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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 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 ten 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 cerebro-cerebellar 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 cerebro-cerebellar 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

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have value in guiding future studies on pathophysiology and treatment of mood and psychotic disorders, in particular.

Keywords

cerebellum; bipolar disorder; psychosis; functional connectivity; networks; resting state

Introduction

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 fMRI (rsfMRI) examines the functional connectivity (FC) of intrinsic brain networks. This technique is particularly well-suited to studying cerebro-cerebellar connectivity because communication between the cerebral cortex and cerebellum is indirect (4), with cerebral cortical signals relayed to pons before they arrive at cerebellum, and with cerebellar outputs projecting to thalamus before reaching cerebral cortex. While the polysynaptic nature of this circuitry has limited its study using traditional retrograde tracer techniques, rsfMRI, which can detect functional relationships across distributed brain areas, reveals connectivity patterns informed by, but not necessarily confined to, direct monosynaptic connections (4). RsfMRI allows investigations of cerebro-cerebellar 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 rsfMRI studies found resting-state abnormalities of 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, though 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 and colleagues analyzed rsfMRI data from 1000 healthy subjects, using a clustering strategy to parcellate cerebral cortex into intrinsic components on the basis of territories sharing similar FC profiles to other regions of cortex, and found that either 7 or 17 distinct networks provide relatively stable parcellation solutions (62). Using the same 1000 subject data set and cortical parcellation solutions as a reference, Buckner and colleagues subsequently developed a parcellation of human cerebellum, assigning every cerebellar voxel to its most strongly associated cortical network using a winner-take-all approach(63). They found that the human cerebellum possesses a roughly

homotopic map of the cerebral cortex and that the majority of the cerebellar cortex is connected to cerebral association networks. These cerebellar FC maps are reliable and robust; other rsfMRI studies of cerebro-cerebellar 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 and colleagues (63) to psychotic BP. Using the 17-network cerebral cortical functional parcellation scheme of Yeo and colleagues (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 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, ages 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 magnetic resonance imaging. Within this patient database, we initially identified 71 BP with psychosis history. Of these, we excluded 22 for quality control reasons: (a) 20 for low (<100) rsfMRI signal-to-noise ratio (SNR = mean/standard deviation of the mean slice intensity time series), and (b) 16 for rsfMRI data containing > 20 outlier volumes, calculated using the SPM-based Artifact Detection Tools (ART; www.nitrc.org/projects/artifact_detect), with z-threshold set to 3, movement threshold 0.5, and rotation threshold 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 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 were also screened for motion outliers, as detected by ART. For the final 49 BP and 55 HC included in the analysis, there were no statistically significant between-group differences in mean motion (in millimeters: BP 0.25 ± 0.14, HC 0.26 ± 0.15; $p = 0.93$).

The Structured Clinical Interview for the DSM-IV-TR (SCID) 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-Asberg Depression Rating Scale (MADRS) (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 antipsychotics. All but two patients were taking at least one antipsychotic, and 42 of the 49 patients were taking lithium or other mood stabilizer.

Image Acquisition

Imaging was performed on a Siemens 3-Tesla Tim-Trio scanner 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 parameters were repetition time, 3000 milliseconds; echo time, 30 milliseconds; flip angle, 85°; $3mm^3$ 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, multiecho, magnetization-prepared, gradient-echo (ME-MPRAGE) 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 (MNI) 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, 2011 (62) containing >30 voxels in the corresponding cerebellar network parcellations of Buckner et al., 2011 (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., 2014 (66), and eroding each network map by one voxel layer using a 3D kernel to avoid potential boundary contamination between networks.

For each participant, the mean BOLD time course was extracted for each of the 10 networks and entered into a general linear model (GLM) using FEAT (www.fmrib.ox.ac.uk/fsl/feat5). Sources of non-neuronal variance were removed by regressing out the six rigid-body motion correction parameters and signal from white matter, ventricles, and whole brain.

Data from first-level analysis were entered into a mixed-effects group analysis using the Bayesian estimation techniques in FLAME (74). As motion can lead to systematic biases in FC, even after regressing motion estimates at the subject level, we entered mean motion (mean absolute displacement of each brain volume compared to the previous volume) (73) as a covariate in between-group analyses (75). We generated group maps for BP and HC, and performed between-group contrasts for BP > HC and HC > BP. Given our goal to investigate between-group connectivity differences in the cerebellum, we restricted our analysis to the cerebellum using the Cerebellar Atlas in FSL as a mask. We used a stringent $p < 0.0005$ voxel threshold, corrected for multiple comparisons using a $p < 0.0025$ cluster threshold. These significance criteria reflect Bonferroni adjustment of both voxel and cluster thresholds by a factor of 20 (i.e., voxel $p < 0.01/20$, cluster $p < 0.05/20$) to account for conducting two one-sided tests (i.e., BP > HC, HC > BP) in 10 different networks.

To quantitatively assess overlap between the group cerebellar maps (BP, HC) and canonical cerebellar maps (63), we calculated accuracy:

$$\text{Accuracy} = \frac{(\text{True positive voxels} + \text{true negative voxels})}{(\text{Positive voxels} + \text{negative voxels})}$$

We identified *positive* voxels as those within the canonical cerebellar map (63). *True positive* voxels were those that intersected between the group map. *Negative voxels* were those voxels within cerebellum, but outside the canonical cerebellar map. *True negative* voxels were calculated as the negative voxels minus false positive voxels, or those voxels in the group cerebellar map falling outside the canonical cerebellar map. We also calculated sensitivity (true positive voxels/positive voxels) and specificity (true negative voxels/negative voxels). See Supplementary Tables S2A–C.

All BP patients were taking psychotropic medications at the time of scanning, and substance use was not a patient exclusion criterion. To examine whether effects of medications, alcohol, and/or cannabis use could be driving between-group differences, we performed post-hoc analyses of only the 49 BP patients, including TML, lifetime alcohol dependence, and lifetime cannabis dependence along with mean motion as covariates in the model. For each network in which we found significant between-group differences, we used the image of the HC > BP finding as a mask, and calculated the percent of voxels in the HC > BP map not overlapping with the map showing the main effect of each potentially confounding variable in the BP-only analysis. Since the between-group findings were significant only for BP *hypo*connectivity (i.e., HC > BP), we looked at the -1 effect of TML, lifetime alcohol dependence, and lifetime cannabis dependence. To more fully examine effects of these potentially confounding variables with minimal risk of Type II error, we used a liberal significance threshold of $p < 0.05$, uncorrected.

Correlation with Symptoms

For BP patients, we extracted, at the single subject level, the BOLD time course of the clusters we found to be significantly different between BP and HC. For networks with more than one significant cluster (i.e., N8, N12), we obtained an average of the clusters combined.

We correlated the averaged time course for the network cluster with that of the corresponding cortical network seed to obtain a quantitative measure of FC for each patient. These Pearson's R-values were z-transformed, and then correlated with the YMRS, MADRS, and PANSS (total score, as well as the positive, negative, and general subscores) for a matrix of six symptom scales and five network contrasts. We used a significance threshold of $p < 0.0016$ ($p < 0.05$ Bonferroni-corrected for 30 tests).

In exploratory analyses, we also examined correlations between the FC finding for the somatomotor B network (N4) and YMRS item 2 ("increased motor activity/energy"); the FC finding for the ventral attention network (N7) and YMRS item 7 ("language/thought disorder," which includes distractibility); and the FC finding for N7 with PANSS item G11 ("poor attention").

Results

Participant Characteristics

Tables 1 and 2 provide clinical and demographic information. The psychotic BP and HC groups were comparable with respect to age and sex.

The 22 excluded patients were comparable to the final group of 49 BP patients with respect to age, sex, duration of illness, medication exposure, and measures of depression and mania (Supplementary Table S1). Since SNR and motion outliers served as bases for exclusion, excluded patients had significantly lower SNR and higher number of motion outliers compared to the final group of BP patients. The group of excluded patients also had greater psychosis severity [as measured by higher PANSS total (Supplementary Figure S1), negative, and general psychopathology scores] and a higher proportion of inpatients at the time of scanning (Supplementary Table S1). Neither of these differences is surprising, as more acutely ill patients are less likely to tolerate the scan environment and more likely to have head motion during scanning.

Within-Group Maps

The HC group maps captured the canonical cerebellar maps of Buckner and colleagues (63) with 76.9% mean accuracy (range 63.8–89.5%) (Figure 2 and Supplementary Table S2A). Thus, we have a high degree of confidence that the methods detected regions in cerebellum that are functionally coherent with their originating cerebral cortical seeds. Mean specificity was 77.1% (range 63.5–89.6%), and mean sensitivity 64.0% (range 14.7–93.8%). Sensitivity in the dorsal attention network was particularly low (14.7%), and results relating to this network should be interpreted with caution.

The BP group maps captured the canonical cerebellar maps with 88.4% mean accuracy (range 80.7–96.7%) (Figure 2 and Supplementary Table S2B). Mean specificity was 89.1% (range 80.7–96.9%). Mean sensitivity was 47.5% (range 12.6–87.5%).

Between-Group Contrasts

Healthy Control > Psychotic BP—As shown in Figure 3 and Table 3, psychotic BP had reduced cerebro-cerebellar FC in somatomotor B (N4), ventral attention (N7), salience (N8),

control A (N12), and control B (N13) networks. Cerebellar regions of greatest difference between BP and HC were in left Crus I for the somatomotor B network, right Crus I in the ventral attention network, left lobule IX and left Crus II in the salience network, right Crus I and left lobule X in the control A network, and right lobule X in the control B network.

Post-hoc analyses showed that medications (i.e., TML) may have contributed to the findings in N8 and N12 but could not explain 97% of the between-group differences in N8 and 92% in N12. Lifetime alcohol dependence may have contributed to the between-group findings in all five significantly different networks, but could not explain 93% of the between-group differences in N8, 86% in N13, 75% in N12, 72% in N4, and 71% in N7. There appeared to be no effect of lifetime cannabis dependence on any between-group findings.

Psychotic BP > Healthy Control—We found no networks in which psychotic BP had increased cerebro-cerebellar FC relative to HC.

Correlation with Symptoms

We found no statistically significant correlations between FC of any of the five networks for which we found significant between-group differences and clinical scale scores (Supplementary Table S3A). We also found no correlation between somatomotor B FC and the YMRS item “increased motor activity/energy,” and no correlations between ventral attention FC with either the YMRS item “language/thought disorder” or the PANSS general item “poor attention” (Supplementary Table S3B).

Discussion

Using ten well-defined cerebral cortical networks as functional connectivity (FC) seeds, we investigated abnormalities of cerebro-cerebellar circuitry in psychotic BP, and found evidence of alterations in selective networks. Specifically, we found reduced cerebro-cerebellar FC in somatomotor B, ventral attention, salience, control A, and control B networks in psychotic BP relative to HC. Of interest, no networks showed increased cerebro-cerebellar FC in psychotic BP compared to HC.

Disrupted cerebro-cerebellar FC in ventral attention, salience, and frontoparietal control networks are consistent with abnormalities in cognitive processing in psychotic BP. The ventral attention network, with nodes in parietal operculum, medial parietal, medial frontal, precentral ventral frontal, precentral frontal, insula, and temporal brain areas (66), detects salient or behaviorally relevant stimuli in the environment that are outside the current focus of attention (76). The ventral attention network interacts dynamically with the dorsal attention network, which, in contrast, enables the selection of stimuli based on internal goals or expectations (76). Focusing attention produces sustained activation of the dorsal attention network and sustained deactivation of the ventral attention network, while reorienting attention to an unexpected but salient event produces transient activation of both dorsal and ventral attention networks (76). BP is characterized by deficits in sustained attention (77, 78), and these deficits are present during remission (79), as well as during acute mania (80, 81). Cerebro-cerebellar hypoconnectivity in the ventral attention network may reflect

reduced cerebellar integration and modulation of cognitive functions required for sustained attention.

The salience network in the 17-network parcellation scheme of Yeo and colleagues (62)– consisting of cingulate sulcus, ventral prefrontal cortex (PFC)/anterior insula, lateral PFC, medial posterior PFC, and a lateral parietal area– is distributed adjacent to the brain areas of the ventral attention network, and carries out closely related functions. The salience network detects potentially important stimuli, and by integrating external stimuli with homeostatic signals from the body, it marks objects for further processing by the brain's attentional and working memory systems (82, 83). The salience network is proposed to facilitate access to these attentional and working memory systems by dynamically switching from engagement of the internally oriented default mode network (DMN) to the task-oriented central executive (i.e., frontoparietal control) network (82). Psychosis is believed to reflect a state of aberrant salience (84), in part, and structural abnormalities in the salience network have been linked to reality distortion in the form of hallucinations (85, 86) and delusions (85). A previous study reported reduced FC between cerebellar and salience networks in schizophrenia, but not in BP (56); however, the BP sample consisted of clinically stable outpatients, and it is unclear what proportion of those BP patients had histories of psychosis. Our observation of reduced cerebro-cerebellar salience network FC in psychotic BP patients could possibly reflect misattribution of salience to otherwise irrelevant external and/or internal stimuli due to a dysfunctional switching mechanism. We did not examine dynamic interactions between networks, but this could be investigated in future studies.

The frontoparietal control network was also disrupted in psychotic BP. This network consists of portions of dorsolateral prefrontal, dorsomedial prefrontal, cingulate, orbitofrontal, precuneus, inferior parietal, and temporal cortical brain areas. Not unlike the dynamic models featuring the ventral attention and salience networks described above, a model proposes that the frontoparietal network flexibly modulates DMN and dorsal attention networks, and depending on the network to which it is coupled, the frontoparietal network dynamically facilitates both internally and externally oriented goal-directed planning (87). Accordingly, dysfunction in the frontoparietal network leads to aberrant mediation between internal and external cognitive processes, as occurs in psychotic disorders, in which individuals misattribute control of their own thoughts to external sources, misinterpret behaviors and intents of others, and experience false perceptions. Our group previously found the frontoparietal control network to be disrupted, with extensive network hypoconnectivity, in patients with psychosis (66). Dysconnectivity within cerebral cortical regions of the frontoparietal control network in psychosis appears to be mirrored within cerebellum not only in SZ, as we previously reported (61), but also, as seen here, in BP with psychotic features.

Finally, our finding of reduced somatomotor FC suggests that dysfunction in psychotic BP is not isolated to higher-order cognitive domains; it also extends to networks lower in the processing hierarchy. Though neurological soft signs are most frequently associated with schizophrenia, NSS are also common in BP (88, 89). We do not have behavioral data about NSS in our sample to determine whether our observation of abnormal somatomotor cerebro-cerebellar FC is associated with NSS, and this may be a valuable subject for future studies.

The cerebellum has a modular, lattice-like organization consisting of repeating cerebro-ponto-cerebello-thalamo-cerebral loops (60). While multiple different cerebral cortical networks are topographically represented within cerebellum, the highly stereotyped circuit arrays that make up the architecture of cerebellar cortex suggests that cerebellum may perform common computational functions for diverse tasks (60, 90). The cerebellum has been proposed to act as a forward controller, using corollary discharges to predict sensory consequences of motor and other commands (60). According to Schmahmann, the cerebellum "regulates the rate, force, rhythm, and accuracy of movements" and also of other mental processes, and lesions to cerebellum cause problems of timing and adjustment (91). Similarly, Andreasen's "cognitive dysmetria" model (92, 93) proposes that the myriad symptoms of schizophrenia result from a unitary pathophysiology, namely incoordination of mental activity, due in part to misconnections in cerebro-cerebellar circuitry. Thus, cerebro-cerebellar hypoconnectivity in specific brain networks may underlie abnormal timing, integration, coordination, and signal processing observed as the cognitive, emotional, and behavioral symptoms of BP and other mood and psychotic disorders.

BP, especially psychotic BP, has many clinical (94, 95), genetic (96–101), and neuroimaging features (102–104) in common with schizophrenia such that these disorders appear to be overlapping syndromes rather than biologically discrete diseases (105). Using analogous methods, our group previously showed schizophrenia to have aberrant cerebro-cerebellar FC in many of the same networks found in the current study to be disrupted in psychotic BP, i.e., somatomotor, ventral attention, salience, and control networks (61). Schizophrenia was also characterized by DMN abnormalities, which we did not observe here in psychotic BP. The current study differed from our schizophrenia study with respect to both participant recruitment and imaging parameters; thus firm conclusions about cerebellar FC similarities and differences in these two disorders cannot be drawn from these two studies. We plan to pursue head-to-head comparisons in future studies.

The findings from this study should be considered in light of several limitations. First, data were not acquired for the purposes of this analysis, and though the patients were well-characterized with regard to depression, mania, and psychosis, they lacked measures of cognitive and motor (e.g., NSS) functioning. Second, alcohol (106) and cannabis (107–109) can have detrimental effects on cerebellum, and substance use was not an exclusion criterion for patients. However, we assessed the potential contribution of alcohol and cannabis dependence by examining their effects on cerebro-cerebellar FC among BP patients, and found that while FC differences associated with alcohol dependence may have contributed to diagnostic differences, these differences cannot explain the totality of our findings. Third, though we assessed potential contributions of medication effects using a composite score accounting for all current psychotropic medications, patients were on many different treatment regimens, with different mechanisms of action, and we cannot confidently separate disease-related and medication-related effects. Fourth, by excluding patients with lower quality image data, we necessarily excluded more severely symptomatic patients, almost all of whom were inpatients at the time of scanning. This reflects the challenges of acquiring high quality data in acutely ill BP psychosis patients, and may limit the ability to generalize our findings to sicker patients. Notably, however, though PANSS scores for the excluded and included groups were statistically significantly different, the overall effect size was modest,

as the total PANSS score in both the final and excluded BP groups were in the mild range for schizophrenia (110). Fifth, we focused our analyses on BP and HC group differences in cerebro-cerebellar FC. However, large-scale FC networks appear to interact with one another in dynamic ways, and future studies should investigate between-network relationships within cerebellum.

In spite of limitations, the findings from the current study may have value in guiding future studies on pathophysiology and treatment of BP and related disorders. The discovery of specific functional abnormalities in cerebellum suggests that the cerebellum might be a target for treatment intervention. Standard medications may already affect cerebellar activity, but currently employed electromagnetic therapies, such as ECT and transcranial magnetic stimulation (TMS), as well as still experimental direct and alternating current stimulations, TDCS and TACS, have all been applied to cerebrum, but rarely to cerebellum. No single cause or mechanism explains psychosis, but cerebellar mechanisms deserve further characterization in patients with mood and psychotic disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Network Yeo et al., 2011 (62)	Network name Baker et al., 2014 (66)	Cerebral cortical regions Yeo et al., 2011 (62); Baker et al., 2014 (66)	No. of voxels in eroded cerebral cortical seed	Cerebellar representation Buckner et al., 2011 (63)	
				Anat-omical regions	No. of voxels
N1	Visual peripheral	Striate, extrastriate	-	N/A	0
N2	Visual central	Striate, extrastriate	-	Vermis VI	14
N3	Somato-motor A	Central sulcus, secondary somatosensory	178	I-V, VIIb	489
N4	Somato-motor B	Central sulcus, secondary somatosensory, insula, auditory	356	V	241
N5	Dorsal attention A	Posterior temporal occipital, superior parietal, inferior parietal occipital	-	N/A	0
N6	Dorsal attention B	Posterior temporal, postcentral gyrus, frontal eye fields, precentral ventral frontal	67	VIIb-VIIIa	238
N7	Ventral attention	Parietal operculum, medial parietal, medial frontal, precentral ventral frontal, insula, temporal, precentral frontal, posterior temporal	117	VI, VIIIa	750
N8	Salience	Medial posterior prefrontal, ventral prefrontal, cingulate sulcus, inferior parietal, lateral prefrontal	193	VI, Crus I-II, VIIb	439
N9-10	Limbic	Temporal pole, orbitofrontal	492	White matter	1024
N11	Control C	Precuneus, posterior cingulate	-	Crus I	9
N12	Control A	Intraparietal sulcus, lateral prefrontal, posterior temporal, dorsal prefrontal, cingulate, orbitofrontal, medial posterior prefrontal, lateral posterior prefrontal	110	VI, VIIb	426
N13	Control B	Lateral posterior prefrontal, lateral anterior prefrontal, inferior parietal, temporal, medial posterior prefrontal	258	Crus I, VIIb	1154
N14	Default D (Auditory)	Temporal cortex	-	N/A	0
N15	Default C	Retrosplenial, parahippocampal complex, ventral inferior parietal	-	X	30
N16	Default A	Medial prefrontal, posterior inferior parietal, posterior cingulate, dorsal prefrontal, orbitofrontal, temporal	472	IX, Vermis IX, Crus I, Crus II	799
N17	Default B	Dorsal prefrontal, temporal, anterior inferior parietal	236	Crus I-II	1387

Figure 1. The cerebral cortex network seeds and their cerebellar representations

The figures of the left and right 17-network parcellation of the human cerebral cortex are adapted with permission from Yeo et al., 2011 (62), page 1139, figure 13. The network names and the cerebral cortical regions that compose the 17 networks are from the supplementary video in Baker et al., 2013 (66). The number of voxels in each of the eroded cerebral cortical seeds was determined after the 17-network cortical parcellation (publicly available at http://www.freesurfer.net/fswiki/CorticalParcellation_Yeo2011) was resampled from 1mm to 2mm space, segmented into individual network maps, and eroded (see methods). The number of voxels within each of the Buckner et al., 2011 cerebellar network maps (63) was determined after the 17-network loose estimate of the cerebellum (publicly available at http://www.freesurfer.net/fswiki/CerebellumParcellation_Buckner2011) was resampled from 1mm to 2mm MNI space and segmented into individual network maps. This figure was originally published in Shinn et al., 2015 (61).

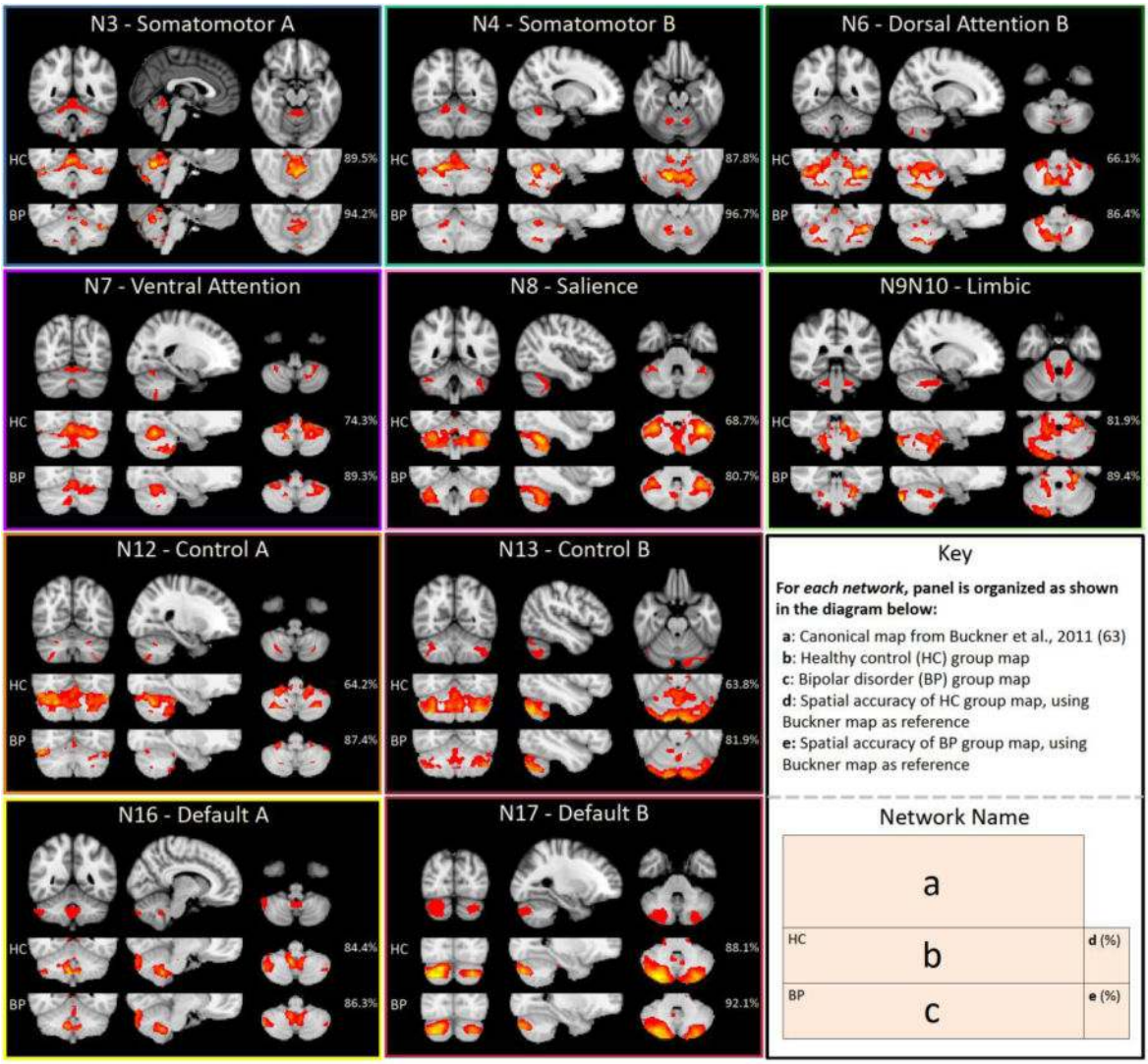

Figure 2. The within-group maps capture the canonical cerebellar maps with 64–97% accuracy

The canonical cerebellar maps (depicted in the uppermost rows) are from Buckner et al., 2011 (63), in which data from 1,000 healthy individuals were used to map every voxel within the cerebellum to its most strongly associated cerebral cortical network (62) using a winner-take-all approach. The percentage to the right of each healthy control (HC) or bipolar disorder (BP) group map is the estimation of the map's spatial accuracy (=true positive voxels + true negative voxels)/(positive voxels + negative voxels), using the canonical (63) map as the reference. The HC and BP group maps were liberally thresholded at a significance level of $p < 0.05$, uncorrected. The boxes around each of the networks are highlighted to match the color coding of the networks in Figure 1.

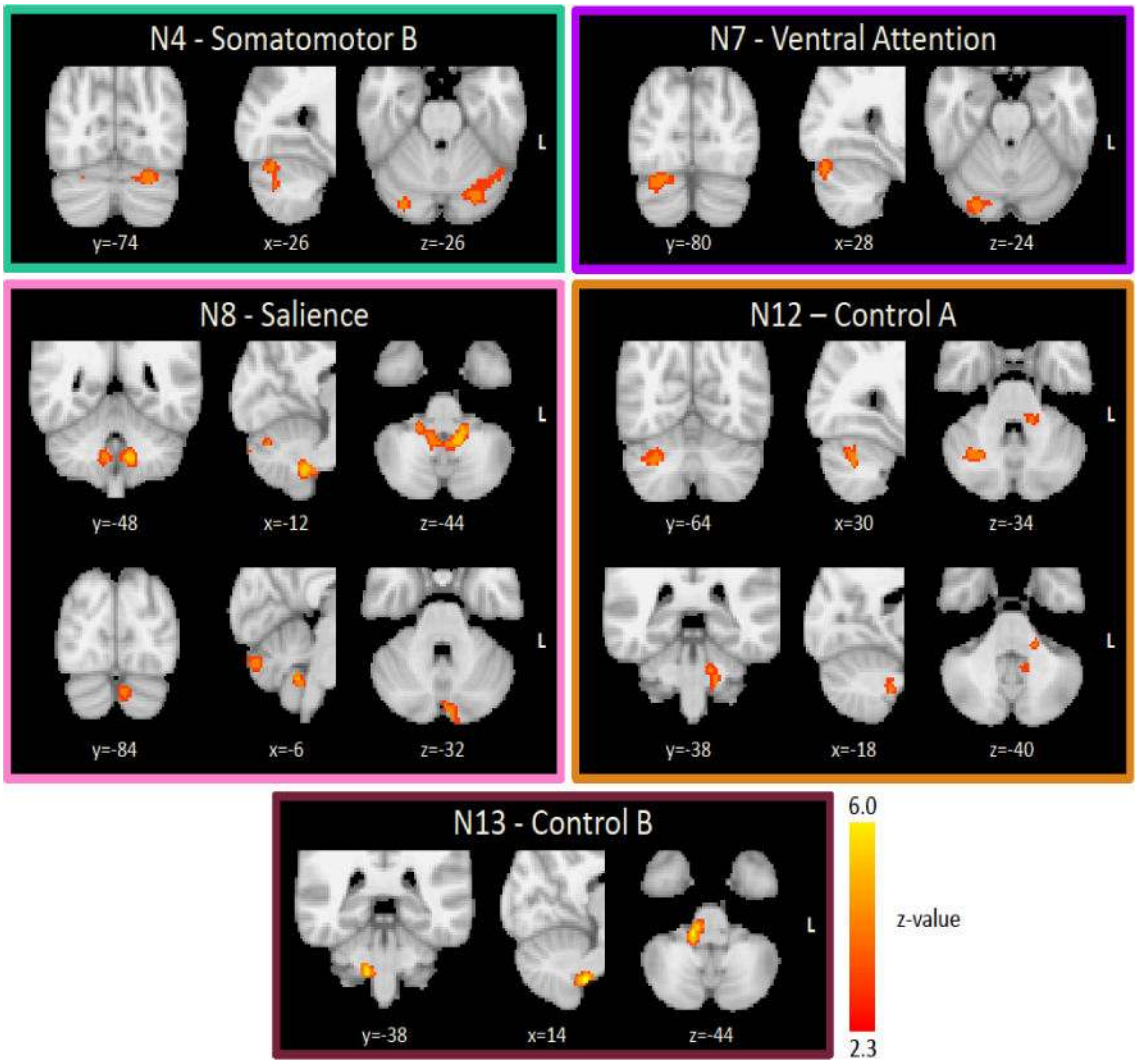

Figure 3. Decreased cerebro-cerebellar functional connectivity in somatomotor and higher-level association networks in psychotic bipolar disorder

Regions in the posterior lobe of the cerebellum, especially Crus I/II, are preferentially affected in the somatomotor B, ventral attention, salience, and control A networks. Images were generated using a $p<0.0005$ voxel threshold, corrected for multiple comparisons using a $p<0.0025$ cluster threshold. The boxes associated with each network finding are highlighted to match the color coding of the networks in Figure 1.

Table 1

Participant characteristics

	BP	HC	Statistic	Significance
Sample size (N=104)	49	55		
Age, mean ± SD (range), y	31 ± 12 (18–62)	30 ± 11 (18–56)	t = 0.4993	$p = 0.619$
Female sex, no. (%)	15 (31)	17 (31)	$X^2 = 0.001$	$p = 0.974$

Table 2

Additional characteristics of BP patients.

	BP
Illness duration, mean ± SD (range), y[a]	9 ± 10 (0–42)
Inpatient hospitalized, no. (%)	33 (67)
YMRS, mean ± SD	20.2 ± 11.8
MADRS, mean ± SD	15.6 ± 10.0
PANSS, mean ± SD	55.7 ± 13.7
PANSS positive, mean ± SD	18.7 ± 7.4
PANSS negative, mean ± SD	9.4 ± 2.8
PANSS general, mean ± SD	28.6 ± 7.2
Chlorpromazine Equivalent	364 ± 301 mg
Antipsychotic-free, no. (%)	2 (4)
Typical Antipsychotic, no. (%)[b]	3 (6)
Atypical Antipsychotic, no. (%)	
Aripiprazole	6 (12)
Clozapine	3 (6)
Lurasidone	3 (6)
Olanzapine	11 (22)
Quetiapine	12 (24)
Risperidone	15 (31)
Ziprasidone	3 (6)
Mood stabilizer, no. (%)	42 (86)
Lithium	30 (61)
Lamotrigine	12 (24)
Valproate	6 (12)
Oxcarbazepine	5 (10)
Gabapentin	3 (6)
Antidepressant, no. (%)	5 (10)
Sedative-hypnotic, no. (%)	14 (29)

[a] Data missing for 3 patients

[b] chlorpromazine: $n = 2$; perphenazine $n = 1$.

TABLE 3

Differences between bipolar disorder with psychosis and healthy controls in cerebro-cerebellar network connectivity.

Group Contrast	Network	Cerebral cortex network seed	Cluster size (voxels)	Hemisphere	Anatomical region in cerebellum	Z-values(†Z-max forentire cluster	Coordinates of local maxima		
							X(mm)	Y(mm)	Z(mm)
HC > BP	N4	Somatomotor B	336	L	Crus I	†4.28	−26	−74	−26
					Crus II	3.95	−24	−70	−38
					VI	3.48	−14	−74	−24
	N7	Ventral Attention	212	R	Crus I	†4.43	28	−80	−24
	N8	Salience	445	L	IX	†5.15	−12	−48	−44
				R	X	4.39	18	−40	−46
					IX	4.31	8	−50	−42
			150	L	Crus II	†4.15	−6	−84	−32
					Crus I	3.89	−12	−76	−28
	N12	Control A	172	R	Crus I	†4.34	30	−64	−34
					VI	4.29	34	−60	−28
			144	L	White matter	†4.21	−18	−38	−40
					X	3.84	−14	−42	−44
					IX	3.71	−10	−54	−38
	N13	Control B	163	R	X	†5.57	14	−38	−44

Controlling for mean absolute displacement.