Disrupted Modular Architecture of Cerebellum in Schizophrenia: A Graph Theoretic Analysis

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Recent studies of schizophrenia have revealed cognitive and memory deficits that are accompanied by disruptions of neuronal connectivity in cortical and subcortical brain regions. More recently, alterations of topological organization of structural networks in schizophrenia are also being identified using graph theoretical analysis. However, the role of the cerebellum in this network structure remains largely unknown. In this study, global network measures obtained from diffusion tensor imaging were computed in the cerebella of 25 patients with schizophrenia and 36 healthy volunteers. While cerebellar global network characteristics were slightly altered in schizophrenia patients compared with healthy controls, the patients showed a retained small-world network organization. The modular architecture, however, was changed mainly in crus II. Furthermore, schizophrenia patients had reduced correlations between modularity and microstructural integrity, as measured by fractional anisotropy (FA) in lobules I–IV and X. Finally, FA alterations were significantly correlated with the Positive and Negative Syndrome Scale symptom scores in schizophrenia patients. Taken together, our data suggest that schizophrenia patients have altered network architecture in the cerebellum with reduced local microstructural connectivity and that cerebellar structural abnormalities are associated symptoms of the disorder.

Key words: cerebellum/diffusion tensor imaging/schizophrenia/structural connectivity/structural network/modular architecture

Introduction

The cerebellum is known to play an important role in the coordination of movement.1 A number of motor behaviors are strongly dependent on the cerebellum including maintenance of balance,2-4 voluntary eye movements,5 and motor learning.6-9 During recent years, however, a growing number of studies have also indicated that the cerebellum contributes to higher cognitive functions,10-11 including language,12,13 and memory.14-16 With the advent of trans-synaptic tracing techniques, it has been demonstrated that the cerebellum is highly interconnected with the cerebral cortex via subcortex, ie, cortico-cerebellar-thalamic-cortical circuits.17,18 According to this circuitry, the cerebellum forms a distinct internal module that plays a prominent role in the whole brain functional network linked with anatomical connections.19-21 Studies have shown evidence of cerebellar involvement in a number of diseases associated with both motor deficits and cognitive dysfunction. First, the cerebellum plays an important role in a number of movement disorders such as dystonia,22 ataxia,23,24 tremor,25,26 and Parkinson’s disease.27 Also, a number of studies have revealed cerebellar abnormalities in neuropsychiatric disorders such as autism, major depressive disorder, bipolar disorder, and anxiety disorders (for a review, see Hoppenbrouwers et al28). In addition, Diamond29 showed that cerebellar injury causes a similar developmental effect as injury to the dorsolateral prefrontal cortex. These previous findings have consistently suggested a closed functional and anatomical loop between the cerebellum and cerebral cortex in the whole brain network. In schizophrenia, a neuropsychiatric disorder characterized by various cognitive deficits and the motor impairments, cerebellar abnormalities have been reported and may underlie symptoms of the disorder.30,31 Recent neuroimaging studies have shown morphologically decreased vermal volume in schizophrenia patients.32-34 Furthermore, studies using proton magnetic resonance spectroscopic imaging have revealed reduced N-acetylaspartic acid in cerebellar cortex and vermis.35-37 Behavioral evidence from
cerebellar-dependent tasks including eyeblink conditioning, finger tapping, and postural sway also indicates that individuals with schizophrenia show impaired performance. Additionally, diffusion tensor imaging (DTI) studies have revealed reduced white matter integrity in the cerebellar peduncles. However, it still remains unclear whether the structural organization of the whole cerebellar network circuit is affected in schizophrenia.

Recently, functional and structural brain studies of network architecture (for a review, see Bullmore and Sporns) have indicated that individuals with schizophrenia have less optimal structural brain networks, a significantly reduced rich club organization suggesting a lower level of connectivity among brain hubs, impaired task and resting-state functional network characteristics, and a disrupted modular architecture. However, these studies have focused on cortical cerebral regions and excluded cerebellar regions. This is because it is difficult with current fiber extraction algorithms to disentangle unique axonal pathways based on their origin in the cerebellum (see supplementary figure 1). Nonetheless, this does not preclude the examination of within-cerebellum network structure. Network analyses have revealed that the human brain is organized in a hierarchically modular manner, suggesting that brain structure and function can be modularized within segregated submodules.

Accordingly, the cerebellum was considered here as a distinct subnetwork—one which is well-known to communicate with neuronal networks of the cerebral cortex. Studies of intracerebellum connectivity and communication are rare, owing to the predominance of fiber tracks connecting the cerebellum to the cerebrum through the cerebellar peduncles and the comparatively small number of known intracerebellar fiber tracts. However, the present work is in line with several previous studies investigating intracerebellar connections using fiber tractography.

In this study, we hypothesized that schizophrenia patients would show disturbed cerebellar structural network topology, supporting evidence of previous structural network studies on the cortical level and underlying cerebellar abnormalities in schizophrenia. We also hypothesized that the schizophrenia patients would show abnormal microstructural integrity in the cerebellum and that these abnormalities would be associated with measures of cerebellar network topology and neuropsychiatric symptom scores. To our knowledge, this is the first study to investigate cerebellar brain organization and topology in schizophrenia.

Materials and Methods

Subjects

Twenty-five individuals with schizophrenia (SZ; mean age = 31.8 ± 10.7 years, male:female = 17:8) and 36 healthy control subjects (NC; mean age = 28.5 ± 9.5 years, male:female = 18:18) were evaluated, and their demographic data are presented in the supplementary table 1. All participants were between 18 and 55 years of age and had completed at least grade-school level education. Patients were recruited through physician referrals from clinics affiliated with the Indiana University School of Medicine in Indianapolis, Indiana, United States. Control participants were recruited using flyers and advertisements. Exclusion criteria for all participants included serious head injury (with loss of consciousness >5min), a history of neurological disorders, alcohol or substance dependence in the previous 3 months, and intoxication (via urine screen) at the time of testing. The clinical ratings for symptoms of schizophrenia were measured using the Positive and Negative Syndrome Scale (PANSS) for severity of psychopathology, which was administered by psychologists at the PhD level or by experienced research assistants closely supervised by them. Diagnostic status for the schizophrenic group was determined using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders-IV Axis I Disorders, Patient Version (SCID-I/P) sections for mood disorders, psychotic disorders, and substance abuse disorders, as well as chart review. Kappa interrater reliability in our lab has been >0.95 for schizophrenia vs mood disorders, or other diagnoses in patients who have been prescreened for psychosis. Control participants were interviewed using the nonpatient version of SCID-I sections for mood disorders, psychotic disorders, and substance abuse and the SCID-II personality questionnaire to exclude psychiatric disorders, including a history of current substance abuse or dependence, a diagnosis of any current or past Axis I psychiatric illness, or first-degree relatives with schizophrenia. After providing a complete description of the study to all participants, written and verbal informed consents were obtained. The research protocol was approved by the Indiana University–Purdue University Indianapolis Human Subjects Review Committee.

Data Acquisition and Processing

Whole brain T1-anatomical and diffusion tensor magnetic resonance imaging (MRI) scans (40 weighted directions) were acquired on a 3T MRI system (Magnetom TrioTim, Siemens). Preprocessing of magnetic resonance images was carried out using FMRIB (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/). The cerebellar regions of T1-weighted images were spatially normalized into the Montreal Neurological Institute space using the probabilistic spatially unbiased infratentorial template cerebellar atlas, which has 28 spatially unbiased cerebellar lobules, see supplementary table 2. Whole brain fiber tractography by Fiber Assignment by Continuous Tracking algorithm was performed in the native DTI volume using the Diffusion Toolkit (http://trackvis.org), and fractional anisotropy (FA), a measure of the directional coherence for white matter tracts, was calculated for each lobule for each participant. Details can be found in the supplementary material.
Structural Connectivity and Network Analysis

The structural connectivity between 2 cerebellar lobules was defined as a weight reflecting the product of the number of tractography streamlines and the corresponding FA. For each subject, a full $28 \times 28$ connectivity matrix was created and then graph theoretical analysis was used to quantify structural cerebellar network properties. Clustering coefficient ($\gamma$), characteristic path length ($\lambda$), small-worldness ($\omega$), and global/local efficiency were computed as measures representing topological network characteristics using the Brain Connectivity Toolbox (https://sites.google.com/site/bctnet/). The clustering coefficient represents the extent to which the network can be segregated and was defined by a fraction of the neighboring nodes also being nodes of each other. Characteristic path length was computed as the averaged shortest path length between all pairs of nodes, which reflects the structural integration of the cerebellar network. These 2 metrics were normalized by comparison with a population of 1000 randomized networks to provide null distributions of each metric. The network’s small-worldness (the extent to which the network is highly clustered with short path lengths) was computed as the ratio of the normalized clustering coefficient and the normalized path length. In addition, we computed a modularity measure ($Q$: see next section) of the structural cerebellar network as a statistic that quantifies the degree to which the network is subdivided into clearly delineated subgroups. All mathematical details can be found in previous studies. As noted in van Wijk et al, the proportion of the total connections can be varied to investigate the network properties by varying a threshold (ie, removing the weaker connections based on their weighting). In this study, we constructed networks over a range from 5% (sparse matrix including only strong connections) to 50% (dense matrix including weak connections) of connection density.

Modular Architecture in Cerebellum

A module in the network can be defined as a subdivision that has more connections within the module than outside the module. It quantifies the degree to which the network can be optimally partitioned into distinct subcommunities. There are a number of approaches to constitute the modular decomposition in a network. We adopted Newman’s method as a measure of modularity ($Q$). Once the maximum modular partition was computed in the network, the corresponding optimal community structure was also identified using a method described by Rubinov and Sporns. Then, the likelihood of being identified as a specific module was computed for each cerebellar region. Modular architecture of the cerebellum was defined by winner-take-all representations by labeling each cerebellar region with the highest likelihood.

Statistical Analysis

The independent 2-sample $t$ test was employed to investigate whether schizophrenia patients and healthy controls showed significant differences in lobular FA values. For the cerebellar network measures, the permutation test with 10 000-times random permutations for each group was performed as in previous network studies. In addition, the relationship between FA, network measures, and PANSS scores for the schizophrenia group was computed by using partial correlation coefficients ($r$) controlling age and gender as possible confounding variables. A significance level of $P < .05$ was used with a correction for false discovery rate (FDR).

Results

No Cerebellum-wide Differences in Structural Connectivity

There was a nonsignificant difference for the sum of all fiber tracts in cerebellum (SZ: $9783 \pm 2614$, NC: $11123 \pm 3508$, $P = .993$, $d = 0.22$), the mean FA value of the connected tracts between regions (SZ: $0.218 \pm 0.021$, NC: $0.223 \pm 0.021$, $P = .318$, $d = 0.13$), and the defined connectivity ($w$; SZ: $13.423 \pm 3.584$, NC: $14.788 \pm 4.728$, $P = .205$, $d = 0.16$). Higher modularity represents more segregation of nodes.

Lobular FA Characteristics of Schizophrenia

Cerebellar tissue integrity, as measured by FA, was significantly decreased in lobule I–IV (left: $t_{(59)} = 2.995$, $P = .004$, $d = 0.40$; right: $t_{(59)} = 2.720$, $P = .008$, $d = 0.36$) and lobule V (left: $t_{(59)} = 3.249$, $P = .002$, $d = 0.43$) in the schizophrenia group (figure 1. All lobular FA values are displayed in the supplementary figure 2). Additionally, group differences were nonsignificant for the total (supplementary figure 3) and lobular (supplementary figure 4) volumes of cerebellum.

Intact Small-World Properties in Cerebellum

Both schizophrenia and control participants exhibited a small-world network property of structural cerebellar architecture (ie, as indicated by clustering coefficients $\gamma > 1$, characteristic path length $\lambda \approx 1$, and small-worldness $\omega > 1$; see figure 2). Meanwhile, there was some evidence of longer characteristic path length (across connection densities 5%–25%; figure 2) and decreased small-worldness (across densities 15%–35%) in schizophrenia. But the main effects of characteristic path length and small-worldness were not significant.

Modular Architecture

Higher modularity represents more segregation of nodes into distinct subnetworks. Cerebellar networks of patients and healthy controls were consistently modular over the whole range of connection densities (figure 2).
The modularity quotient $Q$ monotonically decreased as a function of increasing connection density, suggesting the modules would be more distinct for the sparse but strong connections in the networks, supporting a previous finding in functional networks. While the patients’ and healthy controls’ structural networks were both comprised of 5 distinct cerebellar modules, the modular architecture differed between the groups (figure 3 and supplemental supplementary figure 5). In the healthy controls, module 1 and module 2 consisted of lobules I–IV, V, VI, and crus I/II for each hemisphere, where vermis VI and crus II were included in module 1. Modules 1 and 2 mostly covered the anterior and superior part of the cerebellum. Modules 3 and 4 included lobule VIIb, VIIIa, VIIIb, IX, and X in left and right inferior side, respectively. The vermis VIIb, VIIIa, VIIIb, IX, and X were classified as module 5. All modules of healthy controls were symmetrically segregated (except for vermis VI and VIIb in module 1). The modular structure of schizophrenia patients had the left lobule I–IV, V, VI, and crus I as module 1. Crus II was designated as a distinct module with vermis crus II, and the vermis (module 5 in healthy controls) was merged into module 3, suggesting disrupted modular cerebellar organization in patients, while module 4 was the same in both groups.

**Correlation Analysis**

We examined the relationship between microstructural integrity and cerebellar network properties in schizophrenia. The results showed that the FA values in lobule I–IV and X were positively correlated with the modularity quotient $Q$ in healthy controls ($P < .05$, FDR corrected) but not in patients (figure 4). This finding suggests that subjects with more coherent organizations of microstructural tissues exhibited more distinct subdivisions of the network (cf. supplemental figure 6). Additionally, FA values were negatively correlated with PANSS positive, general, and composite scores in crus II for patients (figure 5; $r < −.43$, FDR $P < .05$), suggesting that disruption of regional integrity in the cerebellum affects symptoms of schizophrenia, possibly as a disconnection syndrome.

**Fig. 1.** Decreased fractional anisotropy (FA) values in the cerebellum in schizophrenia. * represents that the mean lobular FA was significantly lower in schizophrenia patients (SZ) compared with controls (NC; 2-tailed $t$ test, false discovery rate [FDR] $P < .05$). Lobule V in the right hemisphere showed a trend of FA decrease in patients ($P = .063$). Error bars are SDs.

**Fig. 2.** Small-world network properties of structural cerebellar brain networks for schizophrenia patients (SZ: red) and healthy controls (NC: black) as a function of connection density. Error bars are 95% CI, and * denotes the significant group difference (10000-times permutation test, $P < .05$).
Discussion

This study used a graph theoretical analysis to investigate the topological organization of cerebellar structural networks in schizophrenia. Our main findings are (1) schizophrenia patients showed grossly intact small-world network organization in the cerebellum; but (2) the modular organization of the cerebellum in schizophrenia...
patients was altered; (3) the significant correlation between network modularity and regional FA values observed in controls was absent in schizophrenia; and (4) the FA values in schizophrenia patients were significantly associated with PANSS symptom scores. Taken together, our findings support the hypothesis that the network architecture of cerebellar structural brain networks is disrupted in schizophrenia patients with reduced local microstructural connectivity.

Intact Small-World Properties in the Cerebellum in Schizophrenia

In the schizophrenia group, the structural cerebellar architecture as a whole exhibited small-world network properties, which is consistent with findings of intact small-world properties in the cerebral cortex in schizophrenia. While the network in schizophrenia as a whole reflected intact small-world properties, there was trend-level evidence of longer characteristic path length and decreased small-worldness (figure 2). The fact that we did not find main effects of characteristic path length and small-worldness may be due to insufficient statistical power or may indicate that cerebellar network disturbances are subtle in this disorder compared to what has been reported for the cerebral cortex. These findings in the cerebellum are comparable to previous studies that have investigated cortical network alterations in the cerebrum in schizophrenia, which have reported that cerebellar network properties are more clustered with relatively shorter path length than a random network. However, it should be noted that the preservation of small-worldness in structural brain networks can be explained by 2 observations: increased clustering coefficient and path length, or no changes. In this study, even though a trend of increased path length and decreased network clustering was observed, we also found a preserved small-worldness in the cerebellum for both schizophrenia and healthy controls, consistent with observations in cortical regions reported by van den Heuvel et al (but see figure 2). This suggests that overall structural network characteristics of the cerebellum are highly conserved even in schizophrenia.

Modularity and Modular Architecture of the Cerebellum

By definition, optimal modules in the network tend to have dense intramodular connections with relatively sparse intermodular connectivity. Because a randomly connected network is unlikely to have such modules, its maximum modularity would be low. The results showed that cerebellar structural networks were consistently modular (Q > 0.4) in both groups over a wide range of connection densities (see figure 2). For both groups, network modularity monotonically decreased as the network density increased, ie, the sparser network was more highly modularized due to the absence of potentially noisy weak connections. We found few significant group differences between schizophrenia and healthy controls in terms of modularity (Q) of cerebellar networks, implying that modular organization is conserved even in this psychotic disorder. However, there were marked differences of modular pattern at the regional level of modules (figure 3). For the healthy controls, the cerebellar hemisphere was grossly subdivided into superior (rostral to the ansoparamedian fissure including anterior lobules) and inferior (VII, VIII, IX, and X) parts. This finding is consistent with a previous functional study indicating that the cerebellum is divided such that anterior/superior lobules are generally related to motor function and inferior lobules to memory and cognition. It is notable that crus II was modularized into the superior module even though it is anatomically located in the inferior lobe caudal to the
Horizontal fissure. In addition, the vermis was shown as (1) merged lobules into the superior hemispheric module and (2) a distinct module including vermis VII through X. While the vermis is classically known as one of the anatomically segregated regions of the spinocerebellum and, therefore, has been considered functionally distinct, a recent study indicated a portion of the vermis is also interconnected with the frontal regions of the brain—e.g., primary, supplementary, and dorsal cingulate motor cortex. Because the anterior-superior module in this study fully covers the lobules related to motor execution and preparation, our results may indicate additional structural evidence to support vermal involvement with both the normal control of movement and cognitive processing.

In contrast, schizophrenia patients showed a different modular architecture where the hemispheric and vermal crus II regions were classified as a distinct module (figure 3). Specifically, the schizophrenia group showed a different modular architecture where the hemispheric and vermal regions of crus II were classified together as a distinct module (i.e., module 5 in figure 3), whereas in healthy controls these 2 regions were classified with a larger set of regions (i.e., module 1 in figure 3). Given that crus II receives inputs from the prefrontal regions of the cerebrum associated with higher cognitive functions and decision making, additional findings from this study might also indicate that abnormal modular organization in this region contribute to the symptom severity of individuals with schizophrenia (figure 5). It would be also indirectly supported by a previous cortical study showing a disrupted modularization in functional networks in schizophrenia.

Regional Alterations

While decreased cerebellar volume has not been consistently reported in schizophrenia, many DTI studies show FA decreases in the cerebellar peduncle and cortico-cerebellar tracts. Because schizophrenia has been conceptualized as a disorder of interregional disconnection, the impairment in white matter integrity in those specific cerebellar regions might be related to the abnormality of gray matter or intercerebellar connections among lobules. In this study, schizophrenia patients showed decreased FA values in the anterior lobe (I–IV and V; figure 1), suggesting that schizophrenia patients have alterations in the intrinsic microstructural properties of cerebellar neurons and the internal circuitry of cerebellar networks. Given that functional hypoactivations for cognitive, executive, emotional, and perceptual processing have been found mainly in these lobules, we could speculate that those regional alterations in schizophrenia might give rise to the functional network disruption in the cerebellum. Interestingly, the network modularity showed a positive correlation with the lobular FA measures in I–IV and X of healthy controls, but it was not present in schizophrenia patients (figure 4). This finding suggests that the disruptive segregation of the large-scale cerebellar networks in schizophrenia could arise from decreased microstructural integrity in those regions. Furthermore, the PANSS positive, general psychopathology, and composite scores were negatively correlated with FA values in crus II (figure 5), which is highly connected with Brodmann’s area 46 in prefrontal cortex.

This correlation suggests that crus II abnormalities might be associated with illness severity (excluding negative symptoms, which were not correlated with crus II FA). In summary, it could therefore be speculated that schizophrenia patients have disturbed cerebellar network organization arising from microstructural disruption in the cerebellum, suggesting that neural disconnectivity would be present within the cerebellum and may be involved in the pathology of schizophrenia. In future studies, more specific neuropsychological experiments will be required to evaluate the network characteristics related with cognitive functions of schizophrenia.

Methodological Issues

First, in terms of the connectivity analyses, we made the assumption that a limited anatomical subdivision of the whole brain, the cerebellum, could be meaningfully examined as an independent network. The weakness of this assumption is that the cerebellum is known to be highly connected with the cerebrum. Thus, until suitable methods are available to disentangle the densely packed fiber tracts coursing through the cerebellar peduncles, findings from graph theoretic network analyses of the cerebellum and cerebrum separately will have to be similarly qualified for excluding one or the other brain region. Second, the cerebellum has significantly fewer known intracerebellar connections compared with cerebro-cerebellar connections. The extent to which fiber tractography methods appropriately capture such intracerebellar connections and separate them from interspersed cerebrocerebellar connections is not fully known and will require extensive investigation. Recent fiber tractography studies indicate progress in this regard.

Nevertheless, the present connectivity findings must be cautiously interpreted until their specific neuroanatomical substrates can be elucidated. Third, compared with recent cerebellar connectivity studies using higher angular resolution diffusion imaging and probabilistic tractography, the method we used in this study is based on the conventional deterministic approach using a streamline technique. Therefore, this study has a potential limitation in...
being able to identify the deep intrapathways (eg, via dentate nucleus) within cerebellar connections. To improve the quantitation of cerebellar structural networks, it would be beneficial in future studies to employ methods in which multiple fiber crossings can be accounted for. Fourth, the cerebellar network of this study was constructed with relatively low spatial resolution (ie, number of nodes = 28) with varying lobular sizes, potentially limiting the precise demarcation of the topological aspects of the cerebellum. However, approaches to find the optimal number and volume of cerebellar regions as network nodes still remain unclear. We employed an a priori anatomical classification building on lobular structures that are carefully documented; however, finer grained regions of interest would be needed to detect more subtle network alterations by avoiding the spatial averaging effects of weak connectivity changes. Fifth, the structural connectivity defined in this study depends on the FA values through fiber tracts and the number of fibers between cerebellar regions. The FA variation in fiber tracts is likely to influence the resulting network characteristics (cf. the FA decreases in cerebellar lobe in figure 1) because there are significant FA differences within cerebellar white matter (see the supplementary figure 7). In addition, even though no significant differences were found in head motion parameters for the 2 groups (relative displacement—SZ:NC = 0.86 ± 0.23:0.75 ± 0.25 mm, P = .26; and absolute displacement—SZ:NC = 3.01 ± 0.95:2.73 ± 1.16 mm, P = .08), it is also possible that the relatively larger movement of the SZ group might still be a potential source of variation in FA and extracted fiber numbers. Sixth, we found a significant positive association in healthy controls between lobular FA values and network modularity (Q). The absence of this correlation in the schizophrenia group might be due to the relatively smaller sample size (NC:SZ = 36:25); alternatively, it could in fact reflect a true dissociation. Seventh, although there were consistent trends of our network measures comparing schizophrenia patients and controls, the significance of between-group differences appeared to be attenuated due to the large intersubject variation of network measures. Accordingly, statistical significance was not consistently observed across varying density thresholds. In addition, correlations between FA values and PANSS scores were moderate in this data set. The relatively low statistical power of this study should be addressed in future work. Overall, the extent to which observed differences in modularity reflect local changes in FA, different patterns of segregation among cerebellar afferents and efferents, or subtle changes in intercerebellar connectivity remains to be determined.

Conclusion

This is the first study to investigate cerebellar network organization in schizophrenia patients using DTI and graph theoretical analysis. In schizophrenia patients, the small-world network properties were retained, but the modular architecture was altered particularly in the crus II region of the cerebellum. Tissue integrity measures were also highly associated with the network modularity and participants’ symptom scores. Our findings suggest that schizophrenia patients have an abnormal network structure in the cerebellum, indicating a relationship between the disruption of the cerebellar organization with increased symptomatology.

Supplementary Material

Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org.

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