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Brainstem alterations contribute to catatonia in schizophrenia spectrum disorders

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ABSTRACT

Catatonia is a severe psychomotor syndrome that frequently occurs in patients with schizophrenia spectrum disorders (SSD). Accumulating neuroimaging evidence suggests orbitofrontal, frontoparietal and cerebellar network dysfunction in catatonia. Very little is known about contributions of brainstem regions (as part of the dopaminergic-based subcortical-cortical motor circuit) to catatonia in SSD patients. Here, we used structural magnetic resonance imaging (MRI) at 3 T to examine volumes of brainstem regions in catatonic SSD patients compared to non-catatonic SSD patients. Catatonia severity was measured with the Northoff Catatonia Rating Scale (NCRS). The segmentation of the brainstem in order to investigate the volumes of medulla oblongata, pons, superior cerebellar pedunculus, and midbrain was carried out using FreeSurfer vers. 6.0. Catatonic patients (NCRS total score ≥ 3; at least 1 point in the three different symptom categories; i.e., motor, behavioral, and affective; n = 30) had significantly smaller midbrain volumes ($p = 0.004$, Bonferroni corr.) when compared to non-catatonic patients (NCRS total score = 0; n = 29). In catatonic patients, significant correlations were detected between NCRS motor scores and whole brainstem ($p = 0.015$, Bonferroni corr.) volumes. These results support a neuromechanistically important role of brainstem structures in catatonia in SSD, particularly in motor symptom expression.

1. Introduction

Catatonic syndrome occurs in 9–17% of patients with acute psychiatric disorders (Rasmussen et al., 2016). Among others, previous studies reported a prevalence of 7–15% of catatonia among schizophrenia spectrum disorders (SSD) patients (Kleinhaus et al., 2012; Solmi et al., 2018). From a clinical perspective, catatonic syndrome is characterized by motor, behavioral and affective symptoms assuming a direct interaction between motor and psychic function including their neurobiological mechanism (Northoff et al., 1999a).

Despite the fact that catatonia has been known for more than 140 years, the precise neural mechanisms underlying this condition remain unclear. The extant body of neuroimaging evidence suggests a biological model of catatonia that includes abnormalities of the medial and lateral orbitofrontal cortex (OFC), prefrontal cortex, supplementary motor area (SMA), primary motor cortex (M1), posterior parietal cortex, thalamus, and cerebellum, respectively (for systematic review see Walther et al. (2019), Hirjak et al. (2020a) and Haroche et al. (2020)). It is noteworthy though, that studies using motor/behavioral catatonia rating scales/criteria found both cortical and subcortical motor regions associated with catatonia (Joseph et al., 1985; Satoh et al., 1993; Scheuerecker et al., 2009; Viher et al., 2020; Walther et al., 2017; Wilcox, 1993), whereas studies relying on Northoff Catatonia Rating Scale (NCRS), which emphasizes a psychomotor concept of catatonia, found crucial contributions of aberrant higher-order frontoparietal networks (Hirjak et al., 2020a; Hirjak et al., 2020b; Northoff et al., 2004; Northoff et al., 1999c). However, unlike fronto-parietal regions, the involvement of brainstem structures in catatonia of SSD patients is poorly understood. The notion that catatonia could be related to aberrant brainstem integrity is already known for several decades. Sternbach and Yager (1981) were the first to hypothesize midbrain and brainstem abnormalities in catatonia. In an early computerized tomography (CT) study, Joseph et al. (1985) indeed showed an association between catatonia and brainstem atrophy. Surprisingly, previous magnetic resonance imaging (MRI) studies on psychiatric disorders that used voxel-based morphometry (VBM) or earlier FSL-based algorithms did not identify any significant association between brainstem

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volume and catatonic symptoms (Dean et al., 2020; Hirjak et al., 2020b; Walther et al., 2017). This may be related to the signal-to-noise ratio and the lack of robust brainstem segmentation, which would contribute to a differentiated examination of the individual structures. In comparison to VBM and earlier FSL versions (Grimm et al., 2015; Smith et al., 2004), the FreeSurfer vers. 6.0 brainstem segmentation algorithm of four brainstem structures (midbrain, pons, medulla and superior cerebellar pedunculus (SCP)) carries more a priori information and is based on a probabilistic atlas and Bayesian inference (Iglesias et al., 2015). This method is robust to MRI contrast changes or acquisition hardware and timely efficient (Iglesias et al., 2015).

In particular, the present study used both a categorical and a dimensional (correlational) approach to investigate the relationship between morphological variations of the brainstem structures [medulla oblongata, pons, SCP, and midbrain] and catatonic symptoms assessed with the NCRS in SSD patients. First, using categorical approach, we hypothesized that brainstem structures volumes will differ between catatonic (NCRS total score ≥ 3; at least 1 point in the three different symptom categories; i.e., motor, behavioral, and affective) and non-catatonic (NCRS = 0) SSD patients. Second, using the dimensional approach (low and high severity of catatonia according to DSM-IV-TR) and in accordance with the model of dopaminergic-driven subcortical-cortical motor circuit (Hirjak et al., 2020a; Maia and Frank, 2017; Walker et al., 2018; Wei and Wang, 2016), we hypothesized that brainstem structures volumes are significantly associated with distinct catatonic symptoms, that is, namely motor symptoms.

2. Methods

2.1. Study participants

We evaluated a total of 111 right-handed (Oldfield, 1971) subjects satisfying DSM-IV-TR (Sass et al., 2003) criteria for schizophrenia (n = 104) or schizoaffective disorder (n = 7) (Hirjak et al., 2019; Hirjak et al., 2020b). 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: (i) they were aged <18 or >65 years; (ii) they had a history of brain trauma or neurological disease (especially movement disorders); or (iii) they had shown alcohol/substance use disorder within 12 months prior to participation. Medical conditions potentially affecting central nervous system function, as well as cardiovascular or metabolic diseases in SSD patients were excluded by physical examination, laboratory control, ECG, EEG and MRI. Further, no complication of catatonia symptoms, such as dehydration or electrolyte disorders, as indicated by laboratory findings were detected in any of the patients on the day of MRI investigation. The local 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.

2.2. Clinical assessment

All study participants were examined during inpatient treatment within one week after partial remission of acute psychopathological symptoms. All relevant study procedures (e.g. psychometric testing, motor assessment and MRI examination) were completed within 3 days. None of the SSD patients were treated with benzodiazepines or anticholinergic agents at the time of the psychometric testing, motor assessment and MRI examination. All but five patients (5/111 = 4.5% antipsychotic-free) were on a stable daily dose of antipsychotic medication for at least 14 days. For a better comparability among studies, the daily doses of antipsychotic medication were converted to olanzapine equivalents (OLZ) (Leucht et al., 2015). For the examination of the catatonic syndrome we used the German version of the NCRS (Hirjak et al., 2017). The scale measures the presence and severity of motor (13 items), affective (12 items), and behavioral (15 items) catatonic symptoms.

First, we used a clear cut-off to identify SSD patients with (NCRS total score ≥ 3; at least 1 point in the three different dimensions; i.e., motor, behavioral, and affective) and without (NCRS = 0) catatonic symptoms (presence vs. absence of catatonia). This said, we compared SSD patients with manifest catatonic symptoms and SSD patients without a single catatonic symptom. Using this particular approach, we examined the brainstem alterations underlying the catatonic syndrome controlling for the effects of SSD (Dazzan et al., 2004; Gay et al., 2013). Furthermore, this approach enabled us to avoid ethical and methodological obstacles (need of an immediate treatment with electroconvulsive therapy (ECT) and/or with higher dosages of benzodiazepines) when recruiting SSD patients selected for their more or less severe catatonic symptoms (i.e., catatonic subtype of schizophrenia as defined by the ICD-10) (Dazzan et al., 2004). Second, assuming a neurobiological continuum between SSD patients with low and high severity of catatonia, we used both the NCRS criteria (NCRS total score ≥ 3) and the DSM-IV-TR criteria for catatonia [1 motor and at least 1 other symptom (behavioral or affective)] to examine the morphological brainstem alterations in SSD patients underlying the catatonic syndrome (Sass et al., 2003). This approach sought to cover a broader spectrum of the catatonic symptoms truly reflecting the dimensional view on catatonia (low and high expression of symptoms).

2.3. Structural MRI data acquisition

MRI scans were acquired using 3.0 Tesla Siemens Trio whole-body imaging system, using T1-weigthed magnetization-prepared rapid gradient-echo (MP-RAGE) with 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.

2.4. Image processing

FreeSurfer vers. 6.0 (Khan et al., 2008) was used in order to explore the correlation between catatonia and brainstem regions alterations in the study sample (Dale et al., 1999; Fischl and Dale, 2000; Fischl et al., 1999). For more details on the method see (http://surfer.nmr.mgh.harvard.edu/). This segmentation tool is implemented in Freesurfer vers. 6.0 and is able to perform a volumetric segmentation of four brainstem regions (medulla oblongata, pons, SCP and midbrain) from T1 (MP-RAGE) images. This Bayesian segmentation algorithm relies on a probabilistic atlas of the brainstem (and neighboring brain structures) (Iglesias et al., 2015). Furthermore, this segmentation tool uses soft segmentation (i.e. a voxel can be assigned to multiple structures/tissues), which results in improved performance regarding the partial volume effects of the surrounding cerebrospinal fluid (Iglesias et al., 2015). Finally, the estimated total intracranial volume (eTIV) was calculated with FreeSurfer as recommended. FreeSurfer exploits a relationship between the ICV and the linear transform to MNI305 space (the talairach.xfm) as described in Buckner et al. (2004).

2.5. Statistical analyses

We used SPSS for Windows version 22. Initially, a descriptive analysis for demographic, clinical and volumetric data in catatonic and non-catatonic SSD patients (Table 1) was performed. Then, homogeneity of variances of all brainstem regions and NCRS scores in both patients' groups was asserted using Levene's test.

In a first step, we used the two-way ANCOVA (also referred to as a "factorial ANCOVA") based on General Linear Model as implemented

Table 1
Clinical, demographic and morphological variables in SSD patients with (n = 30) and without (n = 29) catatonia according to NCRS.

	Patients with catatonia (n = 30)	Patients without catatonia (n = 29)	T[1]	Df[1]	Sig. (2-tailed)[1]
Age	39.40 ± 10.49	38.00 ± 11.25	0.494	57	0.623
Gender (m/f)[2]	16/14	14/15	–	1	0.698
Education (years)	13.77 ± 2.41	13.17 ± 3.12	0.818	57	0.417
Packyears	12.02 ± 13.06	11.48 ± 10.23	0.175	57	0.861
Olanzapine equivalents	18.03 ± 9.64	18.41 ± 12.51	−0.133	57	0.894
Duration of illness (years)	12.27 ± 11.53	7.31 ± 8.86	1.846	57	0.07
PANSS total score	80.27 ± 20.73	56.72 ± 19.42	4.497	57	**<0.001**
PANSS positive score	18.93 ± 8.18	13.1 ± 6.16	3.083	57	**0.003**
PANSS negative score	21.17 ± 8.63	13.83 ± 6.75	3.628	57	**0.001**
PANSS global score	40.4 ± 11.85	29.9 ± 9.64	3.725	57	**<0.001**
BPRS total score	43.17 ± 13.92	31.83 ± 11.75	2.484	57	**0.017**
GAF score	57.97 ± 14.96	75.17 ± 15.72	−4.306	57	**<0.001**
CGI-S	4.50 ± 0.9	3.48 ± 0.68	4.865	57	**<0.001**
NCRS motor score	1.87 ± 1.33	0	7.544	57	**<0.001**
NCRS affective score	2.8 ± 1.66	0	9.031	57	**<0.001**
NCRS behavior score	2.27 ± 1.2	0	10.156	57	**<0.001**
NCRS total score	6.9 ± 2.6	0	14.263	57	**<0.001**
SAS total score	3.27 ± 2.24	2.14 ± 2.13	1.979	57	0.053
AIMS total score	1.83 ± 3.05	0.59 ± 1.93	1.867	57	0.067
BARS global score	1.2 ± 1.51	0.48 ± 0.98	2.144	57	**0.036**
Medulla[3]	4666.84 ± 532.21	4745.1 ± 576.36	4.102	59	**0.048**
Pons[3]	14,692.14 ± 1790.84	15,005.83 ± 2027.73	3.525	59	0.066
SCP[3]	284.31 ± 65.6	282.61 ± 53.98	0.285	59	0.59
Midbrain[3]	5827.62 ± 506.8	6113.31 ± 535.47	9.19	59	**0.004***
Whole brainstem[3]	25,470.93 ± 2713.53	26,146 ± 2993.83	5.448	59	**0.024**
eTIV	$1.48 \times 10^6 \pm 1.79 \times 10^5$	$1.44 \times 10^6 \pm 2.46 \times 10^5$	0.65	57	0.519

Data are mean ± standard deviation. Significant results ($p < 0.05$) are displayed in bold font. Abbreviations: eTIV = estimated total intracranial volume, PANSS=Positive and Negative Symptoms Scale (p = positive, n = negative, g = global), BPRS=Brief Psychiatric Rating Scale, GAF = Global Assessment of Functioning, CGI-S=Clinical Global Impression Scale (Severity), SAS=Simpson and Angus Scale, AIMS = Abnormal involuntary movement scale, BARS=Barnes Akathisia Rating Scale, NCRS=Northoff Catatonia Rating Scale.

[1] The F- and *p*-values were obtained using an independent samples *t*-test;

[2] The *p*-values for distribution of gender were obtained by chi-square test.

[3] Data are mean ± standard deviation (in mm^3). The F- and *p*-values were obtained using two-way analysis of covariance (ANCOVA) adjusted for age, gender, education, medication, eTIV, PANSS total and BARS global scores as covariates.

* Results surviving the Bonferroni correction for multiple comparisons ($p < 0.005$).

in SPSS for Windows version 22 to determine whether there is an interaction effect between brainstem structures volumes (dependent variables) and catatonic (NCRS total score ≥ 3) as well as non-catatonic (NCRS total score = 0) group (fixed factors), after adjusting for age, gender, education, medication, PANSS total score and BARS global score. In the second step, we explored the association between significantly different brainstem structures and NCRS scores in patients with catatonia (as defined by NCRS total score ≥ 3) using Pearson's correlation coefficient. For completeness, associations between brainstem structures and NCRS scores in patients with catatonia according to DSM-IV-TR [1 motor and at least 1 other symptom (behavioral or affective)] was explored using partial correlations by treating age, gender, medication, PANSS total score, SAS total score and eTIV as covariates.

A nominal significance threshold of $p \leq 0.05$ was defined. To account for false positive findings within the identified between-group differences and structure/symptom-associations, *p*-values were corrected after each step for the number of applied statistical tests using the Bonferroni method. For this reason, the corrected threshold was set to $p = 0.005$ [$\alpha = 0.05/10$ tests (5 structures × 2 study groups)], $p = 0.016$ [$\alpha = 0.05/3$ tests (3 significant different brainstem structures)] and $p = 0.01$ [$\alpha = 0.05/5$ tests (5 structures)].

3. Results

3.1. Clinical, demographic and volumetric characteristics

Demographic, clinical and volumetric characteristics of the two study groups are shown in Table 1. Thirty out of 111 SSD patients (27%) were operationally defined as having catatonia according to NCRS. The control group which comprised twenty-nine SSD patients operationally defined as not having catatonia according to NCRS (NCRS total score = 0) was well balanced (propensity matched) for age, gender, education and OLZ equivalents. 30 SSD patients with and 29 SSD patients without catatonia according to NCRS were considered for between-group analyses. For completeness, forty-three out of 111 SSD patients (38,7%) were identified as having catatonia according to DSM-IV-TR (Sass et al., 2003) and considered for correlation analysis. 39 SSD patients (39/111 = 35.1%) did not satisfy NCRS or DSM-IV-TR criteria for catatonia and were excluded from further analyses.

3.2. Group differences

Catatonic patients (NCRS total score ≥ 3; n = 30) had smaller medulla oblongata ($p = 0.048$), midbrain ($p = 0.004$; Fig. 1) and whole brainstem ($p = 0.024$) volumes when compared to non-catatonic patients (NCRS total score = 0; n = 29). Only midbrain volumes survived

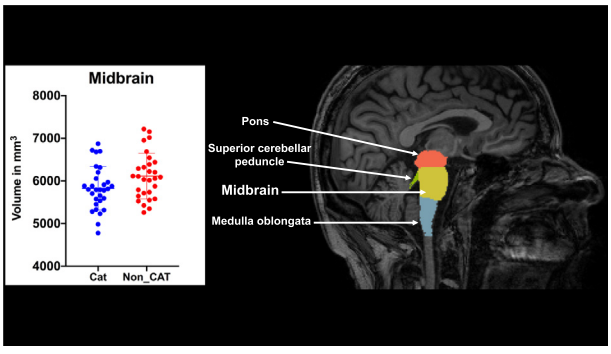

Fig. 1. Scatter plot showing midbrain volumes in catatonic (Cat, n = 30) and non-catatonic (Non_CAT, n = 29) SSD patients.

Bonferroni correction for multiple comparisons ($p < 0.005$). Anatomical and statistical details of volumetric differences are presented in Table 1.

3.3. Structure-symptom associations

In the next step, correlations between medulla oblongata, midbrain and whole brainstem volumes and NCRS scores in catatonic patients (NCRS total score ≥ 3; n = 30) were assessed using Pearson's coefficient (two-tailed). Higher NCRS motor scores were positively associated with midbrain ($p = 0.023$) and whole brainstem volumes ($p = 0.015$) (Table 2). Only the whole brainstem volumes-NCRS motor scores correlation survived the Bonferroni correction ($p < 0.016$). Finally, a partial correlation (two-tailed) between brainstem structures and NCRS scores in catatonic patients according to DSM-IV-TR revealed a significant relationships between pons ($p = 0.029$) and whole brainstem ($p = 0.048$) volumes and NCRS motor score (Supplementary Table 1). No association survived the Bonferroni correction ($p < 0.01$).

4. Discussion

This study explored alterations of specific brainstem regions underlying catatonic syndrome in SSD. Two main findings emerged: (1) Catatonic patients had significantly smaller midbrain volumes when compared to non-catatonic patients. (2) In catatonic patients, significant correlations were detected between NCRS motor scores and whole brainstem volumes.

These two finding are important for a number of reasons: First, catatonia is a truly psychomotor syndrome and its particular relevance in SSD has been discussed since the days of Kahlbaum (1874) and Kreapelin (1899). There is a number of neuroimaging studies that emphasized altered structure and function of the midbrain (e.g. abnormal dopamine-related subcortical-cortical circuitry dysconnectivity) in the pathophysiology of SSD (Fritze et al., 2019; Martino et al., 2018; Nopoulos et al., 2001; Tuppurainen et al., 2006). In particular, Nopoulos et al. (2001) found smaller midbrain volumes in male patients with schizophrenia. Later on, Tuppurainen et al. (2006) emphasized decreased $D_{2/3}$ density in the substantia nigra (SN) and an altered release of dopamine in the basal ganglia (e.g. striatum) of SSD patients. More recently, Martino and colleagues suggested that aberrant function of dopaminergic neurons in the SN leads to abnormal subcortical-cortical circuitry synchronization, complementing the current dopamine hypothesis of SSD (Martino et al., 2018). According to this hypothesis, tonic activity of dopaminergic neurons of SN and ventral tegmental area (VTA) is decreased (Martino et al., 2018). This might consequently lead to up-regulation and stimulus-related hypersensitization of dopaminergic receptors (especially D_2 receptors) in subsequent subcortical and cortical structures and the striato-thalamo-cortical pathway (Martino et al., 2018). Furthermore, functional MRI studies have shown aberrant VTA-hippocampus functional connectivity patterns in schizophrenia compared to normal controls (Hadley et al., 2014; Nakamura et al., 2020). Second, the finding of lower midbrain volume in catatonia corroborates the model of a dopamine-driven subcortical-cortical motor circuit (Wei and Wang, 2016). Third, midbrain contains SN and VTA. Both midbrain nuclei are of particular interest in terms of motor behavior –one dimension of catatonia syndrome- since SN and VTA are crucial in the modulation of nigrostriatal and mesocorticolimbic pathways in SSD, respectively (Conio et al., 2020). In particular, the nigrostriatal circuit is involved in the pathogenesis of extrapyramidal motor symptoms which might, as hypothesized by Woodbury, represent an earlier stage of drug-induced catatonia (Strawn et al., 2007; Woodbury and Woodbury, 1992). Fourth, this study is also in line with earlier work that suggested significant associations between midbrain shape and Neurological Soft Signs (NSS) subscale "hard signs", i.e. arm-holding test and mirror movements. Both NSS items clearly indicate motor impairment. Fifth, these findings are in line with an earlier study, which showed atrophy of the brainstem and cerebellar vermis on CT scans in five catatonic patients (four with affective disorder and one with temporal lobe epilepsy) (Joseph et al., 1985). In 1991, another CT study compared catatonic patients (determined by clinical assessment of mutism, motor rigidity, irrational behavior and absence of frank neurological and metabolic disease) with "non-catatonic schizophrenia patients", "non-psychotic affective disorder" and controls, reporting an association of catatonia with cerebellar atrophy (Wilcox, 1991). Yet, the study by Wilcox (1991) did not find any brainstem atrophy. Both CT studies have highlighted the involvement of "motor regions" such as brainstem in the pathogenesis of catatonia. However, clinical and methodological differences between CT and MRI make the comparison of results difficult.

Finally, we observed a positive correlation between brainstem volumes and catatonia symptom severity (similar to Hirjak et al., 2020b). From a statistical point of view, brainstem volume comparisons and correlations with catatonic symptoms project two different variables. The first one is a diagnostic category, the latter is parametric. The more the categorical loading is reduced, the more severe the parametrically rated catatonic symptoms might get. This said, the positive association should not be interpreted as an association between the categories themselves (where the positive correlation is indeed paradoxical) but as the degree of their loading (where the positive correlation is in line with stronger loading entailing more severe catatonic symptoms). This finding corroborates the study by Yu et al. that found a positive correlation between cuneus and lingual gyrus GMV reduction and AIMS scores (Yu et al., 2018). Two other studies also found a significant positive correlation between MRI measures in frontoparietal circuits and sensorimotor dysfunction (Hirjak et al., 2020b; Kindler et al., 2019). From a neurobiological perspective, positive associations putatively may reflect compensatory mechanism for aberrant sensorimotor processing.

Taken together, our findings build on previous MRI studies on catatonia (Northoff, 2000, 2002; Northoff et al., 2004; Northoff et al., 1999b; Northoff et al., 1999c; Northoff et al., 2000; Walther et al., 2017) and are very much in line with a previous study of Viher et al. (2020), who found that catatonic patients (≥2 items on the Bush Francis Catatonia Rating Scale (BFCRS) for a minimum of 24 h; n = 13) showed left-lateralized higher fractional anisotropy (FA) in the cortico-spinal tract (CST) and internal capsule when compared to non-catatonic patients. The authors concluded that FA reorganization within the CST is necessary to compensate for the impaired top-down modulation of higher-order cortical areas and aberrant motor behavior in catatonia (Northoff, 2002; Viher et al., 2020). In conjunction with previous MRI studies on catatonia, the present study suggests specific morphologic alterations of the brainstem to be involved in the pathogenesis of sensorimotor abnormalities.

4.1. Limitations

This structural MRI study has some limitations: First, we focused on brainstem volumes only, so we cannot appreciate further the functional interplay between brainstem and other subcortical (particularly thalamus) and cortical regions. Second, using FreeSurfer vers. 6.0 brainstem toolbox, we were only able to detect more pronounced structural changes and/or atrophy of the four brainstem structures. Other potentially relevant brainstem structures were not covered by this approach. Further, refinement of data analysis methods, together with magnets at higher field strength may have the potential to reveal additional differences in brainstem nuclei such as SN and nucleus ruber. Both nuclei have been coined crucial in the pathogenesis of psychomotor abnormalities (Northoff et al., 2020). Third, no statement can be made regarding the state or trait markers of catatonia. Whereas the majority of MRI studies examined SSD patients as close as possible to the acute catatonic episode and found significant morphological differences between catatonic and non-catatonic patients (Hirjak et al., 2020a), Dean et al. (2020) examined brain structure in SSD patients with history of

Table 2
Association between brainstem structures and NCRS scores in SSD patients with catatonia according to NCRS (n = 30).

Region	NCRS motor score	NCRS affective score	NCRS behavioral score	NCRS total score
Medulla	$r = 0.245$	$r = -0.029$	$r = 0.003$	$r = 0.063$
	$p = 0.093$	$p = 0.838$	$p = 0.985$	$p = 0.638$
Midbrain	$\mathbf{r = 0.331}$	$r = -0.107$	$r = 0.134$	$r = 0.136$
	$\mathbf{p = 0.023}$	$p = 0.445$	$p = 0.341$	$p = 0.391$
Whole brainstem	$\mathbf{r = 0.354}$	$r = -0.003$	$r = 0.203$	$r = 0.229$
	$\mathbf{p = 0.015}^{*}$	$p = 0.985$	$p = 0.151$	$p = 0.089$

The *p*-values were obtained using Pearson's correlation coefficient (two-tailed). Significant associations ($p < 0.05$) are in bold. Abbreviations: NCRS=Northoff Catatonia Rating Scale.
* Results surviving the Bonferroni correction for multiple comparisons ($p < 0.016$).

catatonia. The study by Dean et al. (2020), using VBM, did not find any morphological differences between patients with and without a history of catatonia. Furthermore, using a cross-sectional design, it is impossible to attribute changing patterns of catatonic symptoms to any of the identified (stable) structural brainstem alterations. Therefore, the question concerning the symptom stability vs. dynamics could be robustly answered using longitudinal monitoring of the three catatonia domains, preferably complemented by instrumental and ecological momentary assessments. Further, schizophrenia itself has been associated with brain atrophy in several cortical and subcortical regions (Lawrie and Abukmeil, 1998) which might limit sensitivity of our method at detecting atrophy that may exclusively apply to individuals with catatonia. Finally, antipsychotic medication has to be considered as a potential confounder when interpreting and discussing our results. Although catatonic symptoms are considered to be independent of antipsychotic medication influence (Hirjak et al., 2020a), the cumulative antipsychotic exposure might modulate the midbrain morphology that could not have been excluded by covarying for OLZ.

5. Conclusion

These results suggest significant contributions of abnormal midbrain and whole brainstem volumes to catatonia.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2020.09.025.

Declaration of competing interest

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

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Contributors

DH and RCW designed the study and wrote the protocol. SF and DH performed the motor assessments in all study subjects. CET and KMK managed the literature searches and analyses. SF and DH undertook the statistical analysis. SF, GN, RCW and DH interpreted the results. SF and DH wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

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