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Aberrant Cerebellar Connectivity in Bipolar Disorder With Psychosis

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ABSTRACT

BACKGROUND: The cerebellum, which modulates affect and cognition in addition to motor functions, may contribute substantially to the pathophysiology of mood and psychotic disorders, such as bipolar disorder. A growing amount of literature points to cerebellar abnormalities in bipolar disorder. However, no studies have investigated the topographic representations of resting-state cerebellar networks in bipolar disorder, specifically their functional connectivity to cerebral cortical networks.

METHODS: Using a well-defined cerebral cortical parcellation scheme as functional connectivity seeds, we compared 10 cerebellar resting-state networks in 49 patients with bipolar disorder and a lifetime history of psychotic features and 55 healthy control participants matched for age, sex, and image signal-to-noise ratio.

RESULTS: Patients with psychotic bipolar disorder showed reduced cerebrocerebellar functional connectivity in somatomotor A, ventral attention, salience, and frontoparietal control A and B networks relative to healthy control participants. These findings were not significantly correlated with current symptoms.

CONCLUSIONS: Patients with psychotic bipolar disorder showed evidence of cerebrocerebellar dysconnectivity in selective networks. These disease-related changes were substantial and not explained by medication exposure or substance use. Therefore, they may be mechanistically relevant to the underlying susceptibility to mood dysregulation and psychosis. Cerebellar mechanisms deserve further exploration in psychiatric conditions, and this study's findings may have value in guiding future studies on pathophysiology and treatment of mood and psychotic disorders, in particular.

Keywords: Bipolar disorder, Cerebellum, Functional connectivity, Networks, Psychosis, Resting state

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The cerebellum modulates affect and cognition in addition to motor performance (1–4) and may play a significant role in psychiatric disorders, such as bipolar disorder (BP). Indeed, a growing body of evidence points to clinical (5–14), molecular (15–19), neurochemical (20–22), structural (23–39), and functional (40–44) abnormalities of the cerebellum in BP. The cerebellum is reciprocally connected to higher-level association areas in prefrontal (45) and posterior parietal (46) cortices and limbic regions in medial temporal lobe (47–49), and cerebellar dysfunction may mirror or contribute to well-established dysfunctions of these higher-level association areas in BP.

Resting-state functional magnetic resonance imaging (rs-fMRI) examines the functional connectivity (FC) of intrinsic brain networks. This technique is particularly well suited to studying cerebrocerebellar connectivity because communication between the cerebral cortex and cerebellum is indirect (4), with cerebral cortical signals relayed to the pons before they arrive at the cerebellum, and with cerebellar outputs projecting to the thalamus before reaching the cerebral cortex. While the polysynaptic nature of this circuitry has limited its study using traditional retrograde tracer techniques, rs-fMRI, which can detect functional relations across distributed brain areas, reveals connectivity patterns informed by, but not necessarily confined to, direct monosynaptic connections (4). rs-fMRI allows investigations of cerebrocerebellar circuits in humans in vivo and in the absence of tasks, which can limit the participation of more severely ill patients and also constrain evaluation to specific functional networks.

Previous rs-fMRI studies found resting-state abnormalities of the cerebellum (50–52) or cerebellar FC in BP (53–57). However, in all of these studies, the cerebellum was among the regions identified as abnormal during the course of whole-brain investigations. No studies have focused specifically on cerebellar FC in BP. Importantly, although the cerebellum is a complex brain region, consisting of parallel closed-circuit modular loops, with distinct circuits specific for association cortices versus motor and somatosensory cortices (45,58–60), no studies have investigated the topographic representations of resting-state cerebellar networks in BP, specifically their FC to cerebral cortical networks.

As we previously summarized (61), Yeo *et al.* (62) analyzed rs-fMRI data from 1000 healthy subjects, using a clustering strategy to parcellate the cerebral cortex into intrinsic

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components on the basis of territories sharing similar FC profiles to other regions of the cortex, and found that either 7 or 17 distinct networks provide relatively stable parcellation solutions. With the use of the same 1000-subject data set and cortical parcellation solutions as a reference, Buckner *et al.* (63) subsequently developed a parcellation of the human cerebellum, assigning every cerebellar voxel to its most strongly associated cortical network using a winner-take-all approach. They found that the human cerebellum possesses a roughly homotopic map of the cerebral cortex and that most of the cerebellar cortex is connected to cerebral association networks. These cerebellar FC maps are reliable and robust; other rs-fMRI studies of cerebrocerebellar connectivity in healthy humans, using different techniques, have provided remarkably consistent cerebellar network topography (64,65).

In this study, we applied an approach approximating that of Buckner *et al.* (63) to psychotic BP. With the use of the 17-network cerebral cortical functional parcellation scheme of Yeo *et al.* (62) as the basis for our FC seeds, we systematically investigated the topographic representations of resting-state networks within the cerebellum in psychotic BP. We hypothesized that psychotic BP would show a pattern of reduced FC in higher-level association networks, particularly in limbic and/or salience networks, reflecting the mood dysregulation characteristic of the BP phenotype.

METHODS AND MATERIALS

Participants

We compared 49 BP patients with lifetime histories of psychosis and 55 healthy control (HC) participants. All participants provided written informed consent. Data for patients were drawn from an ongoing psychosis study approved by the McLean Hospital Institutional Review Board, a subset of which was previously described (66). Patients were men and women with psychotic illness, aged 18–65 years, recruited from inpatient and outpatient clinical services at McLean Hospital. Exclusion criteria included any current medical or neurological illness, pregnancy, electroconvulsive treatment in the previous 3 months, history of head trauma with a significant loss of consciousness, and contraindications to MRI. Within this patient database, we initially identified 71 BP patients with psychosis history. Of these, we excluded 22 for quality control reasons, 20 for low (<100) rs-fMRI signal-to-noise ratio (SNR = mean ± SD of the mean slice intensity time series) and 16 for rs-fMRI data containing >20 outlier volumes, calculated using the SPM-based Artifact Detection Tools (www.nitrc.org/projects/artifact_detect), with *z* threshold set to 3, movement threshold of 0.5, and rotation threshold of 0.05. Fourteen of the 22 excluded patients had both low SNR and high number of motion outliers. We evaluated whether there were any significant differences in clinical and demographic factors between the 22 excluded and 49 included BP patients.

HC participants were selected from an existing database of 2292 adults, aged 18–83 years, scanned previously using identical pulse sequences on an identical scanner, and selected to match patients on age, sex, handedness, and image SNR. HC participants were also screened for motion outliers, as detected by Artifact Detection Tools. For the final 49 BP patients and 55 HC participants included in the analysis, there were no statistically significant between-group differences in mean motion (BP patients: 0.25 ± 0.14 mm; HC participants: 0.26 ± 0.15 mm; $p = .93$).

The Structured Clinical Interview for the DSM-IV-TR was used for diagnosis (67). Patients were assessed for symptoms within 24 hours of scanning using the Young Mania Rating Scale (YMRS) (68), the Montgomery–Åsberg Depression Rating Scale (69), and the Positive and Negative Syndrome Scale (PANSS) (70). We calculated total medication load (TML) (71), a composite score of all psychotropic medications a patient was on at the time of scanning, in addition to chlorpromazine equivalent doses, because many patients were on multiple medications, including antidepressants and mood stabilizers in addition to antipsychotic drugs. All but two patients were taking at least one antipsychotic drug, and 42 of the 49 patients were taking lithium or other mood stabilizer.

Image Acquisition

Imaging was performed on a Siemens 3T Tim-Trio scanner (Siemens Medical Systems, Malvern, PA) with a 12-channel phased-array head coil. Functional data were acquired using gradient-echo echoplanar imaging sensitive to blood oxygenation level–dependent (BOLD) contrast. Participants were instructed to remain still, stay awake, and keep their eyes open. No fixation image was used, but patients were monitored via eye tracking video to ensure that eyes remained open during functional scans.

The echoplanar imaging variables were repetition time, 3000 ms; echo time, 30 ms; flip angle, 85°; 3 mm^3 voxels; field of view, 216; and 47 axial sections interleaved with no gap. Functional runs lasted 6.2 minutes (124 time points). Whole-brain coverage was achieved with sections aligned to the anterior commissure–posterior commissure plane using an automated alignment procedure, ensuring consistency among participants. Structural data included high-resolution, multi-echo, magnetization prepared rapid acquisition gradient-echo T1-weighted images allowing increased contrast through weighted averaging of four derived images.

Image Analysis

We used the FMRIB Software Library (FSL v5.0.6) (72) for image analysis, following methods previously published (61). We discarded the first four volumes of the resting BOLD image to account for magnet stabilization. Images were slice-time and motion corrected (73), smoothed with a 6-mm Gaussian kernel, and affine registered to Montreal Neurological Institute space. Images were low-pass filtered at 0.08 Hz (sigma = 2.09 volumes) to reduce high-frequency noise from cardiac and respiratory sources and high-pass filtered at 0.009 Hz (sigma = 18.5 volumes) to remove low-frequency scanner drift.

We identified 10 of 17 networks in the cortical parcellation map of Yeo *et al.* (62) containing >30 voxels in the corresponding cerebellar network parcellations of Buckner *et al.* (63) (Figure 1). We created a FC seed for each of these 10 networks by segmenting the 17-network image into 17 separate maps, combining networks 9 (temporal pole) and 10 (orbitofrontal cortex) into a single limbic network to maintain consistency with the naming scheme in Baker *et al.* (66), and eroding each network map by one voxel layer using a