Structural alterations in brainstem, basal ganglia and thalamus associated with parkinsonism in schizophrenia spectrum disorders

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Abstract
The relative roles of brainstem, thalamus and striatum in parkinsonism in schizophrenia spectrum disorder (SSD) patients are largely unknown. To determine whether topographical alterations of the brainstem, thalamus and striatum contribute to parkinsonism in SSD patients, we conducted structural magnetic resonance imaging (MRI) of SSD patients with (SSD-P, \( n = 35 \)) and without (SSD-nonP, \( n = 64 \)) parkinsonism, as defined by a Simpson and Angus Scale (SAS) total score of \( \geq 4 \) and < 4, respectively, in comparison with healthy controls \( (n = 20) \). FreeSurfer v6.0 was used for segmentation of four brainstem regions (medulla oblongata, pons, superior cerebellar peduncle and midbrain), caudate nucleus, putamen and thalamus. Patients with parkinsonism had significantly smaller medulla oblongata \( (p = 0.01, \text{ FDR-corrected}) \) and putamen \( (p = 0.02, \text{ FDR-corrected}) \) volumes when compared to patients without parkinsonism. Across the entire patient sample \( (n = 99) \), significant negative correlations were identified between (a) medulla oblongata volumes and both SAS total \( (p = 0.034) \) and glabella-salivation \( (p = 0.007) \) scores, and (b) thalamic volumes and both SAS total \( (p = 0.033) \) and glabella-salivation \( (p = 0.007) \) scores. These results indicate that brainstem and thalamic structures as well as basal ganglia-based motor circuits play a crucial role in the pathogenesis of parkinsonism in SSD.

Keywords Sensorimotor domain · Parkinsonism · MRI · Freesurfer · Basal ganglia · Brainstem

Introduction
Parkinsonism in schizophrenia spectrum disorders (SSD) is a multidimensional syndrome characterized by tremor, rigor, akinesia and hypersalivation [1–3]. The neurobiological mechanisms underlying parkinsonism in SSD are thought to reflect an interplay between spontaneous (i.e. disease-related) and antipsychotic drug-exacerbated movement disorder [1, 4–8]. Previous multimodal magnetic resonance imaging (MRI) and other studies have considered several putative neurobiological mechanisms including prominent striatal contributions [9] and disturbed structural–functional coupling between cortical and subcortical systems, particularly in cortical-striatal-thalamocortical networks [5, 6, 10, 11]. However, previous structural MRI studies used techniques that were unable to account sufficiently for the convoluted morphological relationships among brainstem, striatal and thalamic structures [12]. In addition, there is a paucity of evidence concerning structural brainstem abnormalities in SSD patients with parkinsonism.

Therefore, the present MRI study used both a categorical and a dimensional (correlational) approach to investigate the relationships between morphological variations of subcortical structures [medulla oblongata, pons, superior cerebellar peduncle (SCP), midbrain, caudate nucleus, putamen and thalamus] and parkinsonism assessed with the Simpson and Angus Scale (SAS) [26] in SSD patients. Currently, the
SAS is the only instrument that allows robust estimation of parkinsonism in SSD patients. The SAS estimates rigor, tremor, hypokinesia, hypersalivation, and glabellar tap. Particularly noteworthy is glabella tap, as this is ascribed to frontal release signs [13] and is considered an intrinsic sensorimotor sign (i.e. reflecting vulnerability to and emergence of illness) that is not related to effects of medication. This study had two main hypotheses: first, using a categorical approach, we hypothesized that brainstem structures, caudate nucleus, putamen and thalamus volumes will differ between SSD patients with (SSD-P, SAS total score ≥ 4) and without (SSD-nonP, SAS total score < 4) parkinsonism. Second, using a dimensional approach (i.e. across increasing severities of parkinsonism) and in accordance with a model of dopaminergic-driven subcortical-cortical motor circuitry [14–17], we hypothesized that the volumes of these structures will be associated with distinct symptom dimensions of parkinsonism.

**Methods**

**Study participants**

We evaluated a total of 111 right-handed [18] subjects satisfying DSM-IV-TR [19] criteria for schizophrenia (n = 104) or schizoaffective disorder (n = 7) [20, 21]. Diagnoses were made by staff psychiatrists and confirmed using the German versions of the Structured Clinical Interview for DSM-IV-TR axis I and II disorders (SCID) and examination of the case notes (D.H. and S.F.). Patients were excluded if: (1) they were aged < 18 or > 65 years; (2) they had a history of brain trauma or neurological disease (especially movement disorders); or (3) they had shown alcohol/substance use disorder within 12 months prior to participation.

Twenty-eight healthy right-handed control subjects (HC) were also studied. Exclusion criteria included MRI contraindications, a history of psychiatric, neurological, cardiovascular or metabolic illness, prior head trauma, and current alcohol or drug abuse. None of the control subjects had a first-degree relative with a psychiatric disorder or were receiving psychopharmacological treatment.

The study protocol adhered to the Declaration of Helsinki. The local Research Ethics Committee (Medical Faculty at Heidelberg University, Germany) approved the study. We obtained written informed consent from all study participants after all aims and procedures of the study had been fully explained.

**Clinical assessment**

Patients were recruited and examined by SF and DH within 1 week after partial remission of psychotic symptoms. The duration between the evaluation of psychopathology (Positive and Negative Syndrome Scale [PANSS] [22], Brief Psychiatric Rating Scale [BPRS] [23], Clinical Global Impression Scale [CGI] [24]), functional capacity (Global assessment of functioning [GAF] [25]), sensorimotor assessment (Simpson-Angus Scale (SAS) [26] and Northoff Catatonia Rating Scale (NCRS) [27, 28]) and MRI examination was less than 3 days. At the time of examination, none of the SSD patients were treated with benzodiazepine or anticholinergic medication and all but 4 patients were receiving stable antipsychotic medication for at least 2 weeks. Daily doses of antipsychotic medication were converted to olanzapine equivalents (OLZ) [29].

For assessment of parkinsonism, we used the SAS [26]. We then excluded 12 SSD patients from the original study sample (111 − 12 = 99) to create two well-balanced (in terms of age, sex, education and OLZ-equivalent dose) groups of SSD patients with parkinsonism (SSD-P; SAS total score ≥ 4, n = 35) and without parkinsonism (SSD-nonP; SAS total score < 4, n = 64) according to previously described cut-off criteria [30]. The patient groups were carefully matched with respect to sex and education because both variables can influence sensorimotor functioning in SSD [2, 31]. Similarly, we excluded 8 HC from the original sample (28 − 8 = 20) to create a well-matched (in terms of age, sex and education) control group (n = 20). Finally, we followed a correlative approach, assuming dimensional symptom expression along a neurobiological continuum in SSD patients with various degrees of parkinsonism (n = 99) [32].

**MRI data acquisition**

MRI scans were acquired at the Central Institute of Mental Health, Mannheim, Germany, using a 3.0 T Siemens Trio whole-body imaging system and a T1-weighted magnetization-prepared rapid gradient-echo (MP-RAGE) sequence with the following parameters: repetition time (ms): 2530; echo time (ms): 3.8; inversion time (ms): 1100; flip angle: 7°; number of averages: 1; slice thickness (mm): 1; image columns: 256; image rows: 256; phase encoding direction: ROW; voxel size x (mm): 1; voxel size y (mm): 1; number of volumes: 1; number of slices: 176; number of files: 176.

**Image processing**

FreeSurfer v6.0 [33] was used for the segmentation of four brainstem regions and the caudate nucleus, putamen and thalamus [34–36]; for further details on these methods see (http://surfer.nmr.mgh.harvard.edu/). This segmentation tool is able to perform volumetric segmentation of four brainstem regions (medulla oblongata, pons, SCP and midbrain) from T1 (MP-RAGE) images using a
Bayesian algorithm that relies on a probabilistic atlas of the brainstem and neighboring brain structures [12]. Furthermore, this tool uses soft segmentation, i.e. a voxel can be assigned to multiple structures/tissues, which results in improved performance regarding partial volume effects from surrounding cerebrospinal fluid [12]. The volumes of the caudate nucleus, putamen and thalamus were performed using the aseg.stats command. Since we did not have an explicit laterality hypothesis, we calculated a mean value from the left and right volumes of these three structures. Finally, the estimated total intracranial volume (eTIV) was calculated with FreeSurfer as recommended. FreeSurfer exploits a relationship between intracranial volume and linear transformation to MNI305 space (talairach.xfm) as described previously [37].

### Statistical analysis

We used SPSS version 26. Initially, a descriptive analysis for demographic, clinical and volumetric data in SSD-P and SSD-nonP patients (Table 1) was performed. Then, homogeneity of variance for each subcortical region and SAS scores in both patient groups was evaluated and confirmed using Levene’s test.

Group differences: in a first step, one-way analysis of variance (ANOVA), based on the General Linear Model procedure as implemented in SPSS, was used to identify any significant differences between the means of the three study groups. In a second step, we performed a one-way ANCOVA using eTIV, OLZ and PANSS-P scores as covariates to identify any significant differences between SSD-P and SSD-nonP patients. Then, we performed a

| Variable                      | SSD-P (n = 35) | SSD-nonP (n = 64) | HC (n = 20) | F/χ²/t | df  | p     |
|------------------------------|----------------|-------------------|-------------|--------|-----|-------|
| Age (years)                  | 40.9 ± 11.2    | 40.7 ± 9.7        | 40.7 ± 13.6 | 0.002  | 2116| 0.99  |
| Sex (male/female)            | 19/16          | 32/32             | 9/11        | 0.44   | 2116| 0.79  |
| Education (years)            | 13.2 ± 2.9     | 13.2 ± 2.6        | 13.5 ± 1.8  | 0.06   | 2116| 0.93  |
| Duration of illness (years)  | 13.7 ± 12.4    | 10.6 ± 10.4       | –           | 1.30   | 97  | 0.19  |
| OLZ                          | 20.1 ± 11.3    | 17.2 ± 8.9        | 0.0 ± 0.0   | 1.69   | 97  | 0.17  |
| Duration of illness (years)  | 13.7 ± 12.4    | 10.6 ± 10.4       | –           | 1.3    | 97  | 0.19  |
| PANSS-P score                | 13.4 ± 5.6     | 16.3 ± 7.6        | –           | 1.96   | 97  | 0.051 |
| PANSS-N score                | 17.3 ± 7.8     | 15.27 ± 7.1       | –           | 1.34   | 97  | 0.18  |
| PANSS-G score                | 32.3 ± 8.4     | 35.2 ± 11.4       | –           | 1.39   | 97  | 0.19  |
| PANSS-total score            | 62.9 ± 17.0    | 66.7 ± 22.0       | –           | 0.88   | 97  | 0.37  |
| GAF score                    | 68.6 ± 16.5    | 71.2 ± 16.9       | –           | 0.75   | 97  | 0.45  |
| CGI-S                        | 3.9 ± 1.0      | 3.9 ± 0.9         | –           | 0.16   | 97  | 0.86  |
| SAS hypokinesia              | 1.1 ± 0.7      | 0.4 ± 0.5         | –           | 5.72   | 97  | <0.0001|
| SAS rigidity                 | 2.6 ± 2.2      | 0.3 ± 0.5         | –           | 8.38   | 97  | <0.0001|
| SAS tremor                   | 0.9 ± 0.7      | 0.4 ± 0.5         | –           | 4.49   | 97  | <0.0001|
| SAS glabella-salivation      | 1.3 ± 0.9      | 0.5 ± 0.7         | –           | 4.92   | 97  | <0.0001|
| SAS total score              | 5.9 ± 2.2      | 1.5 ± 1.1         | –           | 13.43  | 97  | <0.0001|
| NCRS motor                   | 1.1 ± 1.5      | 0.6 ± 0.8         | –           | 2.30   | 97  | 0.024 |
| NCRS affective               | 1.8 ± 1.4      | 1.5 ± 1.9         | –           | 1.0    | 97  | 0.31  |
| NCRS behavioral              | 1.2 ± 1.5      | 0.7 ± 1.1         | –           | 1.88   | 97  | 0.062 |
| NCRS total score             | 4.1 ± 3.4      | 2.7 ± 3.0         | –           | 2.16   | 97  | 0.03  |
| eTIV                         | 1.47 ± 0.20 × 10^6 | 1.50 ± 0.20 × 10^6 | 1.51 ± 0.22 × 10^6 | 0.29 | 2116| 0.74 |

Data are mean ± standard deviation. Significant results (p < 0.05) are displayed in bold font. SSD schizophrenia spectrum disorders, SSD-P SSD patients with Parkinsonism, SSD-nonP SSD patients without Parkinsonism, HC healthy controls, OLZ mean daily dose of antipsychotics in olanzapine equivalents, PANSS Positive and Negative Syndrome Scale, as -total score, and -positive (P), -negative (N) and -general (G) subscale scores, BPRS Brief Psychiatric Rating Scale, GAF Global Assessment of Functioning, CGI-S Clinical Global Impression Scale for Schizophrenia, SAS Simpson and Angus Scale, with total and subscale scores, NCRS Northoff Catatonia Rating Scale, with total and subscale scores, eTIV estimated total intracranial volume (mm³)

a F, df, and p values were obtained using ANOVA

b χ², df and p values were obtained using the Chi-squared test

c t, df and p values were obtained using independent sample t tests (two-tailed)
one-way ANCOVA using eTIV and OLZ as covariates to determine whether there are any significant differences between SSD-P and SSD-nonP patients and HC.

Structure-symptom associations: in a third step, partial correlations (Pearson coefficient, two-tailed) using age, sex, OLZ, eTIV, and PANSS-N scores as covariates were run to determine the relationships between medulla oblongata and putamen volumes and SAS scores in the whole sample of SSD patients (n = 99). A nominal significance threshold of p ≤ 0.05 was defined. Finally, out of concern that some parkinsonian features might be misinterpreted as catatonic symptoms, thus inflating SAS scores, in a further step NCRS total scores were included as covariates in all structure-symptom analyses. To account for false-positive findings within identified between-group differences and structure-symptom associations, p-values were adjusted after each step using the false discovery rate (FDR; p ≤ 0.05) correction [38].

Results

Clinical, demographic and volumetric characteristics

Demographic and clinical characteristics of the three study groups are shown in Table 1. Of the 99 SSD patients analyzed, 35 (35.4%) were operationally defined as having parkinsonism (SSD-P, SAS total score ≥ 4) and compared with 64 (64.6%) who were operationally defined as not having parkinsonism (SSD-nonP, SAS total score < 4); SSD-P and SSD-nonP patients were well balanced (propensity matched) for age, sex, education and OLZ. In further between-group analyses, these 35 SSD-P patients and 64 SSD-nonP patients were each compared with the 20 HC that were similarly well matched for age, sex and education.

Group differences

First, on ANOVA there were significant overall differences between the three study groups in the medulla oblongata (F(2,116) = 4.53, p = 0.01), putamen (F(2,116) = 3.14, p = 0.04).

Table 2 Brainstem and basal ganglia structural volumes in SSD patients with (SSD-P) and without (SSD-nonP) parkinsonism and healthy controls (HC)

| Structure         | SSD-P (n=35) | SSD-nonP (n=64) | HC (n=20) | p values for ANOVA and LSD tests | p values for ANCOVA |
|-------------------|--------------|----------------|-----------|---------------------------------|---------------------|
|                   |              |                |           |                                 | SSD-P vs. SSD-nonP | SSD-P vs. HC | SSD-nonP vs. HC |
| Medulla oblongata | 4476 ± 512   | 4764 ± 541     | 4821 ± 325| ANOVA: **0.01** | 0.01* | **0.04** | 0.61 |
|                   |              |                |           | LSD: SSD-P < SSD-nonP **0.007** |         |         |       |
|                   |              |                |           | SSD-P < HC **0.01**; SSD-nonP vs. HC 0.65 | | | |
| Pons              | 14,329 ± 1888| 14,897 ± 1752  | 15,150 ± 1320| 0.17 | – | – | – |
| SCP               | 261 ± 54     | 277 ± 59       | 295 ± 52  | 0.08 | – | – | – |
| Midbrain          | 5762 ± 558   | 6006 ± 508     | 6003 ± 509| 0.07 | – | – | – |
| Whole brainstem   | 24,829 ± 2792| 25,945 ± 2662  | 26,270 ± 2028| 0.07 | – | – | – |
| Caudate           | 3432 ± 437   | 3638 ± 465     | 3541 ± 458| 0.10 | – | – | – |
| Putamen           | 4802 ± 571   | 5056 ± 522     | 4754 ± 558| ANOVA: **0.02** | **0.02** | 0.94 | 0.72 |
|                   |              |                |           | LSD: SSD-P < SSD-nonP **0.02**; SSD-P vs. HC 0.75; SSD-nonP > HC 0.03 | | | |
| Thalamus          | 6813 ± 756   | 7066 ± 775     | 7353 ± 827| ANOVA: **0.04** | 0.14 | **0.02** | 0.58 |
|                   |              |                |           | LSD: SSD-P vs. SSD-nonP 0.12; SSD-P < HC **0.01**; SSD-nonP vs. HC 0.15 | | | |

Data are mean ± standard deviation (mm³). Significant differences (p < 0.05) in means between all three groups using one-way ANOVA are indicated in bold. Significant differences (p < 0.05) in means between two groups using ANCOVA are indicated in bold.

LSD Fisher’s least significant difference test, SCP superior cerebellar peduncle, eTIV estimated total intracranial volume

F and p values are for ANCOVA with OLZ, eTIV and PANSS-P score as covariates (see Table 1)

F and p values are for ANCOVA with OLZ and eTIV as covariates (see Table 1). ANCOVA were followed by Benjamini & Hochberg correction for false discovery rate [38] to test the differences among groups. Values surviving Benjamini & Hochberg correction are indicated by an asterisk (*)

Mean of bilateral values
and thalamic ($F_{(2,116)} = 3.77, p = 0.02$) volumes (Table 2). There were no significant overall group differences in the midbrain, SCP, pons, whole brainstem or caudate nucleus ($p > 0.05$) volumes. Least significant difference (LSD) post hoc tests were then applied for individual group comparisons. In medulla oblongata (Fig. 1), volume in SSD-nonP patients did not differ from HC, while volume in SSD-P patients was decreased relative to HC ($p = 0.01$); volume in SSD-P patients was reduced relative to SSD-nonP patients ($p = 0.007$). In putamen (Fig. 2), volume in SSD-nonP patients was increased relative to HC ($p = 0.03$), while volume in SSD-P patients did not differ from HC; volume in SSD-P patients was decreased relative to SSD-nonP patients ($p = 0.02$). In thalamus (Fig. 3), volume in SSD-P patients was decreased relative to HC ($p = 0.01$), while volume in SSD-nonP was intermediate and differed from neither SSD-P nor HC.

Second, on ANCOVA (Table 2), there were significant differences (1) between SSD-P and SSD-nonP patients in medulla oblongata ($p = 0.01$) and putamen ($p = 0.02$) volumes, and (2) between SSD-P patients and HC in medulla oblongata ($p = 0.04$) and thalamic ($p = 0.02$) volumes, while these volumes did not differ between SSD-nonP patients and HC.

**Structure-symptom associations**

Higher SAS total and SAS glabella-salivation scores were each negatively associated with medulla oblongata volume ($r = -0.219$, $p = 0.034$ and $r = -0.277$, $p = 0.007$, respectively) and thalamic volume ($r = -0.220$, $p = 0.033$ and $r = -0.274$, $p = 0.007$, respectively); only the associations between SAS glabella-salivation scores and medulla oblongata and thalamic volumes survived FDR correction ($p < 0.05$). Finally, using NCRS total scores as a covariate, higher SAS total scores were negatively associated with medulla oblongata volumes ($r = -0.212$, $p = 0.041$) and SAS glabella-salivation scores were negatively associated with medulla oblongata volumes ($r = -0.267$, $p = 0.009$) and thalamic volumes ($r = -0.259$, $p = 0.012$); only the association between SAS glabella-salivation scores and medulla

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**Fig. 1** Scatter plot showing medulla oblongata volumes in SSD patients with (SSD-P, $n = 35$) and without (SSD-nonP, $n = 64$) parkinsonism and healthy controls (HC, $n = 20$). Significant between-group differences are designated with one asterisk ($p < 0.05$) or two asterisks ($p < 0.01$); ns not significant

**Fig. 2** Scatter plot showing putamen mean volumes in SSD patients with (SSD-P, $n = 35$) and without (SSD-nonP, $n = 64$) parkinsonism and healthy controls (HC, $n = 20$). Significant between-group differences are designated with one asterisk ($p < 0.05$); ns not significant
oblongata and thalamic volumes survived FDR correction \((p \leq 0.05)\).

**Discussion**

Using subcortical segmentation tools implemented in FreeSurfer v6.0, we investigated structural differences in brainstem structures, caudate nucleus, putamen and thalamus between SSD patients with and without parkinsonism in comparison with healthy controls. Three main findings emerged: firstly, SSD-P patients showed a reduced volume of the medulla oblongata and putamen compared to SSD-nonP and HC; secondly, SSD-P patients did not show the increase in volume of the putamen that was evident in SSD-nonP patients compared to HC; thirdly, SAS glabellasalivation scores were associated negatively with medulla oblongata and thalamic volumes in the whole SSD sample.

**Group differences**

To our knowledge, this is the first MRI study that specifically aimed to compare volumes of subcortical sensorimotor brain regions in SSD patients with and without parkinsonism and HC. In line with our hypothesis, SSD-P patients showed reduced volumes of the medulla oblongata and putamen compared to SSD-nonP patients. These findings are important for better understanding the pathogenesis of parkinsonism for several reasons:

First, the medulla oblongata is the lowest part of the brainstem and contains multiple nuclei (e.g., nucleus ambiguus, the dorsal vagal motor nucleus and the raphe nucleus) and tracts that connect the spinal cord with the forebrain. In particular, the medulla oblongata contains the inferior olivary nuclei, the pyramidal decussation of the motor pathways, and the spinothalamic tract [39]. The inferior olivary nuclei are responsible for proprioception, muscle tension and motor intention [39]. These nuclei are also closely connected to the cerebellum. The medulla oblongata is a location where the majority of motor pathways from the cortex decussate to form the corticospinal tract (CST). In addition to the CST, the medulla oblongata includes the spinothalamic tract and serves as a switch point between motor pathways from the cortex, thalamus, cerebellum, and spinal cord. In line with this functionality, atrophy of the brainstem and medulla oblongata [40] are associated with neurological disorders characterized by parkinsonian symptoms [41].

More recently, Fritze and colleagues [42] found that medulla oblongata volumes are associated significantly with motor coordination abilities in SSD. Taken together, structural abnormalities of the medulla oblongata can result in aberrant signal transmission between sensorimotor regions that lead to the development of sensorimotor abnormalities, and the present findings extend this to parkinsonism in SSD. Patients with SSD show an overall decrease in volume of the medulla oblongata, which is subject to broad genetic regulation [43] in a manner that may differ between SSD-P and SSD-nonP patients.

Second, SSD-P patients did not show the increase in putamen volume that was evident in SSD-nonP patients relative to HC. The putamen, together with the caudate nucleus, is now considered to play a critical role in the pathobiology of SSD [44] in addition to its classical role in sensorimotor abnormalities; it is interconnected with the primary motor cortex and the supplementary motor area and hence has a fundamental role in motor...
control. Previous reports have indicated that overall increases in the volume of the putamen in SSD patients involve a trophic effect of treatment with antipsychotic drugs at a site rich in D2 dopamine receptors, which are the primary targets for antipsychotics. Therefore, such a trophic effect of antipsychotic treatment may contribute to the increase in putamen volume found in SSD-nonP patients, perhaps as a compensatory mechanism to overcome impaired sensorimotor functioning intrinsic to the disease process of SSD. In contrast, the absence of an increase in putamen volume in SSD-P patients may reflect a reduced capacity to invoke such a response to antipsychotic treatment, which is reflected in the overt sensorimotor dysfunction of parkinsonism. Increase in putamen volume appears to be under specific genetic regulation in a manner that is weakened in SSD and may differ between SSD-P and SSD-nonP patients.

Third, SSD patients showed a graded decrease in thalamic volume (SSD-P < SSD-nonP < HC). The thalamus is an important component in cortical-striatal-thalamocortical networks that have fundamental roles in the sensorimotor function and movement disorder and the volumes of several thalamic nuclei are known to be decreased in SSD. Decrease in thalamic volume is associated with polygenic risk for SSD, which may vary between SSD-P and SSD-nonP patients.

Structure-symptom relationships

The SAS glabella-salivation scores were negatively associated with medulla oblongata and thalamic volumes. Interestingly, glabellar tap is a frontal release sign, which can be detected early after birth but disappears in the process of further brain development. Consequently, the origin of the glabellar tap sign, like other frontal release signs associated with movement disorder in SSD, may be ascribed not to antipsychotic treatment effects but, rather, to frontal lobe dysfunction intrinsic to the underlying disease process. In the present study, the negative association between glabellar tap scores and medulla oblongata and thalamic volumes suggests a disturbance of bottom-up modulation via subcortical-extrapyramidal circuits leading to disinhibition of cortical sensorimotor regions (as reflected by frontal release signs), particularly on taking into account thalamic function as a ‘gatekeeper’.

Salivation is under M<sub>3</sub>- and M<sub>4</sub>-mediated cholinergic control and the antipsychotic clozapine is associated with hypersalivation, while other antipsychotic drugs are more prone to anticholinergic side effects such as dry mouth. Hypersalivation in SSD-P can be due to increased production or decreased swallowing, the latter possibly due to bradykinesia or clozapine-associated decrease in laryngeal peristalsis. However, the influence of clozapine on the salivation item of the SAS in our sample seems rather limited when taking into account that only 19 of 99 patients (19%) received clozapine treatment.

Limitations

Despite the advantages of the study (sample size, systematic comparisons between HC, SSD-nonP and SSD-P patients), there are some limitations: first, the cross-sectional design does not allow conclusions about the stability or dynamics of the findings over time, as both parkinsonian symptoms and subcortical structure and function may vary over the course of illness. Second, our study included SSD patients receiving antipsychotic medication. Although antipsychotic drugs might still be considered as potentially influencing sensorimotor assessment, the contribution of spontaneous sensorimotor abnormalities intrinsic to the disease process of SSD and the effects of such treatment to exacerbate such intrinsic abnormalities (rather than ‘cause’ them de novo) are increasingly recognized. Though it might be argued that there is no way to reliably differentiate spontaneous and drug-induced parkinsonian symptoms in patients receiving antipsychotic medication, this appears to be a false dichotomy given that the latter appear to be an antipsychotic-induced exacerbation of the former within unitary network dysfunction. Furthermore, SSD and parkinsonian movement disorder share genetic risk factors and thus appear to involve overlapping pathobiologies. To clarify these issues would require longitudinal instrumental and momentary ecological assessments in both antipsychotic-naïve and treated SSD patients, including periods both on- and off-medication.

Conclusion

These relationships between parkinsonism in SSD and volumes of the medulla oblongata, putamen and thalamus should not be considered independently. As the medulla oblongata enjoys functionally important efferent and afferent connectivity with the thalamus and putamen as well as the cortex, it interacts closely across several components in the cortical-striatal-thalamocortical networks that have been implicated in the pathobiology of parkinsonian movement disorder. These three brain structures involved in dopaminergically based motor circuits appear to play an important, integrative role in the pathobiology of parkinsonism in SSD.
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Author contributions DH and RCW designed the study. DH, RCW and HT obtained funding. DH, SF, LG, AH and HT recruited, assessed, and scanned subjects. DH preprocessed MRI data. DH and SF performed the statistical analysis. RCW, MMS and KMK supervised analyses. DH, SF and RCW wrote the first draft of the manuscript. J LW, KMK, MO and AML interpreted and critically discussed the results. All authors contributed to and approved the manuscript.

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Data availability All original data are on record and accessible to inspection, but are not available publicly based on local and national data protection regulations.

Code availability All software used in the analyses is based on publicly available code.

Declarations Conflict of interest The authors have declared that there are no conflicts of interest in relation to the subject of this study.

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