Master's Thesis of Brain and Cognitive Sciences

Cerebellar structural abnormalities associated with cognitive function in patients with first-episode psychosis

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Abstract

The fundamental role of the cerebellum in higher cognitive processing has been highlighted in schizophrenia in recent years. However, inconsistent findings exist with respect to the cerebellar substructure volume in schizophrenia, and little is known regarding the association between cerebellar structural abnormalities, and cognitive and clinical dysfunctions in patients. This study aimed to measure the cerebellar structural volume and investigate its association with neuropsychological tests and clinical scores at the early stage of schizophrenia.

Cerebellar volume was measured in 40 patients with first-episode psychosis (FEP) and 40 healthy controls using two complementary approaches: whole-brain voxel-based morphometry (VBM) and automated cerebellar lobule segmentation based on a graph-cut algorithm. A battery of neuropsychological tests and clinical scales were used to investigate the correlation with cerebellar regional volumes.

Both the VBM and automated segmentation analyses indicated a reduced gray matter volume in the superior posterior lobe (Crus I/II in VBM; right VIIb in automated segmentation) in FEP patients. Furthermore, compared with the healthy controls, the FEP patients showed significantly reduced volumes in the right VIIb, the corpus medullare, and the VI vermis, as well as a trend toward reduction in the total vermis volume with the lobular analysis. The volume reduction in the superior posterior lobe was correlated with a worse performance on working memory and immediate recall. The loss of the corpus medullare volume was correlated with higher PANSS (Positive

and Negative Syndrome Scale) positive scores and lower GAF (Global Assessment of Functioning) scores.

Regional structural alterations in the superior posterior lobe and the corpus medullare were identified in FEP patients, and cerebellar volume reductions were associated with working memory, immediate recall, PANSS and GAF scores. Our findings support the involvement of the cerebellar substructure in patients and suggest that the gray matter differences in the superior posterior and corpus medullare are associated with the functioning of FEP patients.

Keyword: Schizophrenia; First-episode psychosis; VBM; MRI; Cerebellum; Working memory

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Chapter 1. Introduction

Increasing evidence suggests that the cerebellum is associated with cerebral networks involved in cognitive and emotional processes as well as motor control. A major focus of cerebellar studies until early in the 19th century was the coordination of voluntary movement and motor function.[1] However, recent research has indicated a role for the cerebellum in cognitive function. Previous neuroanatomical studies have shown that there is a cognitive region of the cerebellum in the lateral hemispheres of the posterior lobe (lobules VI–IX), whereas the anterior lobe (lobules I-V) is responsible for motor function.[2]

In particular, the cognitive area in the posterior cerebellum is linked to cerebral cortices in feedforward networks via the pontine nuclei as well as feedback networks from deep cerebellar nuclei through the thalamus.[3] It has also been argued that the frontal and parietal networks are associated with a role for the cerebellum in cognitive processes.[4] In functional imaging studies with normal subjects, the cerebellum exhibited activation responsible for word generation, working memory, executive function, and language processes.[5-7] In addition, studies of patients with cerebellar atrophy have demonstrated that the performance on working memory[8, 9] and general memory[10, 11] was significantly impaired in patients compared with healthy controls. These findings suggest that the cerebellum is an obligatory component of cognitive functions and support that different cerebellar subregions are responsible for different functions.

There has been increasing interest in the role of the cerebellum in schizophrenia as cerebellar dysfunction on cognition may be relevant to pathophysiology in schizophrenia. Schizophrenia is one of the chronic and complex psychiatric disorders associated with a range of problems related to cognition, behavior, and emotion.[12] Between 75% and 85% of individuals with schizophrenia suffer from cognitive deficits such as impairments in working memory, attention, and language comprehension.[13] One prominent theory referred to as "cognitive dysmetria" has emphasized the potential role of the cerebellum in schizophrenia, which suggests difficulties in coordination and expression of information that results in the core symptoms of schizophrenia.[14]

To date, there has been no consensus regarding the exact nature of cerebellar structural abnormalities in schizophrenia; however, the majority of studies have reported abnormalities of some type (Table 1). In patients with chronic schizophrenia, a reduced whole cerebellar volume has been frequently reported but not consistently replicated[15], as numerous studies have not identified significant cerebellar volume changes in patients.[16-18] Some studies have reported a specific reduction in the cerebellar vermis volume in patients.[19-22] However, other studies have shown an increased white matter vermis volume in patients.[23, 24] In addition to these cerebellar vermis volume findings, specific cerebellar regional volume deficits, including reductions in Crus I/II, have been reported.[25, 26]

Recent reviews have also shown inconsistent results relevant to cerebellar abnormalities and their correlations with cognitive functions in patients with

schizophrenia. A cerebellar lesion study indicated that the total cerebellar volume correlated with delayed verbal memory and global functioning in patients.[27] However, another study showed no correlation between the cerebellar volume and memory, executive, and visuospatial scores in patients.[28]

Potential reasons for these inconsistent findings include the illness chronicity of patients and the various methodologies employed to analyze the cerebellar volume. It is critical to understand whether cerebellar abnormalities are present at the early phase of this illness. However, most previous studies used a chronic sample of schizophrenia patients with varying degrees of illness duration, age, and medication status. To date, studies with relatively small sample sizes have reported that the overall cerebellar gray matter volume, particularly in the vermis, was decreased in patients with a first episode of schizophrenia compared with healthy controls.[29] Furthermore, longitudinal studies have shown a reduced gray matter volume in the right cerebellum in high-risk individuals who subsequently developed schizophrenia illness.[30, 31] These studies support the hypothesis that cerebellar abnormalities are not a result of the adverse effects from a chronic deteriorating course of the illness or medications. However, studies with a small sample size cannot control for significant factors that affect cerebellar morphology, such as sex differences, alcohol dependence, and handedness.

Apart from the heterogeneity of the biological features in schizophrenia, these inconsistent findings may be explained, in part, by the use of different methodological procedures. The cerebellum is a convoluted structure that

consist of I through X vermis and hemisphere lobules.[32] Various automated methods have been used to perform cerebellum segmentation. Fischl et al. (2002)[33] presented FreeSurfer, a whole brain segmentation method, which provides a cerebellar gray and white matter segment; however, it does not provide volumes for individual lobules within the cerebellum. A spatially unbiased atlas template of the cerebellum (SUIT) was developed to parcellate the cerebellum into lobules with a specific standard atlas.[34] Furthermore, to reduce bias toward a specific atlas, the combination of various label fusion methods, referred to a multi-atlas approach, was established.[35, 36] However, these new multi-atlas methods have rarely been used in investigations of cerebellar structural abnormalities in schizophrenia. Thus, the nature of cerebellar structural abnormalities in schizophrenia and their functional significance have not been previously established.

To investigate cerebellar structural abnormalities in schizophrenia, we utilized two complementary methods: voxel-based morphometry (VBM)[37] and automated cerebellar lobule segmentation based on graph-cut algorithm[38] for lobular analysis. The previous region-of-interest (ROI) analysis has a disadvantage. The ROI approach manually or automatically segmented the whole cerebellar hemisphere or the large cerebellar cluster so that cerebellar parcellation is not deliberate.[25] The VBM approach is a recent technique used to examine local differences in the gray matter volume at the whole brain level. VBM independently measures precise voxel-level volumetric differences in the cerebellum and calculates statistically different structures at the whole brain level.[39] Moreover, automated cerebellar lobule segmentation

enables the investigation of a specific cerebellar substructure with better localization. In addition, automated cerebellar lobule segmentation is less sensitive to substantial signal averaging and more statistically powerful than the VBM analysis.[40] However, the VBM approach is expected to benefit from the detection of millimeter resolution cross lobules, and the lobular analysis may underestimate subtle gray matter differences. Thus, we used a combination of VBM and automated cerebellar lobule segmentation approaches to demonstrate cerebellar structural differences, thus leveraging the strengths of each method.

The purpose of this study is to 1) determine the relative significance of cerebellar structural abnormalities compared with other brain structures using the standard whole brain VBM analysis, 2) investigate detailed cerebellar lobular volumes using a novel multi-atlas combined graph-cut segmentation analysis for the cerebellum and 3) investigate the functional significance of cerebellar structural abnormalities in relation to cognitive and clinical outcomes in patients with first-episode psychosis (FEP) compared with healthy controls. Using this first-episode patient sample, we would minimize the confounding effects of illness chronicity and long-term antipsychotic medication on cerebellar abnormalities in patients. We hypothesized that FEP patients would exhibit structural abnormalities of the cerebellum at a regional level (particularly the vermis and the posterior region as shown in previous studies), as well as a cerebellar abnormality at the whole brain level, and these structural abnormalities would be associated with cognitive and clinical dysfunctions in patients.

Chapter 2. Methods

2.1. Subjects

Forty patients with a diagnosis of DSM-IV schizophrenia spectrum disorders with their first-episode were selected from the Seoul Youth Clinic high-risk psychosis cohort between April 2010 and June 2016. All patients underwent the Structured Clinical Interview for DSM-IV Axis I (SCID-I)[41] by experienced psychiatrists to confirm psychiatric illnesses. All patients had a history of less than one year since their first psychotic episode defined as suffering from a brief psychotic disorder, schizophreniform disorder, schizoaffective disorder, or schizophrenia according to the DSM-IV criteria. No patients had comorbidity with alcohol abuse and dependence.

Forty healthy individuals matched for age, gender, and handedness were recruited through Internet advertisements (Table 2). All healthy subjects were included through the SCID non-patient edition[42] screening following the exclusion of major psychiatric disorders, neurological disorder, substance abuse, or first- to third- degree biological relatives with psychiatric illnesses.

The exclusion criteria for both the patient and healthy groups were contraindications to magnetic resonance scanning, neurological disorders, including previous significant head injury, and learning disabilities. After a complete description of the study was provided to the participants, written informed consent was obtained. The study was approved by the Institutional Review Board of Seoul National University Hospital.

2.2. Image processing

All participants were scanned with a 3T scanner (Siemens Magnetom Trio, Erlangen, Germany) at Seoul National University Hospital. 3D (MPRAGE sequence) T1-weighted structural MRI was obtained with the following parameters: 1 mm slice thickness; repetition/echo time 1670/1.89 ms; 208 slices; matrix 256 × 256; field of view 250 mm; flip angle 9°; voxel dimensions 0.82 × 0.82 × 0.82 mm3. The structural T1-weighted images were processed using FreeSurfer (v.5.3.0, http://surfer.nmr.mgh.harvard.edu) to obtain the total intracranial volumes and whole cerebellar gray and white matter volumes (left and right). Voxel-based morphometry (VBM) analysis was performed using SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/) and the CAT12 (Computational Anatomy Toolbox) toolbox (http://dbm.neuro.uni-jena.de/cat/) with MATLAB R2015b. Structural data were smoothed with a 6 mm full-width-at-half-maximum filter (FWHM). For detailed estimation of the cerebellar lobule volumes, an automated segmentation method based on a multi-atlas labeling and graph-cut analysis was used.[38] Each MR image was initially preprocessed using FreeSurfer to register the image into MNI space and perform a skull stripping and intensity normalization for gray-white matter segmentation in the cerebellum. An initial segmentation was subsequently performed for the registration of each lobule with the multi-atlas, and tissue and boundary classification was performed with a graph-cut base segmentation algorithm (http://iacl.ece.jhu.edu/Resources).

2.3. Neuropsychological tasks and clinical ratings

All subjects completed a battery of neuropsychological tasks that assessed verbal fluency, executive function, processing speed, verbal memory, and working memory. Verbal fluency was assessed with the Controlled Oral Word Association Test (COWA), including a letter-fluency task and a category-fluency task.[43] The Trail Making Test Part B (TMT-B) and Wisconsin Card Sorting Test (WCST) were administered to assess processing speed and executive function.[44, 45] The Korean version of the California Verbal Learning Test (K-CVLT) instructed the participants to recall as many words as possible and was used to assess an individual's verbal memory ability.[46] The Digit Span Task was used to measure working memory by assessing an ability to recall the sequence of numerical digits.[47] Schizophrenia symptoms were rated using the Positive and Negative Syndrome Scale (PANSS)[12]. In addition, the Global Assessment of Functioning (GAF) was administered to assess the overall functioning of the patients.[48]

2.4. Data Analyses

All statistical tests were performed using SPSS 23. All cerebellar volumes were normalized to diminish the inter-subject variability in the brain size by calculating a relative cerebellar volume (absolute cerebellar volume was divided by intracranial volume). Two-tailed independent samples t-tests were used to analyze the between-group differences in the cerebellar gray and white matter volumes. The volumetric differences between the FEP patients and healthy controls were measured using uncorrected t-tests to compare each

cerebellar region. Pearson's correlation analysis was also performed to examine the relationships between the neuropsychological assessment scores, the clinical scales, and the cerebellar structural volumes.

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Chapter 3. Results

3.1. Cerebellar analyses

3.1.1. VBM analysis

As shown in Fig. 1, the FEP patients exhibited a significantly reduced gray matter volume compared with the healthy controls in the Crus I/II areas. Specifically, the clusters in the left Crus II (MNI -30 -84 -38, T=8.8, k=4916), the right Crus II (MNI 27 -86 -36, T=7.6, k=1906), and the right Crus I (MNI 41, -41, -36, T=6.4, k=288) were decreased in the patients. There were no cerebellar regions in which the FEP patients had increased gray matter compared with the healthy controls.

3.1.2 Cerebellar Volumetric Measurement

The total right (t=.75, df=78, p=.45) or left (t=1.35, df=78, p=.18) cerebellar volume was not significantly reduced in the FEP patients compared with the healthy controls. The patients also did not show a significant reduction in the total right (t=.87, df=78, p=.39) or left (t=1.17, df=78, p=.25) white matter volumes. At a lobular level volume analysis, the patients showed a significant decrease in the VI vermis (t=2.40, df=78, p=.019), the right Vllb lobule (t=3.36, df=78, p=.001), and the corpus medullare (t=1.97, df=78, p=.05). In addition, the patients exhibited a trend toward reduction in the total vermis volume (t=1.67, df=78, p=.098) (Table 3).

3.2. Correlation findings

There were no correlations between the cerebellar volume and the cognitive

variables within the lobular level and VBM analyses. In view of the significant correlations between the cerebellar volume deficits and cognitive/clinical variables, the cerebellar regions were sub-divided into three domains including the anterior, superior posterior, and inferior superior lobes as previously reported.[49] In the FEP patients, the digit span task scores were positively correlated with the volumes in the left/right anterior (r=.43, p=.006/r=.44, p=.005), left/right superior posterior anterior (r=.37, p=.022/r=.33, p=.039), and left inferior superior lobes (r=.41, p=.009). There was also a positive correlation between the left superior posterior lobes and KCVLT immediate recall scores (r=.37, p=.019). Furthermore, the GAF scores showed a positive correlation with the corpus medullare (r=.45, p=.003), and the PANSS positive total scores were negatively correlated with the corpus medullar (r=-.32, p=.044). No correlation was identified between the other subregions and the cognitive and clinical variables. The superior posterior lobule and corpus medullare, which exhibited volume reductions in the FEP patients compared with the controls, were significantly correlated with the performance in working memory, immediate recall, PANSS positive, and GAF scores (Figure 2).

Chapter 4. Discussion

Our findings confirmed the existence of cerebellar gray matter volume deficits in the superior posterior region at the early stage of schizophrenia. In the VBM analysis, the Crus I/II clusters in the superior posterior lobe were decreased in FEP patients. A detailed cerebellar regional analysis showed that FEP patients had specific gray matter volume deficits in the right VIIb lobule of the superior posterior lobe, the corpus medullare, and the VI vermis. Furthermore, we determined that the lower volume in the superior posterior lobe was significantly associated with worse performance in working memory and immediate recall. The results also showed that higher PANSS positive scores were associated with a lower corpus medullare volume, and higher GAF scores were related to a higher corpus medullare volume. Thus, this study provided evidence for altered cerebellar morphology in the early phases of the disease process, which would be responsible for the cognitive deficits in schizophrenia.

Using the whole brain VBM analysis, we identified significant gray matter reduction in Crus I/II. Our finding is consistent with previous VBM studies in schizophrenia that reported gray matter deficits in Crus I and Crus II.[25, 50] The roles of Crus I and II are associated with cognitive functions. Previous studies have shown that Crus I/II have connections to the prefrontal and parietal cortices.[51, 52] In particular, the right Crus I is activated during executive function and language tasks[53, 54], and a meta-analysis of fMRI studies indicated that Crus I is associated with verbal working memory and executive

functions.[55] These results suggest that structural alterations in Crus I/II may impact the cognitive deficits in schizophrenia.

In the lobular analysis, we determined that the right Vllb lobule, VI vermis, and corpus medullare volumes were specifically reduced in FEP patients. Our results are consistent with previous studies that indicated superior posterior cerebellar lobule atrophy in schizophrenia. Previous studies that have manually or automatically analyzed the cerebellar substructure in schizophrenia have reported reduced cerebellar volumes in the superior posterior regions including the VIIa and Crus I/II.[25, 26, 56, 57] The Vllb lobule in the superior posterior region has been considered responsible for cognitive function. A meta-analysis of neuroimaging studies with healthy subjects indicated an association between the Vllb lobule and the executive and verbal working memory functions.[55] A cerebellar lobule analysis in patients with cerebellar disease also demonstrated that the Vllb volume was associated with supporting phonological storage and working memory performance.[58] Consistent with the findings, the VIIb lobule, as a component of the cognitive control system in the superior posterior cerebellar region may play an important role in the cognitive function of schizophrenia.

Our results provided additional evidence that the VI vermis volume was decreased in the patients, and the total vermis volume was decreased at a trend level. The cerebellar vermis, which is considered a component of the limbic cerebellum, has relevance to the regulation of emotion, cognition, and affect that may be associated with clinical symptoms in schizophrenia.[32] To date, previous cerebellar substructure studies have reported significant differences

in the superior posterior vermis volume in first-episode and chronic patients with schizophrenia.[21, 22, 59, 60] However, a reduced volume in the anterior vermis and an increased volume in the vermis white matter have also been identified in patients with schizophrenia.[23, 24, 59-61] A pathway exists from the fastigial nucleus under the anterior vermis to the ventral tegmental area, which controls the supply of dopamine to the prefrontal cortex via the striatal nucleus accumbens.[62] An alteration in this pathway may result in dopamine dysregulation in schizophrenia and contribute to impairments in emotional functions.

We identified a significance reduction in the corpus medullare in FEP patients. This finding is consistent with previous findings in both FEP and chronic patients.[56, 63] The corpus medullare is a central white matter bundle that connects the cerebellar cortical areas with deep cerebellar nuclei originating cerebellar efferents.[64] Examination of the cerebellar white matter is important because Purkinje cells that connect the origins of cerebellar efferents of the cerebellar cortex to the deep cerebellar nuclei have shown an abnormal cell size and density in schizophrenia.[65]

We also examined the association of the cerebellar regional volumes with cognitive performances. The cerebellar volumes in the anterior, superior posterior, and left inferior superior lobes were associated with better performance on the verbal working memory task. This finding is consistent with previous studies that indicated associations between working memory and lobule IV, V, VI, Crus I, VIIb, and VIII.[58, 66] Working memory is a multi-component system believed to involve temporarily maintaining, storing, and

manipulating information. It consists of the central executive and three storage systems including the visuospatial sketchpad, the episodic buffer, and the phonological loop.[67] The dorsolateral prefrontal cortex (DLPFC) circuitry is critical for working memory function.[68] Moreover, the cerebellar ventral dentate was activated during a working memory task, and the ventral dentate was functionally associated with the DLPFC.[69] Similarly, we identified a relationship between the superior posterior lobe and immediate recall performance, which appears to involve the phonological loop of the working memory model. Taken together, previous studies and the current findings suggest associations between the superior posterior lobules and the phonological loop. These results also implied that there may be interactions between the cerebellum and frontal cortex, which is responsible for executive and phonological functions in FEP patients.

Previous studies have reported significant correlations between the vermis gray and white volumes and clinical scales;[19, 23, 24] we determined that the corpus medullare was positively correlated with the PANSS positive scores and inversely correlated with the GAF scores. The vermis and cerebellar deep nuclei, such as the dentate and fastigial nucleus in the white matter, have connections with the thalamus, limbic systems, and frontal cortex.[70, 71] Alterations in the vermis and the deep white matter may induce interruption of the circuit, which may result in cognitive deficits and positive symptoms in schizophrenia.

Limitations

Several limitations need to be considered in the present study. First, the

methods of Yang et al. (2016)[38] employed in this study analyzed twenty lobules, and a number of regions were simultaneously compared, which may lead to false positive errors. However, as we detected cerebellar gray matter abnormalities in the VBM analysis, it is unlikely that the cerebellar structural abnormalities in our results are associated with false positive errors. Second, as the lobule X is relatively small and an inner region of the cerebellum, the automated segmentation method produced failure cases in the lobule X. We substituted the failure cases for the NL-STAPLE results in the group comparisons. Nevertheless, the lobule X is not part of our significant results. In addition, our results lacked of information regarding the anterior vermis because the method did not take into account the anterior vermis region. Our structural abnormalities in the cerebellum are present at the early stage of schizophrenia at a group level. Thus, longitudinal studies with a full course of schizophrenia including clinical high-risk, first-episode psychosis, and chronic patients are required to determine whether the volume change is progressive in schizophrenia. Our cohort database[72, 73] would be important to answer whether the cerebellar structure pathology is linked to the developmental factors of schizophrenia.

Chapter 5. Conclusion

We employed the most recent and novel cerebellar segmentation tool to demonstrate cerebellar volumetric abnormalities in patients experiencing first-episode schizophrenia. We identified a cerebellar gray matter volume reduction at the whole brain level, as well as a volume alteration in the superior posterior lobe, which is correlated with working memory and immediate recall performance in FEP patients. With respect to clinical symptoms, the reduced volume of the corpus medullare was significantly correlated with the PANSS positive and GAF scores. In this sense, our findings are important, as they provide detailed cerebellar substructure volume alterations together with cognitive and clinical associations in schizophrenia, and this cerebellar dysfunction exists at an early stage of the disease. Malfunction in the cerebellar modulation link to cortical and subcortical areas may be related to the pathophysiology of schizophrenia, and may result in cognitive and clinical deficits in the disease.

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Table

Table 1. Structural MRI studies investigating cerebellar volume in schizophrenia

Source	Illness course	Male Or Female	Number of Patients/Control	Findings
Nasrallah et al., 1991[74]	Chronic	Male	30/30	↑VI, VII vermis volume
Rossi et al., 1993[75]	Chronic	Both	23/16	↓Anterior vermis volume
Jacobsen et al., 1997[76]	Chronic	Both	24/52	↓Vermis & inferior posterior lobe & No differences in total cerebellar volume
Levitt et al., 1999[23]	Chronic	Both	15/15	↑Vermis & white matter vermis & Left volume asymmetry
Nopoulos et al., 1999[61]	Chronic	Male	65/65	↓Vermis volume
Ichimiya et al., 2001[19]	Chronic	Male	20/20	↓Vermis volume
Loeber et al., 2001[20]	Chronic	Both	19/19	↓Inferior vermis & Cerebellar asymmetry
Wilke et al., 2001[77]	Chronic	Both	48/48	↑Gray matter volume
McDonald, 2002[16]	Chronic	Both	66/68	N.S
Saeed and Puri, 2002[78]	Chronic	Both	10/10	N.S.

Hulshoff Pol et al., 2002[17]	Chronic	Both	159/158	N.S.
Cahn et al., 2002[18]	FEP	Both	34/36	N.S.
Okugawa et al., 2002[21]	Chronic	Male	30/18	↓Posterior superior vermis
Okugawa et al., 2003[59]	Chronic	Both	59/57	↓Vermis volume
Joyal et al., 2004[22]	Chronic	Male	38/26	↓Vermis volume
Bottmer et al., 2005[15]	Chronic	Both	37/18	↓bilateral cerebellum volume
Lee et at al., 2007[24]	Chronic	Male	40/40	↑Cerebellar vermis white matter
Okugawa et al., 2007[60]	FEP	Both	14/16	↓Posterior superior & Anterior vermis
Rimol, et al., 2010[79]	Chronic	Both	173/207	↓Left cerebellar cortex
Thomanna et al., 2009[56]	FEP	Both	30/21	↓Corpus medullare
Cohen et al., 2012[29]	FEP	Both	19/13	↓Vermis volume
Kühn, et al., 2012[25]	Chronic	Both	29/45	↓Crus I/II volume
Solowij et al., 2012[63]	Chronic	Both	17/31	↓White matter volume
Dean et al., 2014[26]	UHR	Both	26/29	↓Anterior Crus I & Vermis volume
Hirjak, 2015[57]	FEP	Both	26/26	↓Cerebellar cortex volume

Table 2. Demographic and clinical data

Variable	FEP (40)	Controls (40)	χ2/T/F	*P*
Sex(male/female)	18(22)	20(20)	0.201	0.823
Age(year)	22.9(5.6)	22.6(3.9)	0.076	0.783
Education(year)	13.2(2)	14.1(1.7)	2.032	<.05
Handedness(right/left)	35(5)	35(5)	0	1
IQ	97.5(13.7)	113.6(13.5)	5.267	<.05
Antipsychotics(yes/no)	10/30			
CPZ equivalent dose (mg/day)	257(169.5)			
GAF	46.3(10)			
PANSS positive	16.48(4.86)			
PANSS negative	17.45(5.65)			
PANSS general	35.1(7.62)			
Diagnosis	Schizophrenia=20			
	Schizophreniform disorder=15			
	Schizoaffective disorder=2			
	Brief psychotic disorder=3			

Abbreviations: CPZ, Chlorpromazine; PANSS, Positive and Negative Syndrome Scale Positive scale; GAF, Global Assessment of Functioning

Table 3. Cerebellar lobular volumes with automated graph cut segmentation analysis

Region		t	df	p-value
Anterior	I-V Left	1.52	78	.131
	I-V Right	.23	78	.824
Superior Posterior	XI Left	1.11	78	.554
	XI Right	.59	78	.518
	Crus I Left	-.43	78	.663
	Crus II Left	.60	78	.547
	XIIB Left	1.33	78	.184
	Crus I Right	.61	78	.542
	Crus II Left	.42	78	.674
	XIIB Right	3.36	78	.001***
Inferior Superior	XIII Left	1.15	78	.268
	XIII Right	-.24	78	.807
	IX Left	.12	78	.903
	IX Right	.31	78	.752
White matter	Corpus Medullar	1.97	78	.05*
Vermis	VI	2.39	78	.019**
	VII	1.48	78	.14
	VIII	-.34	78	.73
	IX	1.22	78	.22
	X	-.85	78	.397

Figures

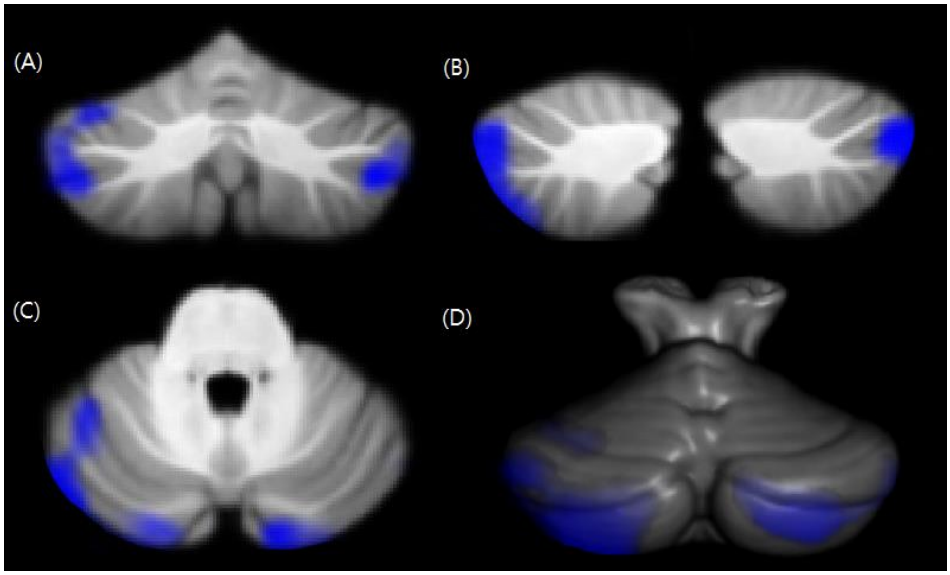

Figure 1. Significant clusters of cerebellar gray matter decrease in Crus I and II in first-episode patients with VBM analysis. (A) Coronal view (B) sagittal (left/right) view (C) Axial view (D) Posterior view.

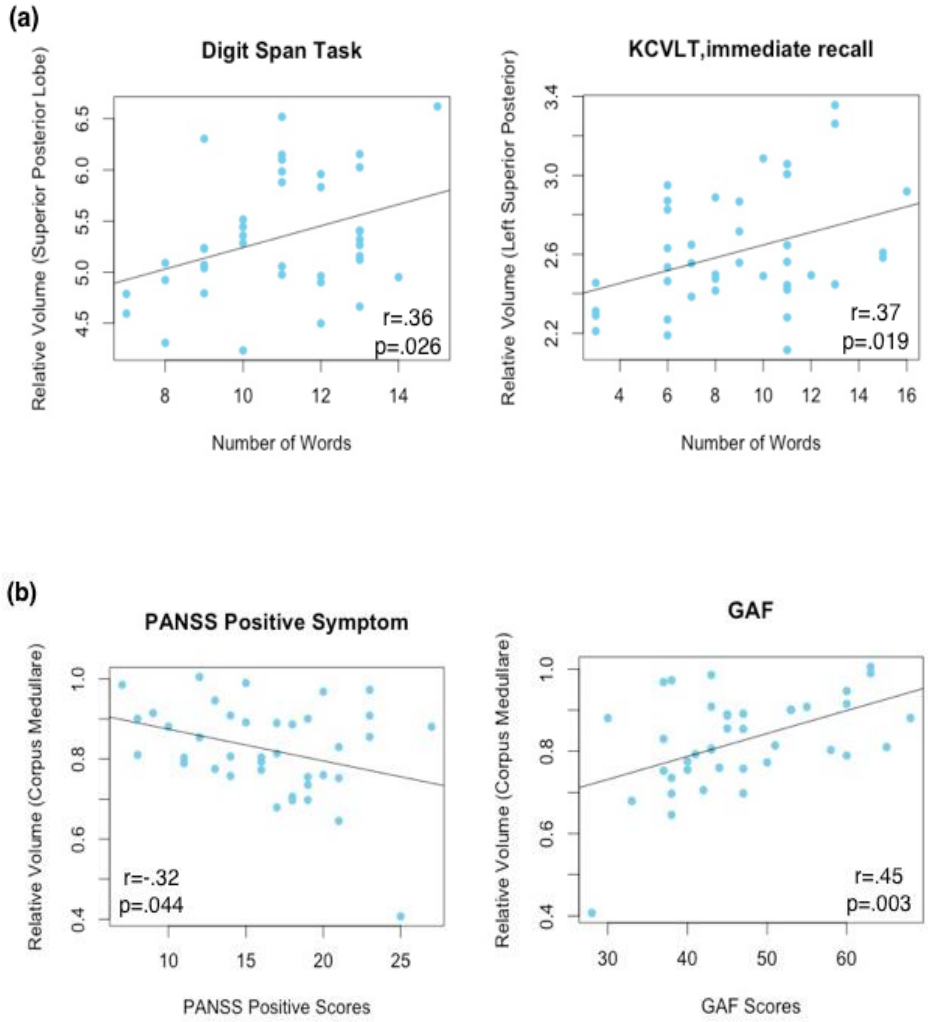

Figure 2. (a) Correlation of the superior posterior region in the cerebellum with neurocognitive function test scores (Digit span, KCVLT) in first-episode psychosis. KCVLT, Korean version of California Verbal Learning Test. (b) Correlation of the corpus medullare with the positive symptoms score of the Positive and Negative Syndrome Scale (PANSS) and GAF (Global Assessment of Functioning) scores in first-episode psychosis.

Abstract

소뇌는 조현병 환자의 고등 인지 과정을 담당하는 핵심 역할을 담당하고 있다고 알려져 있다. 하지만 조현병 환자의 소뇌의 세부 구조적 크기에 대한 연구 결과들이 상이하고 소뇌의 구조적 이상과 인지 및 임상적 기능 장애의 관한 결과들이 충분히 연구 되지 않은 실정이다. 따라서, 본 연구에서는 초발 조현병 환자의 소뇌의 구조적 크기를 정상인과 비교한 뒤 이와 연관된 신경 인지 능력과 임상 증상과의 관련성을 살펴보고자 하였다.

본 연구에서는 질병 만성도에 영향을 받지 않는 총 40명의 초발 정신증환자와 40명의 정상 대조군을 대상으로 하여 전체 뇌를 대상으로한 복셀 기반의 형태 계측과 그래프 커트 기술을 기반으로한 소뇌 분할 알고리즘을 통해 소뇌의 구조적 이상을 측정하였다. 또한 소뇌 구조적 이상과 연관성을 보이는 인지기능과 임상증상을 살펴보기위해 상관분석을 실시 하였다.

복셀 기반의 형태 계측 분석결과, 초발 정신증 환자에게서 소뇌의 후상위 부분인 Crus I/II부분의 감소를 관찰하였다. 소뇌영역을 자세하게 분할해서 크기를 비교해보았을때, 환자군에서 소뇌의 오른쪽 VIIb, 뇌량, 6번째 충부영역 에서 유의미한 감소를 관찰하였다. 전체 충부영역크기는 환자군에서 경향 수준의 감소만을 보였다. 또한 작업기업과 즉시회상능력은 소뇌의 후상위크기와 양의 상관관계를 보였고 소뇌의 뇌량은 PANSS 양의 점수와 음의 상관관계를 보였지만 GAF 점수와는 양의 상관관계를 보였다.

초발 정신증환자에서 소뇌의 국지적 후상위영역의 이상은 작업기억과 즉시 회상 능력과 연관이 있음을 보였고, 뇌량의 크기 감소는 PANSS양의 점수와 GAF점수와 연관성을 보였다. 이를 통하여 소뇌의 국지적 영역들이 조현병 환자의 인지 및 임상 기능들과 연관됨을 밝혔다.