PCN Psychiatry and Clinical Neurosciences

Disclosure statement

The authors declare no conflict of interests.

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Association between globus pallidus volume and positive symptoms in schizophrenia

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Schizophrenia is a psychiatric disorder characterized by positive and negative symptoms and cognitive dysfunction.[1] Positive symptoms are a defining characteristic among the symptoms of schizophrenia and include delusions, hallucinations, and disorganization. Research is underway to elucidate the biological basis of these psychiatric symptoms using various methods.[1,2] Subcortical structures, such as the basal ganglia and thalamus, have been implicated in the psychiatric symptoms of schizophrenia. Among them, the globus pallidus has long been the focus of attention.[3,4] The globus pallidus is involved in the direct and indirect pathways in cortico-basal ganglia-thalamocortical loops, as it receives inhibitory control from the striatum based on the cortical signals, which is then related to controlling one's behavior with a balance of excitation *via* direct pathway and inhibition *via* indirect pathway as intrinsic (external segment) and output nuclei (internal segment) of the basal ganglia circuitry. A large-scale multi-site study demonstrated larger volumes of the left and right globus pallidus in patients with schizophrenia than in healthy controls and schizophrenia-specific leftward asymmetry in the pallidum volume.[5] Recently, a larger left pallidal volume has been reported in individuals with at-risk mental state (ARMS) and subclinical psychotic experiences (SPEs).[6,7] However, the relationship between the globus pallidus and symptom severity remains unclear. Gur *et al*.[3] reported a positive correlation between globus pallidus volume and symptom severity, while Spinks *et al*.[4] reported that in patients not taking antipsychotic medication, the smaller the external segment of the globus pallidus was, the more severe the symptoms. The present study examined the association between structural aspects of the globus pallidus and symptom severity in patients with schizophrenia. To overcome the challenges of previous studies, we used a larger sample and objective analytical methods recently established.

The analysis included 276 patients with schizophrenia recruited at Osaka University Hospital (Table S1). The data from these participants overlap with our previous studies, and hence details of exclusion and inclusion of the participants have been described elsewhere.[8,9] We used the Positive and Negative Syndrome Scale (PANSS)[10] to assess symptom severity, and the volume of the globus pallidus was calculated by FreeSurfer 5.3 software (http://surfer.nmr.mgh.harvard.edu) based on the Enhancing Neuroimaging Genetics through Meta-Analysis (ENIGMA) protocol using T1-weighted magnetic resonance images. The volumes of the globus pallidus were examined for bilateral summation and separately for each side. We also examined a laterality index [(left − right)/(left + right)] to determine whether an abnormal asymmetry of the globus pallidus is related to symptom severity. We further analyzed the striatum as a control region. This study was approved by the Research Ethics Committee of the National Center of Neurology and Psychiatry and Osaka University and was conducted following the provisions of the Declaration of Helsinki. Written informed consent was obtained from all participants. Further details are described in the Supplementary Methods.

Partial correlation analysis, controlling for age, sex, intracranial volume, and MRI scanner, demonstrated a positive correlation between positive symptoms and the right pallidal volume even after Bonferroni correction (Table 1). An additional analysis further controlling for chlorpromazine equivalents showed that the right pallidal volume was still correlated with positive symptom severity ($r = 0.163$, $P = 7.45 \times 10^{-3}$). No significant correlations with psychiatric symptom scales were found in the caudate nucleus and putamen (Tables S2 and S3).

The present findings suggest that patients with a larger volume of the right globus pallidus have more severe positive symptoms. This result is similar to the finding by Gur *et al*.[3] but not that by Spinks *et al*. The volumes of both the right and left globus pallidus of patients with chronic schizophrenia were larger than those of healthy individuals,[5] whereas male individuals with ARMS or subclinical individuals with SPEs showed larger volumes in the left globus pallidus.[6,7] The participants in the present study were chronic patients with schizophrenia. The present finding suggests a relationship between increased right pallidal volume, which becomes more evident after onset, and more severe positive symptoms. Another remarkable feature of brain structures in schizophrenia is a left–right difference in globus pallidus volume.[5] However, our present results did not show any correlation between the laterality index and symptom severity. The left–right differences in the volume of the globus pallidus may reflect other features of schizophrenia. The limitation is that this is a cross-sectional study, and the causal relationships between globus pallidus volume and positive symptoms is unknown. Furthermore, the correlation between globus pallidus volume and symptom severity was weak, suggesting that symptom severity might also be explained by other brain features. Future studies should be designed to resolve these points.

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Table 1. Partial correlations between PANSS symptom scale scores and pallidal volumes

	Positive symptoms		Negative symptoms		General psychopathology	
	Partial *r*	*P* value	Partial *r*	*P* value	Partial *r*	*P* value
Total volume	0.146	1.60×10^{-2}	0.142	1.97×10^{-2}	0.110	7.01×10^{-2}
Left volume	0.090	1.42×10^{-1}	0.121	4.73×10^{-2}	0.080	1.87×10^{-1}
Right volume	**0.185**	$\mathbf{2.27 \times 10^{-3}}$*	0.136	2.47×10^{-2}	0.123	4.29×10^{-2}
Laterality index	−0.078	2.01×10^{-1}	0.015	8.06×10^{-1}	−0.026	6.70×10^{-1}

Raw *P* values were shown. Underlined font represents raw $P < 0.05$. Asterisk with bold and underlined font represents Bonferroni corrected $P < 0.05$ (raw *P* value × 12).

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Appendix S1. Supplementary methods

Table S1. Demographic and clinical characteristics of the participants

Table S2. Partial correlations between symptom severities and caudate volumes

Table S3. Partial correlations between symptom severities and putamen volumes

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Successful electroconvulsive therapy for 22q11.2 deletion syndrome with Schizophrenia and Parkinson's disease

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22q11.2 deletion syndrome (22q11.2DS) is the most common chromosomal microdeletion disorder that occurs in 1 in 2000–4000 live births.[1] 22q11.2DS, the DiGeorge syndrome and velocardiofacial syndrome, includes various clinical presentations such as congenital heart disease, neuropsychiatric illness, cleft palate, along with various endocrine, immunological, and gastrointestinal problems.[1] The patients with 22q11.2DS have a 12–80 fold higher incidence rate for schizophrenia compared to the general population; approximately 30% of patients with 22q11.2DS are diagnosed with schizophrenia.[1] Furthermore, they have an increased risk of early-onset Parkinson's disease (PD).[2] According to a recent systematic review, electroconvulsive therapy (ECT) can be an effective treatment method for treatment-resistant schizophrenia, and improve motor symptoms, depression, and psychosis in PD.[3,4] We had difficulty in treating psychosis in patients with 22q11.2DS who were affected by early-onset PD due to the trade-offs with dopamine; ECT improved psychiatric symptoms, which resolved the motor symptoms and enabled antipsychotic dose reduction.