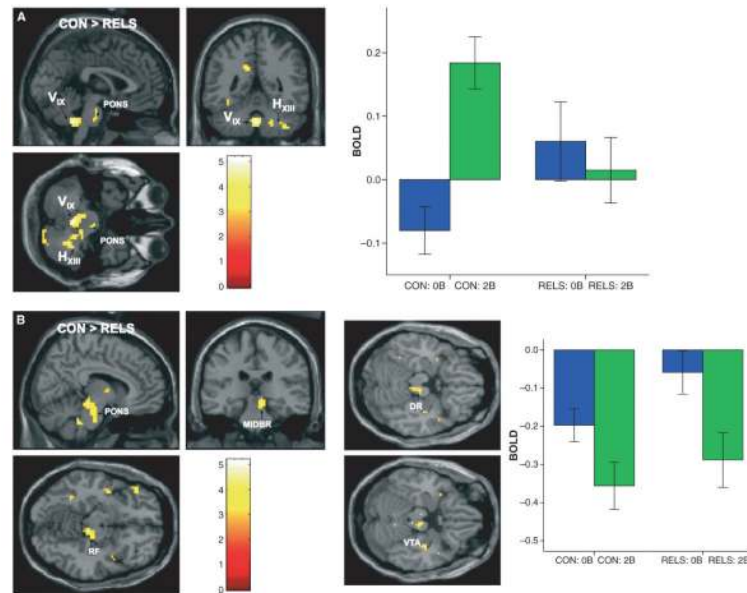
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**Fig. 1.**

SPM(t) maps showing greater blood-oxygen-dependent (BOLD) signal change (activation) in (A) the cerebellar vermis IX (V_{IX}) and hemispheric XIII (H_{XIII}) regions and (B) less deactivation in the midbrain (MIDBR)/pons (PONS) region [including the reticular formation (RF), dorsal raphe (DR), and ventral tegmental area (VTA)] in controls (CON) compared to first-degree relatives of persons with bipolar disorder (RELS) during working memory (WM) [2-back WM > 0-back task contrast; color scale = *t*-value; MNI coordinates of peak voxel: (A) cerebellar vermis: *x* = 0, *y* = -48, *z* = -42; (B) MIDBR/PONS: *x* = 9, *y* = -27, *z* = -12]. Graph depicts parameter estimates (mean BOLD fMRI signal change, with standard error bars) extracted from the cerebellar vermis and MIDBR/PONS clusters for the 0-back (0B) and 2-back (2B) conditions relative to fixation (represented by the zero baseline) for each group.

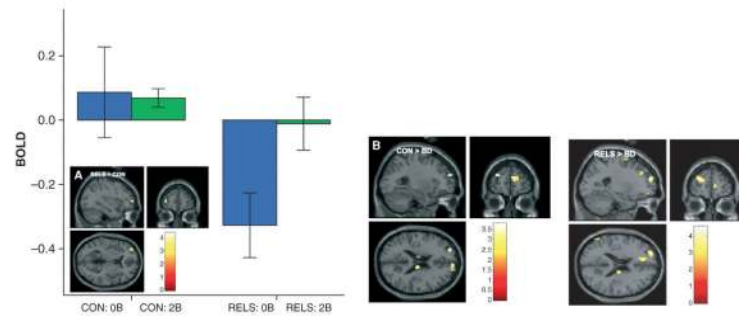
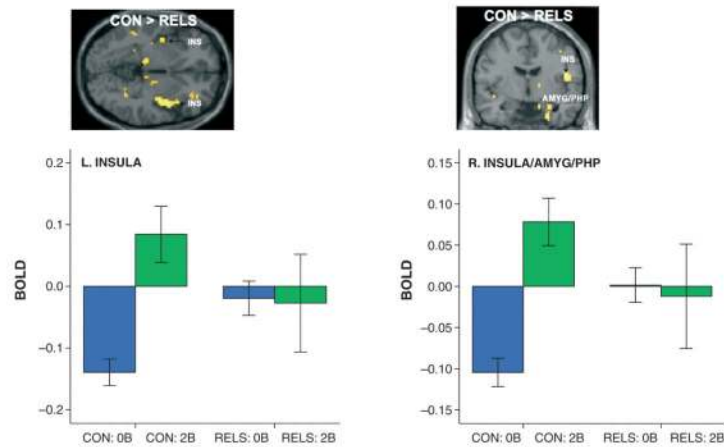


Fig. 2.

(A) SPM(t) maps showing reduced activation during 0-back (relative to fixation) and greater modulation of activation during 2-back working memory (WM) (relative to 0-back) in the left frontopolar cortex (BA 10) in first-degree relatives of persons with bipolar disorder (RELS) compared to controls (CON), replicating (B) our previous work showing a similar pattern in the same region in older adult RELS and CON compared to persons with bipolar disorder (BD) (13). [2-back WM > 0-back task contrast; color scale = t -value; MNI coordinates of peak voxel: (A): $x = -33$, $y = 60$, $z = 9$; (B): $x = -27$, $y = 57$, $z = 21$]. Graph depicts parameter estimates [mean blood-oxygen-dependent (BOLD) fMRI signal change, with standard error bars] extracted from the frontopolar cluster for the 0-back (0B) and 2-back (2B) conditions relative to fixation (represented by the zero baseline) for each group.

**Fig. 3.**

SPM(t) maps showing greater activation of left insula (INS) and right INS (BA 13), amygdala (AMYG), and parahippocampus (PHP) from 0-back to 2-back condition in controls (CON) compared to first-degree relatives of persons with bipolar disorder (RELS), after controlling for Profile of Mood States vigor scores (2-back working memory > 0-back task contrast; MNI coordinates of peak voxel: left INS: $x = -36$, $y = -18$, $z = 6$; right INS/AMYG/PHP: $x = 36$, $y = -15$, $z = -24$). Graph depicts parameter estimates [mean blood-oxygen-dependent (BOLD) fMRI signal change, with standard error bars] extracted from the left INS cluster (left graph) and a right cluster which included the INS, AMYG, and PHP (right graph) for the 0-back (0B) and 2-back (2B) conditions relative to fixation (represented by the zero baseline) for each group.

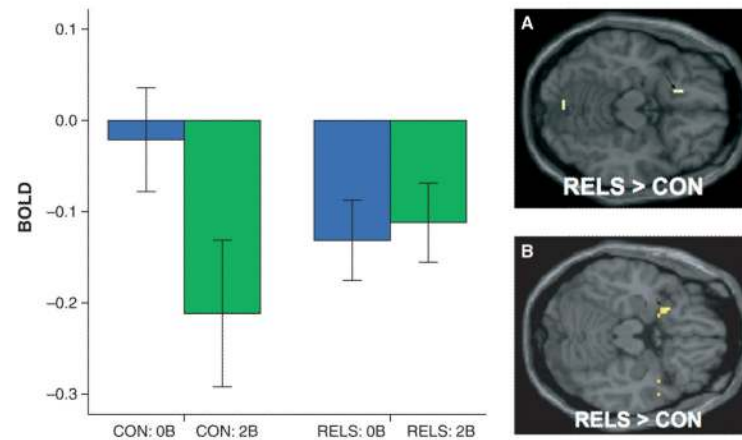


Fig. 4.

(A) SPM(t) maps showing nonsuppression of the left orbitofrontal cortex (OFC) (BA 47) during working memory (WM) in first-degree relatives of persons with bipolar disorder (RELS) compared to controls (CON) after controlling for IQ scores, replicating (B) our previous work showing exaggerated signal in the same region in older adult RELS compared to CON (13). [2-back WM > 0-back task contrast; MNI coordinates of peak voxel: (A): $x = -15$, $y = 27$, $z = -15$; (B): $x = -24$, $y = 12$, $z = -18$]. Graph depicts parameter estimates [mean blood-oxygen-dependent (BOLD) fMRI signal change, with standard error bars] extracted from the OFC cluster for the 0-back (0B) and 2-back (2B) conditions relative to fixation (represented by the zero baseline) for each group.

Table 1

Demographic, neuropsychological, and clinical characteristics of controls (CON) and first-degree relatives of persons with bipolar disorder (RELS)

Variable	CON (n = 10)	RELS (n = 10)	CON versus RELS <i>t</i> (p) or <i>F</i> (p)
Matching variables			
Age at MRI, mean (SD) ^a	17.1 (1.4)	18.4 (4.2)	0.92 (0.37)
Gender (% male)	50	50	0.00 (1.0)
Ethnicity (% Caucasian)	70	100	5.00 (0.17)
Handedness (% right)	80	100	0.56 (0.46)
Socioeconomic status, mean (SD) ^{a,b}	41.8 (10.3)	46.8 (16.4)	0.78 (0.44)
WRAT-3 Reading, mean (SD)	100.9 (12.9)	106.8 (9.2)	1.18 (0.25)
Education and IQ, mean (SD)			
Education, years	10.0 (1.5)	11.6 (3.8)	1.23 (0.24)
IQ estimate ^c	95.4 (16.5)	107.7 (16.9)	1.65 (0.12)
In scanner tasks, mean (SD)			
0-back % correct	98.4 (1.0)	93.3 (9.8)	1.55 (0.17)
0-back reaction time (msec)	530.0 (74.0)	511.0 (61.0)	0.58 (0.57)
2-back % correct	88.5 (5.9)	87.3 (9.0)	0.34 (0.74)
2-back reaction time (msec)	783.0 (180.0)	684.0 (153.0)	1.21 (0.24)
POMS scores, mean (SD)			
Tension/anxiety	34.4 (5.3)	35.2 (5.6)	0.53 (0.74)
Depression	37.1 (5.1)	39.6 (5.6)	0.99 (0.32)
Anger/hostility	43.7 (7.4)	45.0 (4.8)	0.64 (0.65)
Vigor	61.5 (8.9)	54.2 (6.9)	2.02 (0.06)
Fatigue	41.7 (5.5)	44.0 (6.4)	0.99 (0.42)
Confusion	35.3 (5.3)	37.7 (3.7)	1.34 (0.25)

MRI = magnetic resonance imaging; WRAT-3 = Wide Range Achievement Test—third edition (56); POMS = Profile of Mood States.

^aLevene's Test for Equality of Variances was significant, therefore equality of variances was not assumed.

^bParental socioeconomic status measured using the Hollingshead Four Factor Index (103).

^cFull-scale intelligence quotient (IQ) assessed using the Wechsler Intelligence Scale for Children—III (54) or Wechsler Adult Intelligence Scale—III (55) prorated from eight subtests.

Table 2

Regions of significant functional magnetic resonance imaging (fMRI) activation and deactivation in controls during working memory (WM)

Region	L/R	Cluster extent (voxels)	Coordinates (MNI)			fMRI response		
			x	y	z	Comparison	<i>t</i> ^a	p-value
Activation								
Whole-brain analysis ^b								
Cerebellum/posterior lobe/brainstem	R	2045	33	−63	−33	2-back > 0-back	14.55	0.0001
Ventral thalamus/globus pallidus	R	583	18	−12	0	2-back > 0-back	13.00	0.0001
Middle and inferior frontal gyrus (BA 6/45)	R	2071	30	3	51	2-back > 0-back	4.81	0.0001
Inferior frontal gyrus	R	125	33	27	−3	2-back > 0-back	4.17	0.0001
Superior parietal lobule (BA 7/40)	R	1714	27	−69	57	2-back > 0-back	4.70	0.0001
Frontopolar cortex/middle frontal gyrus (BA 10)	L	80	−36	60	12	2-back > 0-back	4.24	0.0001
	R	200	30	54	15	2-back > 0-back	4.05	0.0001
Region-of-interest analysis ^c								
Insula	L	71	−30	27	3	2-back > 0-back	7.19	0.0001
Cerebellar vermis	R	79	3	−57	−15	2-back > 0-back	9.50	0.0001
	L/R	19	0	−48	−42	2-back > 0-back	4.96	0.025
	R	363	6	−30	−12	2-back > 0-back	4.72	0.0001
Deactivation								
Whole-brain analysis ^b								
Inferior parietal lobule (BA 40)	R	644	57	−30	36	0-back > 2-back	14.44	0.0001
Medial frontal gyrus (BA 10) / anterior cingulate (BA 32)	L	665	−9	54	6	0-back > 2-back	9.71	0.0001
Paracentral lobule/anterior and posterior cingulate (BA 32/31)	R	221	3	−12	48	0-back > 2-back	7.68	0.0001
Insula	L	120	−45	−9	3	0-back > 2-back	7.42	0.001
Inferior parietal lobule (BA 40)	L	187	−66	−33	33	0-back > 2-back	6.54	0.0001
Postcentral gyrus	R	61	24	−39	72	0-back > 2-back	3.61	0.05
Region-of-interest analysis ^c								
Orbitofrontal cortex (BA 11)	L	21	−3	33	−21	0-back > 2-back	4.70	0.024
	R	29	3	36	−21	0-back > 2-back	6.43	0.010
Insula	R	17	42	0	9	0-back > 2-back	4.62	0.035
Amygdala	L	4	−21	−3	−24	0-back > 2-back	4.00	0.033

MNI = Montreal Neurological Institute Coordinate System.

^aMaximum voxel-wise *t*-value within the cluster of interest.

^bWhole-brain analysis: cluster-wise family-wise error (FWE)-corrected statistic ($p < 0.05$).

^cRegion-of-interest analysis: for regions of interest defined *a priori*, the cluster-wise statistic was FWE-corrected for multiple comparisons within the *a priori* region, i.e., using anatomical masks created with the Wake Forest University PickAtlas Tool, or using a spherical mask defined around coordinates taken from the literature [i.e., the frontopolar cortex and orbitofrontal cortex as used in our previously published work in adult first-degree relatives of persons with bipolar disorder (13)].

Table 3

Regions of significant functional magnetic resonance imaging (fMRI) activation and deactivation in first-degree relatives of persons with bipolar disorder during working memory (WM)

Region	L/R	Cluster extent (voxels)	Coordinates (MNI)			fMRI response		
			x	y	z	Comparison	<i>t</i> ^a	p-value
<u>Activation</u>								
Whole-brain analysis^b								
Cerebellum/posterior lobe	R	782	3	−75	−27	2-back > 0-back	4.56	0.0001
Region-of-interest analysis^c								
Frontopolar cortex/middle frontal gyrus (BA 10)	L	10	−33	60	12	2-back > 0-back	4.42	0.045
<u>Deactivation</u>								
Whole-brain analysis^b								
Inferior temporal gyrus (BA 20)/posterior insula	L	766	−45	−9	−36	0-back > 2-back	9.21	0.0001
Inferior temporal gyrus (BA 20)/anterior and posterior insula	R	1332	42	3	−39	0-back > 2-back	6.84	0.0001
Medial frontal gyrus (BA 10) / anterior cingulate (BA 32)	R	855	3	57	6	0-back > 2-back	7.94	0.0001
Precuneus	R	231	−9	−48	30	0-back > 2-back	5.96	0.003
Region-of-interest analysis^c								
Insula	L	47	45	3	−3	0-back > 2-back	5.15	0.011
Amygdala	L	10	−27	−3	−15	0-back > 2-back	5.08	0.020
	R	23	24	−3	−18	0-back > 2-back	4.42	0.008

MNI = Montreal Neurological Institute Coordinate System.

^aMaximum voxel-wise *t*-value within the cluster of interest.

^bWhole-brain analysis: cluster-wise family-wise error (FWE)-corrected statistic ($p < 0.05$).

^cRegion-of-interest analysis: for regions of interest defined *a priori*, the cluster-wise statistic was FWE-corrected for multiple comparisons within the *a priori* region, i.e., using anatomical masks created with the Wake Forest University PickAtlas Tool, or using a spherical mask defined around coordinates taken from the literature [i.e., the frontopolar cortex and orbitofrontal cortex, as used in our previously published work in adult first-degree relatives of persons with bipolar disorder (13)].

Functional magnetic resonance imaging (fMRI) signal change differences in controls (CON) compared to first-degree relatives of persons with bipolar disorder (RELS) during working memory (WM)^a

Table 4

Region	L/R	Cluster extent (voxels)	Peak coordinate (MNI)			Original difference in fMRI response between groups				Difference after controlling for POMS vigor scores		
			x	y	z	Group difference	<i>t</i> ^{<i>b</i>}	Effect size (<i>d</i>)	p-value	<i>t</i> ^{<i>b</i>}	Effect size (<i>d</i>)	p-value
Whole-brain analysis ^{<i>c</i>}												
Cerebellar vermis IX and hemispheric XIII regions	L	173	0	-48	-42	CON > RELS	5.20	2.45	0.03	5.21	2.61	0.01
Brainstem/midbrain/pons/reticular formation/raphe nuclei/ventral tegmental area	R	129	9	-27	-12	CON > RELS	4.77	2.25	0.09	4.74	2.46	0.005
Insula (BA 13, anterior and posterior regions)	L	130	-36	-18	6	CON > RELS	-	-	-	4.74	2.37	0.05
Parahippocampal gyrus/amygdala / insula (BA 13)	R	629	36	-15	-24	CON > RELS	-	-	-	4.69	2.35	0.0001
Region-of-interest analysis ^{<i>d</i>}												
Frontopolar cortex (middle frontal gyrus, BA 10)	L	4	-33	60	9	RELS > CON	4.01	1.89	0.004	7.24	3.62	0.06
Insula (BA 13, anterior and posterior regions)	R	81	42	0	-3	CON > RELS	-	-	-	4.44	2.22	0.025
Amygdala/parahippocampal gyrus	R	6	27	-6	-21	CON > RELS	-	-	-	3.31	1.66	0.05

MNI = Montreal Neurological Institute Coordinate System; POMS = Profile of Mood States.

^a2-back WM > 0-back task contrast.

^bMaximum voxel-wise *t*-value within the cluster of interest.

^cWhole-brain analysis: cluster-wise family-wise error (FWE)-corrected statistic ($p < 0.05$).

^dRegion-of-interest analysis: for regions of interest defined *a priori*, the cluster-wise statistic was FWE-corrected for multiple comparisons within the *a priori* region, i.e., using anatomical masks created with the Wake Forest University PickAtlas Tool, or using a spherical mask defined around coordinates taken from the literature [i.e., the frontopolar cortex and orbitofrontal cortex, as used in our previously published work in adult first-degree relatives of persons with bipolar disorder (13)].