

A Neural Signature of Parkinsonism in Patients With Schizophrenia Spectrum Disorders: A Multimodal MRI Study Using Parallel ICA

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Motor abnormalities in schizophrenia spectrum disorders (SSD) have increasingly attracted scientific interest in the past years. However, the neural mechanisms underlying parkinsonism in SSD are unclear. The present multimodal magnetic resonance imaging (MRI) study examined SSD patients with and without parkinsonism, as defined by a Simpson and Angus Scale (SAS) total score of ≥ 4 (SAS group, $n = 22$) or < 4 (non-SAS group, $n = 22$). Parallel independent component analysis (p-ICA) was used to examine the covarying components among gray matter volume maps computed from structural MRI (sMRI) and fractional amplitude of low-frequency fluctuations (fALFF) maps computed from resting-state functional MRI (rs-fMRI) patient data. We found a significant correlation ($P = .020$, false discovery rate [FDR] corrected) between an sMRI component and an rs-fMRI component, which also significantly differed between the SAS and non-SAS group ($P = .042$, $z = -2.04$). The rs-fMRI component comprised the cortical sensorimotor network, and the sMRI component included predominantly a frontothalamic/cerebellar network. Across the patient sample, correlations adjusted for the Positive and Negative Syndrome Scale (PANSS) total scores showed a significant relationship between tremor score and loadings of the cortical sensorimotor network, as well as between glabella-salivation score, frontothalamic/cerebellar and cortical sensorimotor network loadings. These data provide novel insights into neural mechanisms of parkinsonism in SSD. Aberrant bottom-up modulation of cortical motor regions may account for these specific motor symptoms, at least in patients with SSD.

Key words: schizophrenia/parkinsonism/MRI/motor abnormalities

Introduction

Over the last 2 decades, research on motor abnormalities in schizophrenia spectrum disorders (SSD) has witnessed a renaissance, with the majority of neuroimaging studies investigating neurological soft signs (NSS), tardive dyskinesia (TD), and catatonia.¹⁻⁷ In addition to these phenomena, a substantial proportion of both antipsychotic-naïve (median prevalence of 17%) and antipsychotic-treated (prevalence varies from 15% to 30%) SSD patients, independent of medication effects, experience parkinsonism, characterized by rigidity, tremor, bradykinesia, and occasionally positive glabellar tap sign or increased salivation.^{8,9} Using a cutoff of ≥ 4 on the total Simpson and Angus Scale (SAS),¹⁰ recent studies established a clinically meaningful and scientifically relevant distinction between SSD patients with and without parkinsonism.^{8,9,11} However, the neuroimaging evidence on parkinsonism is scarce.¹²

In this study, we employed 2 distinct neuroimaging modalities to specifically investigate function-structure interrelationships which are related to parkinsonism.^{3,13} Thus, in addition to gray matter volume (GMV), we incorporated resting-state functional magnetic resonance imaging (rs-fMRI) and particularly the fractional amplitude of low-frequency fluctuations (fALFF), as fALFF captures the relative magnitude of blood-oxygenation-level-dependent (BOLD) signal changes on intrinsic

neural activity (INA) in specific brain regions. While previous studies have already shown that INA is abnormal in catatonia,^{14,15} we expected that the study of SSD patients with and without parkinsonism would provide further insight into an abnormal local function within selective networks responsible for motor excitation/inhibition and psychomotor organization.¹⁶

This study had 2 major objectives: First, conducting a categorical approach, we predicted a difference in both modality-specific (ie, GMV or INA) and transmodal (ie, GMV and INA) systems comprising frontoparietal and frontostriatal networks between SSD patients with and without parkinsonism. Second, acknowledging the dimensional nature of motor symptoms in SSD,⁴ we expected that distinct dimensions of parkinsonism—ie, hypokinesia, tremor, rigor, glabella/salivation—will be significantly associated with abnormal brain structure and function that can be revealed by transmodal components in distinct cortico-subcortical networks, as involved in motor excitation/inhibition and psychomotor organization and speed.

Methods

Participants

We examined a total of 87 right-handed¹⁷ patients meeting Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition-Text Revision (DSM-IV-TR)¹⁸ criteria for schizophrenia ($n = 84$) and schizoaffective disorder ($n = 3$).^{1,3} The inclusion and exclusion criteria are listed in the [Supplementary Material](#). The local Ethics Committee (Medical Faculty at Heidelberg University, Germany) approved the study. Written informed consent was obtained from all SSD patients after all aims and procedures of the study had been fully explained.

Clinical Assessment

All patients were recruited and examined within 1 week after partial remission of psychotic symptoms. The duration between psychometric testing, motor assessment, and MRI examination was less than 3 days. At the time of examination, none of the SSD patients had taken benzodiazepines or anticholinergic medication, and all patients were on a stable antipsychotic medication for at least 2 weeks (for details on antipsychotic medication see [Supplementary Material](#)). Daily doses of antipsychotic medication were converted to olanzapine (OLZ) equivalents, according to the classical mean dose method.¹⁹ For a detailed assessment of parkinsonism, we used the SAS¹⁰ (for details on SAS domains, see [Supplementary Material](#)). The SAS criteria, according to Cuesta and colleagues,⁸ were used to identify a clear cutoff to distinguish subjects with (SAS total score ≥ 4) and without (SAS < 4) parkinsonism (SAS and non-SAS group). We excluded 43 SSD individuals from the original patient group ($87 - 43 = 44$) to introduce 2 well-balanced (in terms

of age, gender, education, and OLZ) groups of SSD patients with ($n = 22$) and without ($n = 22$) parkinsonism (categorical approach) ([table 1](#)). The patient groups were carefully matched with respect to gender and education because (1) previous gender-specific studies on motor symptoms in SSD showed contradictory results, (2) patients with higher education can recruit alternative brain networks to compensate for aberrant motor functioning, (3) educational status might influence motor performance in Parkinson's disease (PD), and (4) education-associated brain structure and function are more resilient to illness-related abnormalities, respectively.²⁰⁻²³ In the next step, we followed a correlative approach, assuming dimensional symptom expression as well as a neurobiological continuum in SSD patients with various degrees of parkinsonism ($n = 44$).²⁴

MRI Data Acquisition

MRI scans were acquired at the Central Institute of Mental Health, Mannheim, Germany on a 3.0 Tesla Magnetom TIM Trio MR scanner (Siemens Medical Systems) equipped with a 32-channel multi-array head-coil. Technical details on MRI sequences are provided as supplementary information.

MRI Data Analysis

Data Preprocessing. Voxel-based morphometry (VBM) of T1-weighted sMRI images was employed using CAT12 (<http://dbm.neuro.uni-jena.de/cat/>), which is an extension to SPM12 (<http://www.fil.ion.ucl.ac.uk/spm/>). The process included (a) segmentation of images into gray matter, white matter, and cerebrospinal fluid; (b) normalization using the DARTEL approach²⁵; and (c) smoothing the gray matter probability values using an 8-mm full-width half-maximum (FWHM) isotropic Gaussian kernel. The fALFF method was applied to rs-fMRI images using the Data Processing Assistant for rs-fMRI (DPARSF)²⁶ (for details on the pipeline, see [Supplementary Material](#)).

MRI Data Fusion. Parallel ICA^{27,28} on sMRI and rs-fMRI data was applied using the Fusion ICA Toolbox (FIT; <http://mialab.mrn.org/software/fit>) in MATLAB 9.0.0 (R2016a). The number of components for each modality was estimated using both the minimum description length (MDL) and the Akaike information criterion (AIC), as described by Calhoun and colleagues.²⁹ Four components were identified for each modality. ICASSO³⁰ was run 100 times to assess the consistency of the components, and the most central run was selected to ensure replicability and stability. For component visualization, the source matrix was converted back to a 3D image, scaled to unit standard deviations (z), and thresholded at $|z| > 2$. Maps from the 2 components described in results section were overlaid onto a Montreal Neurological Institute (MNI) normalized anatomical template.

Anatomical denominations and stereotaxic coordinates were derived from clusters above a threshold of $z = 3.5$ by linking the ICA output images (ie, the chosen components of interest) to the Talairach Daemon database (<http://www.talairach.org/daemon.html>).

Statistical Analyses. The procedure was similar to that described by Meda and colleagues³¹. First, Pearson's correlations (2-tailed) were used to explore the relationships between the loading coefficients of sMRI and rs-fMRI independent components (ICs). Significant correlations between sMRI and rs-fMRI ICs were further investigated by comparing the correlation coefficients of each IC across groups. The resulting correlation values were compared using Fisher's z -transformation to reveal significant differences between matched SAS and non-SAS groups. Between-group analyses were adjusted for the Positive and Negative Syndrome Scale (PANSS) total scores. Second, 2-tailed Pearson's correlation was used to investigate the relationship between SAS scores and the loading coefficients which showed significant between-group differences. Third, SAS scores of SSD patients ($n = 44$) and their sMRI and rs-fMRI loading coefficients were each computed using partial Pearson's correlation, 2-tailed, again adjusted for PANSS total score. Finally, the abovementioned data analyses, we rerun on the whole sample ($n = 85$) of SSD patients with and without parkinsonism using similar parameters (see [Supplementary Material](#) for details and results). As nominal significance threshold, a P -value $< .05$ was chosen, followed by correction for multiple comparisons using the false discovery rate (FDR).

To examine the relationship between parkinsonism and catatonia in the whole sample ($n = 44$) and the SAS group ($n = 22$), we run a partial correlation (2-tailed) between an individual's SAS and Northoff Catatonia Rating Scale (NCRS) total scores, while controlling for age, gender, OLZ, and PANSS-N score. Further, we run a partial correlation (2-tailed) between an individual's SAS total and PANSS-N scores, while controlling for age, gender, OLZ, and NCRS total score to determine the relationship between parkinsonism and negative symptoms in the whole sample ($n = 44$) and SAS group ($n = 22$). A nominal significance threshold of $P < .05$ was defined, followed by Bonferroni correction for multiple comparisons (corrected $P = .01$). Finally, we also included an additional analysis comparing SSD patients (SAS and non-SAS groups) and 22 healthy controls (HC) matched for age (mean = 39.81 y; SD = 11.79; $F_{(2, 63)} = 0.12$; $P = .88$), gender (14 males, 8 females), education (mean = 14.48 y; SD = 1.28; $F_{(2, 63)} = 0.98$; $P = .38$), and handedness (see [Supplementary Material](#) for details and results).

Results

Results showed significant correlations between 5 sMRI and rs-fMRI IC pairs ([table 2](#)). These significant IC pairs

were examined group-wise ([supplementary table 1](#)), and their correlation coefficients were compared using Fisher's z transformation. A significant difference was observed in 1 structural and 1 functional IC, $P = .042$, $z = -2.04$ ([figures 1](#) and [2](#)). The sMRI component predominantly comprised the middle frontal gyrus (MFG), inferior frontal gyrus (IFG), anterior cingulate gyrus, thalamus, precentral gyrus, and the cerebellar structures (tonsil, uvula, tuber, and culmen) ([supplementary table 2](#)), correspondingly labeled as frontothalamic/cerebellar network. The rs-fMRI component predominantly comprised the lingual gyrus and the cuneus ([supplementary table 4](#)), correspondingly labeled as the cortical sensorimotor network. For other 4 IC pairs, no significant difference was observed, all P -values $> .25$, all z -scores < -1.14 (see [supplementary figure 1](#), [supplementary tables 1](#) and [5](#)). Furthermore, we reanalyzed the ICs' mixing coefficients, while adjusting for the PANSS negative score to control for the influence of negative symptoms. A significant difference was still observed between the frontothalamic/cerebellar network and the cortical sensorimotor network, $P = .045$, $z = -2.01$.

Subsequently, the frontothalamic/cerebellar network showed a significant correlation with the glabella-salivation score, $P < .001$ ([figure 3](#) and [table 3](#)). The cortical sensorimotor network showed significant correlations with the tremor score, $P = .035$, and the glabella-salivation score, $P = .020$ ([figure 3](#) and [table 3](#)). We found no significant association between SAS scores and OLZ equivalents in the study sample ([supplementary table 8](#)).

In the combined sample of SSD patients with and without parkinsonism ($n = 44$), we found no significant association between SAS and NCRS total scores ($r = .108$, $P = .506$). In SSD patients with parkinsonism ($n = 22$), there was no significant association between SAS and NCRS total scores ($r = -.006$, $P = .98$). In the combined sample of SSD patients with and without parkinsonism ($n = 44$), we found no significant association between SAS total and PANSS-N scores ($r = .219$, $P = .176$). In SSD patients with parkinsonism ($n = 22$), there was no significant association between SAS total and PANSS-N scores ($r = -.067$, $P = .791$).

Discussion

This is the first multimodal MRI study that aimed at studying the associations between brain structure and resting-state neural activity in SSD patients with and without parkinsonism. Four main findings emerged: First, correlational coefficients of interrelated frontothalamic/cerebellar sMRI component and a cortical sensorimotor rs-fMRI component differed significantly between SAS and non-SAS groups. Second, the tremor score was associated with the loadings of the cortical sensorimotor rs-fMRI component. Third, the glabella-salivation score was associated with loadings of the frontothalamic/

Table 1. Demographics and Clinical Scores for Schizophrenia Spectrum Disorders Patients Divided Into SAS and SAS Groups

| Variable | non-SAS (<i>n</i> = 22)mean ± SD | SAS (<i>n</i> = 22)mean ± SD | <i>t</i> ^a | <i>df</i> | Significance |
|---------------------------|-----------------------------------|-------------------------------|-----------------------|-----------|--------------|
| Age | 38.64 ± 12.96 | 40.41 ± 11.38 | -0.482 | 42 | .632 |
| Gender (m/f) ^b | 14/8 | 14/8 | | 1 | 1 |
| Education (y) | 13.64 ± 2.80 | 13.36 ± 3.63 | 0.279 | 42 | .782 |
| Olanzapine equivalents | 15.81 ± 10.34 | 19.17 ± 9.56 | -1.118 | 42 | .27 |
| Duration of illness (y) | 11.36 ± 11.37 | 15.50 ± 10.87 | -1.233 | 42 | .224 |
| PANSS | | | | | |
| Positive | 14.22 ± 5.96 | 14.27 ± 6.42 | -0.024 | 42 | .981 |
| Negative | 15.00 ± 6.28 | 18.41 ± 7.82 | -1.594 | 42 | .118 |
| Global | 30.68 ± 6.45 | 35.09 ± 7.71 | -2.056 | 42 | .046* |
| Total | 59.91 ± 14.23 | 67.77 ± 15.51 | -1.752 | 42 | .087 |
| SAS | | | | | |
| Hypokinesia | 0.32 ± 0.48 | 0.91 ± 0.29 | -4.947 | 42 | <.001* |
| Rigidity | 0.14 ± 0.47 | 2.60 ± 2.42 | -4.665 | 42 | <.001* |
| Tremor | 0.36 ± 0.49 | 0.82 ± 0.79 | -2.28 | 42 | .028* |
| Glabella-salivation | 0.45 ± 0.21 | 1.22 ± 0.97 | -5.567 | 42 | <.001* |
| Total | 0.77 ± 0.81 | 5.50 ± 2.17 | -9.543 | 42 | <.0001* |
| NCRS | | | | | |
| Motor | 0.27 ± 0.55 | 1.27 ± 1.60 | -2.758 | 42 | .009* |
| Affective | 1.68 ± 1.91 | 1.73 ± 1.51 | -0.087 | 42 | .931 |
| Behavioral | 0.32 ± 0.71 | 1.00 ± 1.34 | -2.098 | 42 | .042* |
| Total | 2.14 ± 2.39 | 3.91 ± 3.55 | -1.938 | 42 | .059 |
| AIMS | | | | | |
| Total | 0.86 ± 2.33 | 1.91 ± 3.66 | -1.129 | 42 | .265 |

Note: SD, standard deviation; *df*, degrees of freedom; PANSS, The Positive and Negative Syndrome Scale; SAS, Simpson and Angus Scale; NCRS, Northoff Catatonia Rating Scale; AIMS, Abnormal involuntary movement scale.

^aThe *t* values were obtained using a 2-tailed independent samples *t*-test.

^bThe *P*-values for distribution of gender were obtained by chi-square test. Statistically significant (*P* < .05) results are marked with an asterisk.

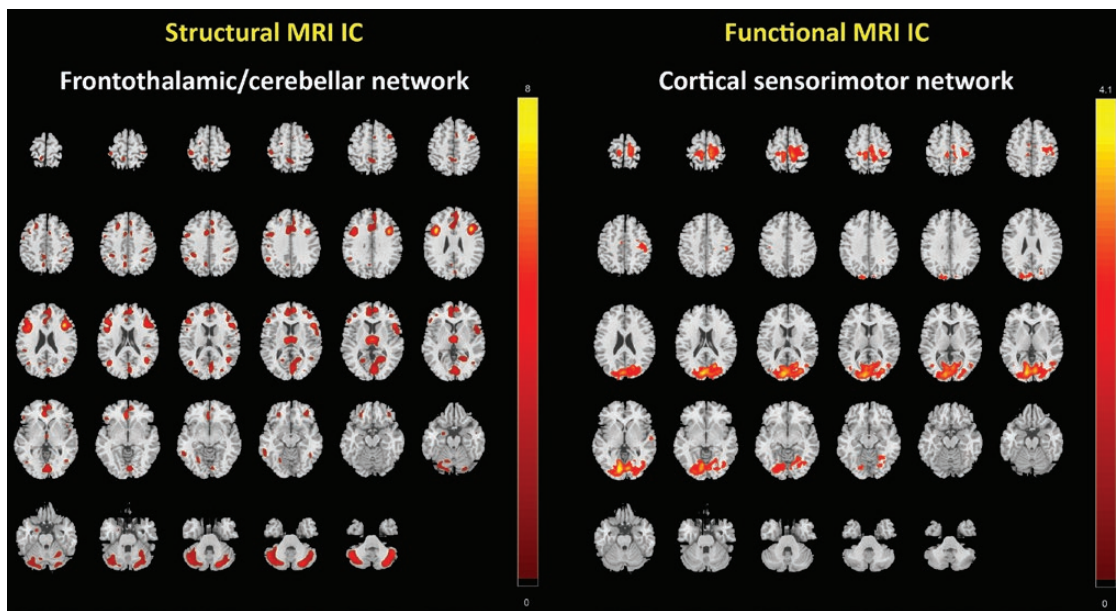


Fig. 1. Spatial patterns of structural magnetic resonance imaging (sMRI) and resting-state functional MRI (rs-fMRI) networks thresholded at *z* > 2 which showed significant differences between non-Simpson and Angus Scale (SAS) group and SAS group.

cerebellar sMRI and cortical sensorimotor rs-fMRI component. Fourth, an interrelated frontotemporal/cerebellar sMRI component and temporo-cerebellar rs-fMRI component differed between SAS and HC groups.

Group Differences

We detected frontothalamic/cerebellar and cortical sensorimotor networks that represent interrelated GMV-INA components that differ between SSD patients with

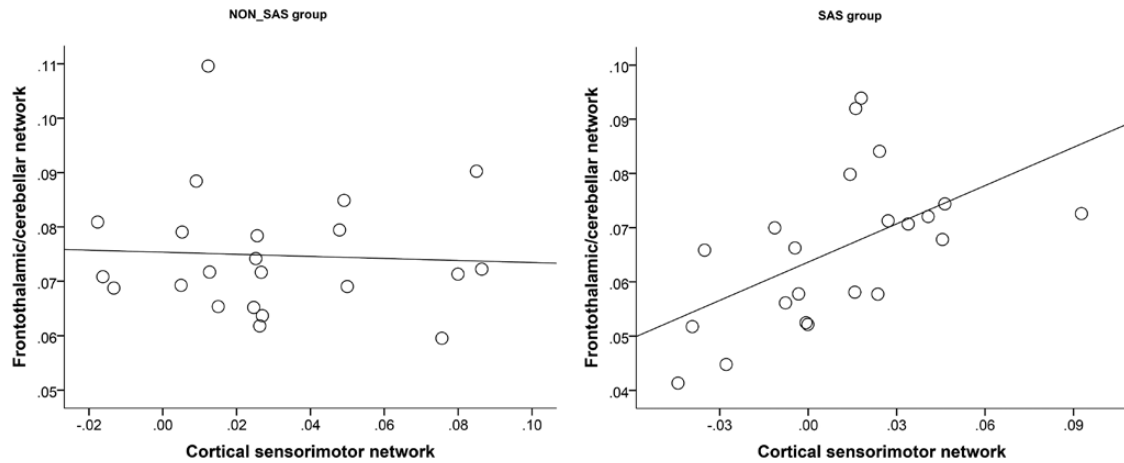


Fig. 2. Scatter plots showing the relationship between the structural frontothalamic/cerebellar network and the functional cortical sensorimotor network in (a) non-Simpson and Angus Scale (SAS) group ($n = 22$) and (b) SAS group ($n = 22$). Using Fisher's z transformation, a significant difference was observed between the correlation coefficients of 2 groups, $P = .042$, $z = -2.04$.

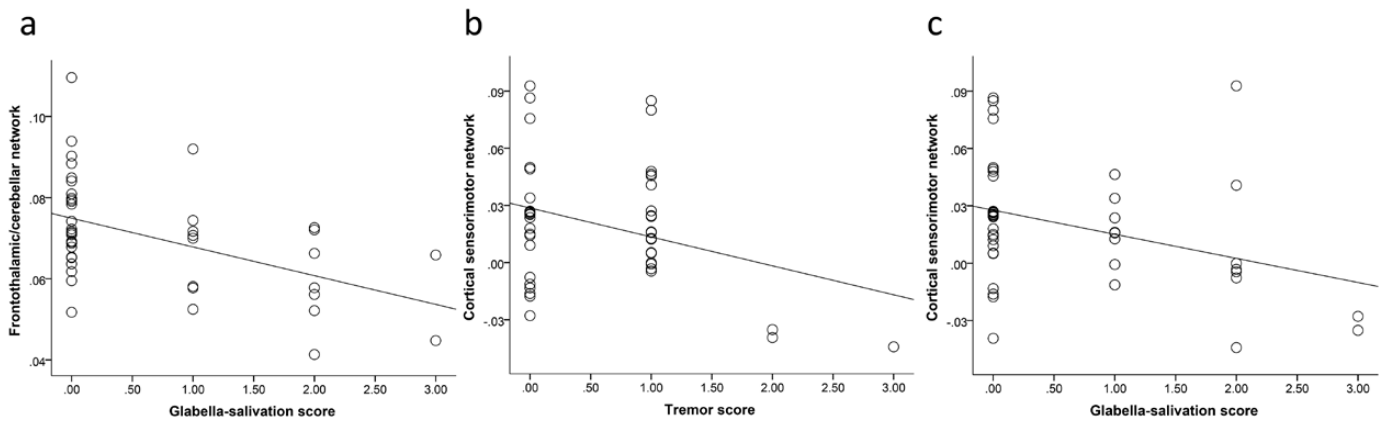


Fig. 3. Scatter plots showing the relationship between (a) frontothalamic/cerebellar resting-state network and glabella-salivation score, (b) cortical sensorimotor structural network and tremor score, and (c) cortical sensorimotor structural network and glabella-salivation score.

and without parkinsonism. Our findings are consistent with the prior suggestion of aberrant “bottom-up modulation” (alterations in the thalamocortical loop) between subcortical (basal ganglia and thalamic motor nuclei) and cortical/motor regions (premotor cortex and M1) in PD.^{7,32} Yet, unlike PD, we did not observe associations between distinctly “striatal” networks and parkinsonism. Nonetheless, our results are in line with previous MRI studies in SSD patients that showed a significant relationship between abnormal involuntary movements (mainly TD) and structural alterations of the frontal gyrus, temporal lobe, and pons, respectively.^{33–37} We essentially expand these studies by showing that SSD patients with significant GMV reduction in regions comprising the MFG and IFG, anterior cingulate cortex (ACC), and M1 as well as the thalamus and cerebellar structures tend to be those who exhibit parkinsonism. These results are important for 4 reasons: First, neurodegenerative conditions in the MFG and IFG, which are part of the

prefrontal cortex, might lead to aberrant response inhibition, motor planning and imagery, decision making, and disordered cognitive processing, particularly executive function, in SSD patients.³⁸ Second, structural alterations in ACC or other limbic structures can lead to aberrant ascending non-dopaminergic projections to cortical regions and hence, to the development of apathy, depression and psychomotor slowing, up to freezing of gait, ie, to characteristic symptoms of parkinsonism.^{39,40} Furthermore, the dorsal part of ACC⁴¹ modulates motor behavior by acting as a major interface between sensorimotor and cognitive networks.⁴² Third, with regard to the symptom triad in parkinsonism, the interaction between cognitive and motor regions in terms of the modulation of motor behavior by cognitive functioning is particularly relevant.^{42–44} Fourth, the cerebellum is crucial for adjustment of time and force of movements or muscle commands.^{44,45} Dysfunction of neuronal loops originating from cerebellar structures, which are modulated by thalamus

Table 2. Pearson's Correlation Between Structural and Functional magnetic resonance imaging (MRI) independent components (ICs) Mixing Coefficients for all Participants ($n = 44$)

| | Resting-State fMRI ICs | | | |
|-----------------------------------|-------------------------------|--------|--------|---------|
| | Cortical Sensorimotor Network | IC2 | IC3 | IC4 |
| Structural MRI ICs | | | | |
| IC1 | | | | |
| Correlation | -0.074 | -0.204 | 0.061 | 0.084 |
| Significance | 0.635 | 0.184 | 0.695 | 0.588 |
| IC2 | | | | |
| Correlation | 0.224 | 0.055 | 0.229 | 0.328* |
| Significance | 0.143 | 0.723 | 0.135 | 0.030 |
| Frontothalamic/cerebellar network | | | | |
| Correlation | 0.349* | 0.015 | 0.148 | 0.562** |
| Significance | 0.020 | 0.922 | 0.338 | <0.001 |
| IC4 | | | | |
| Correlation | 0.205 | 0.007 | 0.319* | 0.344* |
| Significance | 0.182 | 0.964 | 0.035 | 0.022 |

* $P < .05$; ** $P < .01$.

Table 3. Pearson's Correlation Between the Mixing Coefficients of Independent Components (ICs) for all Participants ($n = 44$) and the Simpson and Angus Scale (SAS) Scores

| | SAS Scores | | | |
|-----------------------------------|-------------|----------|--------|---------------------|
| | Hypokinesia | Rigidity | Tremor | Glabella-salivation |
| Frontothalamic/cerebellar network | | | | |
| Correlation | -.139 | -.173 | -.220 | -.487** |
| Significance | .367 | .262 | .151 | .001 |
| Cortical sensorimotor network | | | | |
| Correlation | -.266 | -.222 | -.319* | -.351* |
| Significance | .081 | .147 | .035 | .020 |

* $P < .05$; ** $P < .01$.

nuclei, might give rise to deficits in the smooth control and online updating of bodily movements leading to ataxia and tremor.⁴⁴⁻⁴⁸ Such motor disorders have already been found in SSD patients and persons with psychosis risk syndrome.⁴⁶⁻⁴⁸ Our results are also in line with Walther and colleagues,⁴⁹ who showed a significant correlation between daily activity level (eg, hypokinesia) and baseline perfusion in the cingulate motor area, right M1, and bilateral dorsolateral prefrontal cortex.

Our results are relevant because the abovementioned GMV network changes are closely associated with aberrant INA in the cortical sensorimotor rs-fMRI component. Structural changes of the thalamic nuclei and the cerebellum might contribute to disturbed bottom-up projections into cortical regions such as the lingual gyrus and the cuneus. A recent MRI study found reduced volume in

the cuneus and lingual gyrus in patients with TD.⁵⁰ The authors suggested that structural alterations of visual and frontoparietal regions are characteristic for schizophrenia.^{50,51} The involvement of occipital regions might be related to aberrant modulation of visual stimuli, which can lead to disordered spatial motor coordination. SSD patients might not be able to use their movements purposefully and have serious problems when moving their body in space leading to stiff or even stooped shuffling gait and bumpy movements.

Finally, our results of aberrant interrelated fronto-temporal/cerebellar sMRI component and temporo-cerebellar rs-fMRI component in SAS patients compared with HC revealed the cerebro-cerebellar dysfunction underlying parkinsonism in SSD patients. Specifically, aberrant network-level interaction between temporal and cerebellar regions might lead to disinhibition and disturbed bottom-up modulation of frontal regions and the development of parkinsonism in SSD. Because we found no difference between non-SAS and HC groups, our findings suggest interrelated structural and functional abnormalities, which define SSD patients with but not those without parkinsonism.

Structure/Function Interrelationship Underlying Parkinsonism

First, we found that the tremor score was associated with the loading score of the cortical sensorimotor rs-fMRI component. A possible explanation for this finding is that aberrant INA in the sensorimotor network (involving cuneus und lingual gyrus) leads to impaired visual-motor integration and finally contribute to the development of tremor in SSD patients.^{52,53}

Second, the glabella-salivation score was associated with the interrelated frontothalamic/cerebellar sMRI component and a cortical sensorimotor rs-fMRI component. Remarkably, the glabellar tap belongs to the frontal release signs (also known as primitive reflexes), which can be found early after birth but should disappear in the course of further brain development.⁵⁴ Therefore, the origin of glabellar sign may not be attributed to the antipsychotic effect, but to the underlying SSD itself. In SSD patients, frontal release signs might get disinhibited by alterations of the frontal lobe.⁵⁵ In this study, GMV alterations of the thalamus and cerebellum may have led to disturbed bottom-up modulation of cortical regions and reappearance of glabella tap reflex. Hypersalivation (or drooling) may be caused by increased saliva production and swallowing dysfunction (mainly due to bradykinesia of the oropharyngeal phase) in SSD and PD patients.⁵⁶ This finding has been shown in the studies of PD patients (especially during the "off" period).⁵⁷ On one side, saliva production is modulated by dopamine and can occur in the cases of hypodopaminergic states and/or clozapine treatment.⁵⁷ In the study sample, only 10 patients were receiving clozapine, which might have caused

sialorrhea. The other patients were receiving other antipsychotic drugs causing rather different anticholinergic effects (dry mouth, tachycardia, constipation, etc.). On the other side, the premotor cortex, M1, basal ganglia, pedunculopontine nuclei, and the cerebellum are involved in the oropharyngeal phase of swallowing.⁵³ Our data suggest that GMV alterations in frontothalamic/cerebellar and aberrant INA in the sensorimotor network might to some extent lead to swallowing dysfunction in SSD patients. Therefore, hypersalivation might be caused by disease-related autonomous reduction of spontaneous swallowing and not by antipsychotics. This said, the two symptoms are more likely to be disease-related phenomena of the autonomic nervous system.⁵⁸

To sum up, SSD can present with a variety of overlapping motor signs and symptoms. However, it is unclear whether they share the same, similar, or very different pathomechanism. Understanding the pathogenesis of different motor symptoms can support the development of new treatment strategies. In this regard, 2 recent multimodal fusion studies in SSD patients have shown distinct structure-/function associations with NSS¹³ and catatonia,³ respectively. Research into parkinsonism in SSD may also lead to the identification of regions with a specific receptor profile to develop effective medication against parkinsonism. The present study provides novel insights into complex co-altered neural patterns in fronto-thalamo-cingulate-cerebellar circuit underlying parkinsonism. In comparison to the identified regions underlying NSS and catatonia, parkinsonism is more likely related to aberrant “vertical” (bottom-up)⁷ modulation of cortico-subcortical motor circuits. Last but not least, our results are also in line with the widespread theory of PD that postulates a neurodegeneration of dopaminergic neurons in the substantia nigra pars compacta leading to a depletion of dopaminergic neurons in the striatum (posterior putamen) and further aberrant bottom-up modulation of cortical motor areas (M1, premotor area, and supplementary motor area [SMA]).⁵⁹⁻⁶² For instance, a recent MRI study conducted by Kübel and colleagues showed that limb kinetic apraxia is associated with an intrinsic disruption of the left SMA function in patients with PD.⁶³ Overall, these mechanisms contribute to cardinal motor abnormalities of PD such as rigidity and bradykinesia.⁵⁹⁻⁶²

Strengths and Limitations

The main strength of this study is the multimodal fusion analysis of rs-fMRI and sMRI data in a moderate sample of SSD patients with and without parkinsonism. However, this study is not without limitations. First, our study did not include antipsychotic-naïve SSD patients. Such patients do exhibit parkinsonism as well, as suggested by previous research,⁹ so that medication effects

cannot account for motor symptoms in these individuals. In the present sample, we did not find any significant correlation between current antipsychotic dosage and SAS total score in our sample ($P = .79$, $r = .04$). Our groups were balanced for OLZ, so that the different severity of parkinsonism between the groups is rather independent of medication. It is possible that neural mechanisms of parkinsonism may vary in antipsychotic-naïve persons, yet there are no robust data available suggesting that this may indeed be the case. Second, the present data do not necessarily imply a causal relationship between structural and functional alterations and the presence or absence of parkinsonism. Parkinsonism levels may vary over time, and given the lack of longitudinal data, it is unknown whether neural structure and function could vary along with such clinical changes. Third, we could not accurately record the entire history of antipsychotic medication in the present patient sample. Cumulative antipsychotic dosage is particularly important for the investigation of long-term effects, eg, TD, which usually develops after several months of antipsychotic treatment. Therefore, the current daily dosage may not be a reliable reflection of the lifelong cumulative effects of antipsychotics on sensorimotor networks. However, in this study, only 1 patient received first-generation antipsychotic and the vast majority of patients were treated with second-generation antipsychotics that are less frequently associated with acute extrapyramidal symptoms (EPS). Recent studies showed that the prevalence estimates of motor abnormalities associated with antipsychotic medications are not influenced by treatment duration.^{64,65} Nonetheless, future studies should consider the dimensional nature of motor behavior and dysfunction in SSD in order to differentiate between medication-induced and genuine motor symptoms.¹¹ Fourth, we acknowledge that there are different assessments of motor phenomena in neurological and psychiatric disorders (the St. Hans Rating Scale [HS],⁶⁶ the Drug-Induced Extrapyramidal Symptoms Scale [DIEPSS],⁶⁷ the Extrapyramidal Symptoms Rating Scale [ESRS],⁶⁸ the Schedule for the Assessment of Drug-Induced Movement Disorders [SADIMoD],⁶⁹ the Unified Parkinson's Disease Rating Scale [UPDRS],⁷⁰ and the Cambridge Neurological Inventory [CNI]⁷¹), and the SAS scale may potentially overestimate rigor because it provides a total of 6 items examining this specific symptom.^{8,9} However, Simpson and colleagues¹⁰ were able to show that all 10 items are better in separating specific patient groups (placebo vs 1 mg haloperidol) than the 6 rigidity items alone. We also acknowledge that the SAS was initially developed and validated to rate the severity of drug-induced parkinsonism. In this study, we specifically chose the SAS scale to assess spontaneous parkinsonism to facilitate comparisons with other studies that examined this condition, particularly in schizophrenia patients.^{8,9}

Future studies could benefit from wearable devices that could provide more objective measures of parkinsonism.^{71–73} Furthermore, all SSD patients with a total SAS score ≥ 4 in this study had abnormalities in more than 1 subdomain. Four patients showed dysfunction in 2 subdomains, 11 patients in 3 subdomains, and 7 patients in all subdomains. This distribution suggests that our sample included SSD patients that featured a relatively wide parkinsonism symptom spectrum. Finally, we are aware of the relatively high prevalence of tremor in this patient group. We screened all study participants for the presence of manifest medical conditions potentially affecting central nervous system function, as well as for manifest neurological disorders, including essential tremor. Nevertheless, we cannot fully rule out the possibility of comorbid neurological diseases in prodromal stages, especially disorders that could present with clinically subthreshold tremor.

Conclusion

This study provides novel neuromechanistic insights on parkinsonism in SSD, emphasizing the importance of interrelated structure/function-alterations in neural systems subserving distinct components of coordinated motor behavior. The observed multiple network-level effects reflect parkinsonism in SSD as a multidimensional clinical construct in which subcortical deficits, particularly in thalamus and cerebellum, could lead to alteration in bottom-up (“vertical”) modulation of sensorimotor cortical regions.

Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin* online.

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