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Structural alterations of the motor cortex and higher order cortical areas suggest early neurodevelopmental origin of catatonia in schizophrenia

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ABSTRACT

The neurobiology of catatonia is still poorly understood. Particularly structural MRI studies yielded conflicting results. Heterogeneity of findings was suggested to stem from specifics of different rating scales. This study sought to test grey matter differences between patients with catatonia, patients without catatonia, and healthy controls using the two main instruments of catatonia rating. We included 98 patients with schizophrenia spectrum disorders and 42 healthy controls. Catatonia was measured using the Bush Francis Catatonia Rating Scale and the Northoff Catatonia Rating Scale. According to these scales, patients were classified into those with and those without catatonia. We tested whole brain grey matter volume, cortical thickness, and local gyrification across groups. Both catatonia rating scales correlated at tau = 0.65 but failed to classify identical subjects as catatonia patients. However, group differences in grey matter parameters were broadly similar with either rating scale to identify catatonia cases. Catatonia patients had reduced grey matter volume compared to controls in a large network including orbitofrontal cortex, cingulate, thalamus, and amygdala. While there was no group difference in cortical thickness, catatonia patients had increased local gyrification in premotor, motor, and parietal cortices compared to controls. Hypergyrification of the motor cortex and higher order cortical areas was found in catatonia patients compared to patients without catatonia. Both catatonia rating scales find similar symptom severity and group differences in grey matter indices. Catatonia is linked to reduced grey matter volume and increased local gyrification, suggesting some impact of early neurodevelopmental insults.

1. Introduction

Catatonia is a complex psychomotor syndrome including a heterogeneous set of motor, behavioral, and autonomic symptoms (Walther et al., 2019). The estimated prevalence rate in psychiatry is 9 % (Solmi et al., 2018), while studies suggested an incidence of 10.6 per 100′000 person years (Rogers et al., 2021). Catatonia may present in various mental disorders but has mainly been studied in schizophrenia spectrum disorders (SSD). The heterogeneous response to treatment and the variability in the course of catatonia suggest multiple pathophysiological pathways to the syndrome.

The pathobiology of catatonia is still poorly understood. Alterations in the cerebral motor system have been suspected to give rise to catatonia (Hirjak et al., 2020; Northoff et al., 2021; Walther, 2015; Walther et al., 2019; Walther and Strik, 2012). Among the findings were increased resting state perfusion in the premotor and motor cortices, or increased fractional anisotropy in major motor pathways, such as the corticospinal tract (Foucher et al., 2018; Viher et al., 2020; Walther et al., 2017; Wasserthal et al., 2020). Studies of grey matter structure have been inconsistent with some reporting no differences (Dean et al., 2020), volume reductions in prefrontal cortex and insula (Walther et al., 2017), midbrain (Fritze et al., 2020) or hypothalamus and amygdala (Fritze et al., 2022), reduced cortical surface area in orbitofrontal and parietal cortices (Hirjak et al., 2019) as well as aberrant gyrification (Hirjak et al., 2019; Parekh et al., 2022). In the past decade, research on the neural underpinnings of catatonia has been limited to five small to moderate sized samples (from Bangalore, Bern, Mannheim, Nashville, and Strasbourg), using various imaging modalities, subjects with acute or past catatonia episodes, as well as different catatonia rating scales. Hirjak and colleagues suggested that discrepant findings were largely

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attributable to the choice of the rating scales (Hirjak et al., 2020), in which the Northoff Catatonia Rating Scale (NCRS)(Northoff et al., 1999a) found correlations with an extended psychomotor cortical network, while the Bush Francis Catatonia Rating Scale (BFCRS)(Bush et al., 1996) detected associations in a core motor network. The two rating scales differ in the number of items and slightly in the catatonia concepts. While both scales include motor and behavioral abnormalities, the NCRS specifically recognizes affective symptoms. Here, we tested in a new, large data set whether the two catatonia rating scales correspond and whether group comparisons may identify similar results when classifying patients according to BFCRS or NCRS.

Indices of cerebral grey matter structure may inform on distinct processes. While gyrification is highly heritable, attributed to neurodevelopmental origins and despite continuing decline rather stable later in life (Damme et al., 2019; Hogstrom et al., 2013; Nanda et al., 2014; Norbom et al., 2021), cortical thickness and grey matter volume are considered to reflect a composite of neurodevelopmental effects and more recent structural changes, e.g. following specific training or treatments (Hogstrom et al., 2013; Norbom et al., 2021; Rogge et al., 2018; Takahashi et al., 2020). In SSD, cortical thickness and grey matter volume are locally reduced even in medication naïve first episode subjects, while longitudinal studies suggested a progressive decline of both parameters (Guo et al., 2015; Nelson et al., 2020; van Haren et al., 2011). We tested gyrification, thickness and volume, in order to understand the origins of catatonia symptoms during adulthood.

We hypothesized brain structural alterations specific to catatonia in grey matter volume, cortical thickness, and local gyrification. In addition, we hypothesized that catatonia as determined with the BFCRS would be linked to alterations in the core motor system. Finally, we would expect that catatonia as determined with the NCRS would be linked to alterations in the motor system but also in medial prefrontal and parietal cortices.

2. Methods and participants

2.1. Participants

We included 140 participants (98 patients with SSD (schizophrenia (n = 78), schizophreniform disorder (n = 10), schizoaffective disorder (n = 10)), according to the Structured Clinical Interview for DSM-5 (SCID-5), and 42 age and sex-matched healthy controls (HC)) from the ongoing double-blind randomized placebo-controlled trial OCoPS-P (Overcoming Psychomotor Slowing in Psychosis; ClinicalTrials.gov Identifier: NCT03921450) (see Table 1. Fig. 1). Patients were recruited at the inpatient departments of the University Hospital of Psychiatry and Psychotherapy, Bern, Switzerland, and HC were recruited from the community using advertisement and word of mouth. All patients with SSD and current psychomotor slowing from age 18 to 60 were eligible, in addition we recruited 25 patients with SSD without psychomotor slowing as clinical controls. The protocol adhered to the Declaration of Helsinki and was approved by the local ethics committee (KEK-BE 2018-02164). General exclusion criteria were active substance dependence except for nicotine, neurological disorders which had an impact on motor behavior, severe brain injury with consecutive loss of consciousness, and contraindications for MR scans, i.e. metallic objects in the body or pregnancy. Additional exclusion criteria for healthy controls were a history of any psychiatric disorder or any first-degree relative with psychosis. The current analysis used only baseline data of the trial. All assessments and neuroimaging were performed within 48 h and before the intervention started.

Table 1
Demographic and clinical characteristic.

	HC	SSD	Comparison
N	42	98	
Age (years)	37 ± 13	36 ± 12	W = 2104, p = .84
Sex	21 M	49 M	$\chi2 = 0.03$, p = .86
Medication (OLZ eq.)	–	16.5 ± 10.6	
PANSS total	–	77.2 ± 17.8	
PANSS negative	–	22.1 ± 6.9	
PANSS positive	–	16.1 ± 5.1	
SRRS	–	20.6 ± 8.5	
BFCRS	–	4.8 ± 4.4	
Northoff total	–	8.7 ± 5.4	
Northoff motor	–	2.2 ± 2.0	
Northoff affect	–	3.5 ± 2.3	
Northoff behavior	–	2.9 ± 2.1	
UPDRS III	–	18.6 ± 11.5	

Values represent the mean ± SD. HC: healthy controls. OLZ eq.: Olanzapine equivalent dosage; PANSS: Positive And Negative Syndrome Scale; SRRS: Salpetriere Retardation Rating Scale; BFCRS: Bush Francis Catatonia Rating Scale; UPDRS III: Unified Parkinson's Disease Rating Scale.

2.2. Measures

2.2.1. Psychopathology

We collected data on general symptom severity using the Positive And Negative Syndrome Scale (PANSS)(Kay et al., 1987). Catatonia was rated with the Bush-Francis Catatonia Rating Scale (BFCRS)(Bush et al., 1996) and the Northoff Catatonia Rating Scale (NCRS)(Northoff et al., 1999a). Parkinsonism was rated using the Unified Parkinson's Disease Rating Scale (UPDRS)(Fahn et al., 1987) and psychomotor slowing using the Salpêtrière Retardation Rating Scale (SRRS)(Dantchev and Wildlöcher, 1998). Assessments were conducted by psychiatry residents, who were trained by the first author to achieve high interrater reliability. All patients were on antipsychotic medication at the time of testing and mean olanzapine equivalents (OLZ eq.) were calculated according to (Leucht et al., 2015). Detailed information on the current antipsychotic medication is provided in Supplementary Table 1.

2.2.2. Catatonia classification

We classified the patients as with or without catatonia using two different rating scales and their respective criteria (Sienaert et al., 2011). To be classified as with catatonia based on BFCRS (Catatonia-BFCRS), the patients had to score 1 or more points on at least two of the first 14 items. To be classified as with catatonia based on NCRS (Catatonia-NCRS), the patients had to score at least 1 point in each category (behavioral, affective, and motor) plus a total score higher than 7. Supplementary Tables 2–3 and Supplementary Fig. 1 present the demographics within each classification.

2.2.3. MRI acquisition

Neuroimaging was conducted at the translational imaging center of the Swiss Institute for Translational and Entrepreneurial Medicine, Bern, Switzerland, using a 3T Prisma MRI whole-body scanner with a 20-channel radio-frequency head coil (Siemens, Germany). We acquired a structural T1-weighted MP2RAGE scan (8 min 22 s covering 176 sagittal slices, 1 mm thick, TR = 5000 ms, TE = 2.98 ms, flip angle 1 = 4°, flip angle 2 = 5°, voxel size = 1x1x1 mm) to test three structural neuroimaging markers: grey matter (GM) volume using voxel-based morphometry (VBM), cortex gyrification using computation of local gyrification index (LGI) and cortical thickness (CortTh).

2.2.4. MRI processing

The T1–3D images were segmented into grey matter (GM), white matter and cerebrospinal fluid using the CAT12 toolbox (http://www.neuro.uni-jena.de/cat/) in SPM12 (Version 7771, Welcome Trust, London, UK. https://www.fil.ion.ucl.ac.uk/spm). We used the DARTEL VBM algorithm with SPM 12, following the standard procedure established by J. Ashburner (Ashburner, 2010) to process the GM volume. First, we created a DARTEL template by integrating the sampled patients' brain for spatial normalization. Then, the modulated native GM were normalized and smoothed using a 6 mm FHWM Gaussian kernel to

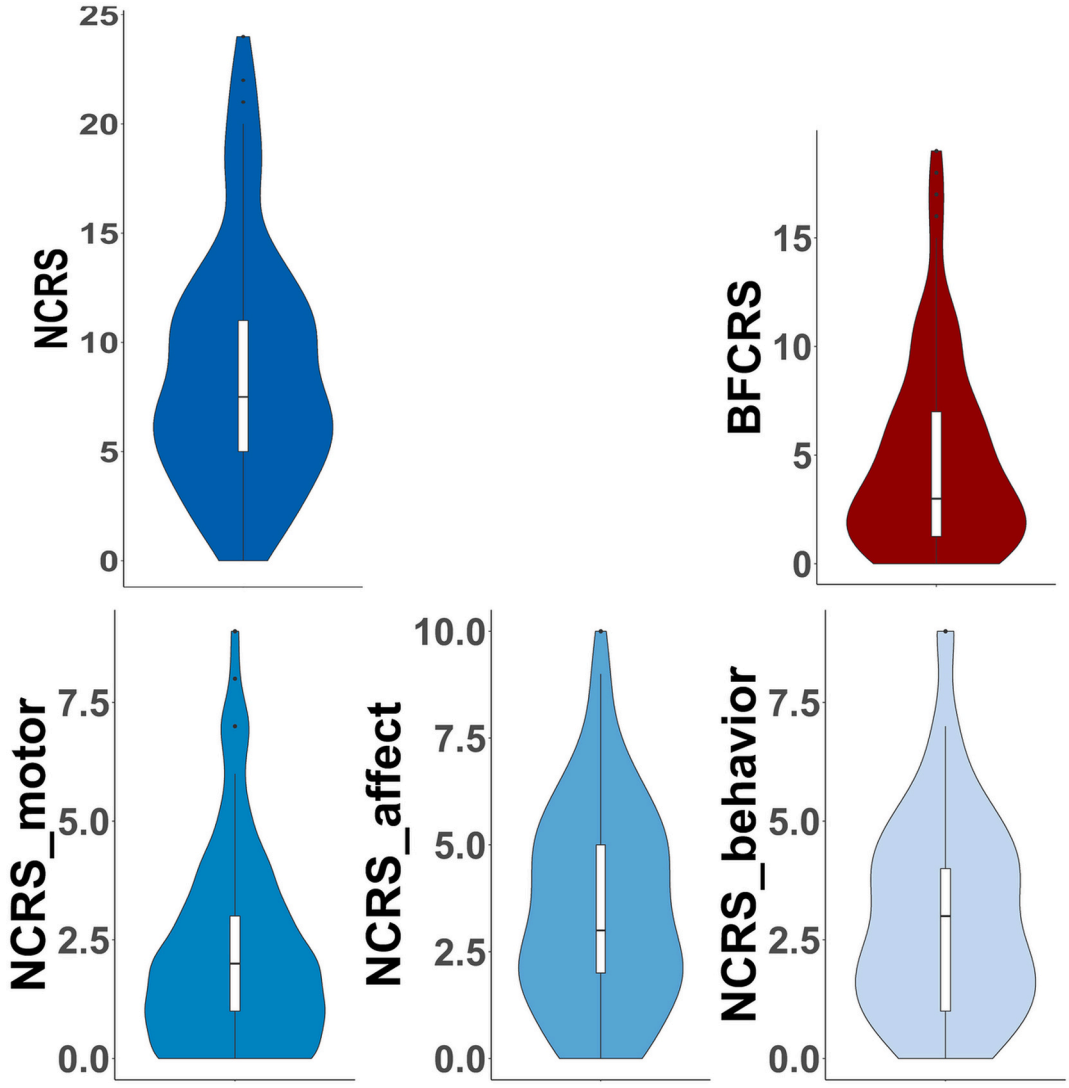

Fig. 1. Catatonia rating scale distribution in SSD patients
Violin plots of the catatonia rating scales scores in all patients. In each violin, a box plot is added. The center line represents the median value, the lower bound of the box represents the 25th percentile, the upper bound of the box the 75th percentile, and the whiskers represent 3 times the interquartile range. NCRS: Northoff catatonia rating scale, BFCRS: Bush Francis catatonia rating scale.

the MNI template for position localization using SPM12. We used the ratings provided by CAT12 to evaluate segmentation quality. All our participants had a good overall image quality ratings (82–87 %), including an excellent rating for noise and bias parameters (>90 %) and a good rating for image resolution (80–90 %).

Preprocessing for CortTh and LGI analyses was performed using the standard FreeSurfer image analysis suite for cortical reconstruction (V 7.2.0) (http://surfer.nmr.mgh.harvard.edu/) (i.e. recon-all with -all -qcache options) (Schaer et al., 2008),(Dale et al., 1999; Fischl, 2012; Schaer et al., 2012). Standard steps of the freesurfer pipeline included translation of individual brains into Talairach space, removal of non-brain tissue from the image using a hybrid watershed/surface deformation procedure and modelling of the boundary between white matter and cortical grey matter as well as the pial surface. The pial and white surfaces of all the participants were visually checked (using Freeview v3.0) for errors during the reconstruction process, manual edits were performed and processes were rerun for the ones edited (using the recon-all autorecon2 autorecon 3 command). The CortTh is calculated based on the shortest distance between the pial surface and the white surface at each surface vertex. Then, the standard LGI (Schaer et al., 2008, 2012) procedure (i.e. the recon-all command with -localGI -qcache -measure pial_lgi options) was computed for all subjects. Steps included the creation of an outer smoothed surface tightly wrapping the pial surface, followed by the delineation of circular regions of interest on the outer surface, and their matching area on the pial surface using a sampling sphere with the default 25 mm radius. The LGI quantifies the amount of cortex buried within the sulcal folds (calculated by the ratio of the total pial cortical surface over the perimeter of the brain), more folding would lead to a higher gyrification index. For quality control, the overall coverage and distribution of the LGI for each participant were also visually checked with tksurfer (tksurfer?h pial -overlay /surf/?h.pial_lgi -fthresh 1; with a threshold of 1, no grey matter cortical area should be visible).

2.3. Statistics

We first tested clinical and demographic differences between groups using Wilcoxon tests and chi-square tests between healthy controls and patients with SSD. Next, we tested clinical differences between patients with and without catatonia according to BFCRS or NCRS (Supplementary Tables 1 and 2). In addition, we calculated Kendall's Tau correlation between the BFCRS and NCRS. Furthermore, we ran Kendall's Tau

correlations between the catatonia rating scales and SRRS, UPDRS, medication (OLZ eq.), and symptom severity (assessed with PANSS) (See Supplementary Fig. 2).

The group comparisons of the three structural MRI markers (VBM, LGI, or CorTh) between patients with and without catatonia and healthy controls were calculated using two different models: First, with a model across three groups, as one-way ANCOVAs with age and total intracranial volume (TIV) as covariates of non-interest. Second, with models within patients, as one-way ANCOVAs between patients with and without catatonia including current antipsychotic medication dosage (OLZ eq.) as additional covariate. These analyses were repeated separately for the two classifications.

2.3.1. VBM analysis

For VBM analysis, we used an absolute threshold of 0.1 to ensure the inclusion of GM voxels with a probability $\geq$0.1 of being GM and we set a cluster-forming threshold of $p = .001$ and a p-value qFDR corrected <0.05 for the cluster-wise threshold.

2.3.2. LGI and CorTh analyses

For both LGI and CorTh, individual CorTh, and LGI maps were registered to the fsaverage template included in FreeSurfer, then we created a generalized linear model (GLM) with DODS ("different offset, different slope"). As the LGI measure is already intrinsically smooth, we did not apply an additional level of smoothing, however, smoothing with a 10 mm FWHM was applied to the CorTh (Hirjak et al., 2019; Marie et al., 2016; Plonka et al., 2020). The main results were corrected for multiple comparisons using a cluster-wise forming threshold of $p < .005$ with 1000 random permutations (Hagler et al., 2006). Statistical models were additionally corrected for the two hemispheres, setting the cluster-level threshold at $p < .025$ (Ni et al., 2020). In addition to the state-based analysis, i.e., being catatonic or not, we also explored the association between catatonia severity (either BFCRS or NCRS) and each of the structural MRI measurements across all patients controlling for age and medication dosage.

3. Results

3.1. Catatonia rating

The total scores of the BFCRS and NCRS showed substantial positive correlation (tau = 0.652, $p < .0001$, Fig. 2). In addition, catatonia ratings correlated with SRRS, UPDRS, and PANSS total and PANSS negative; but not with age, medication, or PANSS positive (see Supplementary Fig. 2).

Fifty-nine patients qualified for catatonia according to the BFCRS, whereas 47 patients qualified for catatonia with the NCRS (Table 2).

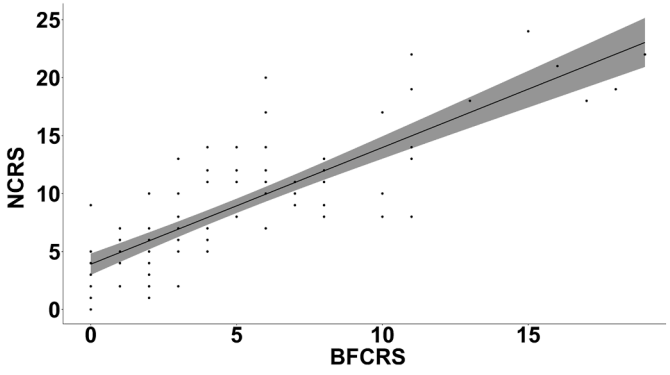

Fig. 2. Correlation between catatonia rating sales. This scatter plot displays the correlation between Northoff catatonia rating scale (NCRS) and Bush Francis catatonia rating scale (BFCRS). The black line is the regression line and the shaded area represents the 95 % confidence interval.

Table 2
Catatonia cases according to NCRS and BFCRS.

		NCRS	
		Catatonia (n = 47)	No catatonia (n = 51)
BFCRS	Catatonia (n = 59)	45	14
	No catatonia (n = 39)	2	37

There was no significant difference between these two distributions ($\chi 2 = 2.5$, $p = .11$). According to both scales, 45 patients had catatonia and 37 did not have catatonia in any scale. Mutual false classifications were seen in 16 patients. Finally, 16 patients qualified for the stricter definition of catatonia according to DSM-5 criteria.

3.2. Catatonia structural neuroimaging

3.2.1. Grey matter volume

Patients with catatonia presented less grey matter volume compared to healthy controls in a large network including orbitofrontal and prefrontal cortices, bilateral visual, parietal, temporal, and anterior cingulate cortices, right thalamus, right amygdala, as well as left insular cortex (see Fig. 2 and Table 3). Patients with catatonia had less GM volume compared to patients without catatonia in left Broca's area. This has been observed with either catatonia classification. The dimensional severity analyses demonstrated no significant association of GM with either the BFCRS or the NCRS score across all patients.

3.2.2. Cortical thickness

There were no group differences in CorTh with either catatonia classification. The dimensional severity analyses demonstrated no significant association of CorTh with either the BFCRS or the NCRS score across all patients.

3.2.3. Gyrification

Patients with catatonia showed higher LGI than HC in bilateral motor, premotor, occipital and parietal areas with both classifications (See Fig. 3 and Table 3). In addition, patients with catatonia had higher LGI in left sensorimotor and premotor areas than patients without catatonia only when using the Catatonia-BFCRS classification. No differences were observed between patients without catatonia and HC. The dimenational severity analyses demonstrated no significant association of LGI with either the BFCRS or the NCRS score across all patients.

4. Discussion

This study tested whether catatonia is associated with aberrant cerebral grey matter using two different rating scales to classify patients and three distinct grey matter parameters (volume, thickness, and gyrification). Five main findings emerged: First, despite strong correlation of the total scores of catatonia rating scales, the scales identified different subjects as catatonic demonstrating some heterogeneity of the behavioral phenotype. Second, with both classifications, catatonia was associated with widespread reductions of grey matter volume compared to healthy subjects, including orbitofrontal cortex, cingulate cortex, insula, and visual cortex. Third, with both classifications, subjects with catatonia demonstrated hypergyrification compared to controls in motor, premotor, and somatosensory cortices. Catatonia according to BFCRS also had higher gyrification than patients without catatonia in the premotor and primary motor cortex. Fourth, we found no group differences in cortical thickness. Fifth, we found no association between any of the three structural measures and the catatonia severity according to BFCRS or NCRS. Collectively, these findings suggest aberrant grey matter within the extended cortical motor areas, including altered neurodevelopment in core motor cortical areas as well as areas of higher order cognitive and affective control.

Table 3
Catatonia MRI substrates. VBM (panel A) and LGI (panel B) difference between HC, patients with and without catatonia using Catatonia-BFCRS and Catatonia-NCRS classifications. NCRS: Northoff catatonia rating scale; BFCRS: Bush Francis catatonia rating scale; Cat: Catatonia; Non-Cat: non-catatonia; VBM: voxel-based morphometry; LGI: local gyrification index; BA: Brodmann area; L: left; R: Right; ACC: anterior cingulate cortex; PCC: posterior cingulate cortex; OrbFC: orbitofrontal cortex; APFC: anterior prefrontal cortex.

A. VBM		mm2	X	Y	Z	Brain area
Catatonia-BFCRS	HC > Cat	6440	3	40	−12	R OrbFC (BA 11)
	$T = 3.154$, $p_{uncorr} < 0.001$		−1	45	0	L Dorsal ACC (BA 32)
	Cluster-corr qFDR < 0.05		−13	49	4	L APFC (BA 10)
		2473	21	3	−21	R Amygdala
			30	0	−27	
		3198	−39	10	−18	L Temporal cortex (BA 38)
			−37	−2	−19	L Insula (BA 13)
			−41	−2	−11	
		1798	29	−97	−5	R Visual cortex (BA 18)
			18	−98	−10	
			23	−98	6	
		3225	41	−76	22	R Visual cortex (BA 19)
			46	−80	13	
			51	−73	27	R Parietal cortex (BA 39)
		2834	1	−14	11	R Thalamus
			1	−13	−2	
			12	−22	0	
		3316	−6	−10	39	L Ventral ACC (BA 24)
			−9	−20	38	
			6	−11	39	R Ventral ACC (BA 24)
	Non-Cat > Cat	7907	−48	13	22	L Broca area (BA 44)
	$T = 3.18$, $p_{uncorr} < 0.001$		−45	5	13	
	qFDR < 0.05		−52	15	30	
Catatonia-NCRS	HC > Cat	7317	0	39	−12	R OrbFC (BA 11)
	$T = 3.154$, $p_{uncorr} < 0.001$		9	42	−10	
	cluster-corr qFDR < 0.05		11	25	25	R Dorsal ACC (BA 32)
		2074	−38	−3	−22	L Insula (BA 13)
			−40	6	−27	L Temporal cortex (BA 38)
			−39	10	−18	
		3005	41	−76	22	R Visual cortex (BA 19)
			46	−80	14	
			51	−73	27	R Parietal cortex (BA 39)
		2172	8	−9	36	R Ventral ACC (BA 24)
			−6	−11	39	L Ventral ACC (BA24)
			−9	−25	36	L Ventral PCC (BA 23)
	Non-Cat > Cat	3353	−48	13	22	L Broca cortex (BA 44)
	$T = 3.18$, $p_{uncorr} < 0.001$		−45	5	13	
	cluster-corr qFDR < 0.05		−52	15	30	

B. LGI (cwp 0.005, 1000 permutations)		mm2	X	Y	Z	Brain area
Catatonia-BFCRS	Cat > HC	8779	−48	−58	7	L Parietal cortex (BA 37)
		5075	−25	−15	61	L Motor/premotor area (BA 4/6)
		1702	−22	−46	−7	L Visual cortex (BA 19)
		8070	20	−64	45	L Parietal cortex (BA 7)
		3593	43	3	45	R Motor/premotor area (BA 4/6)
	Cat > Non-Cat	2530	−41	3	44	L Motor/premotor area (BA 4/6)
Catatonia-NCRS	Cat > HC	5683	−44	−70	7	L Visual cortex (BA 19)
		5220	−25	−15	61	L Motor/premotor area (BA 4/6)
		4919	15	−37	48	R Somatosensory cortex (BA 5)
		3202	44	3	45	R Motor/premotor area (BA 4/6)

The localization of the specific brain alterations in catatonia broadly corroborates prior reports (Hirjak et al., 2020; Northoff, 2002; Walther et al., 2019). In fact, we found reduced grey matter in premotor areas, such as the ventral anterior cingulate cortex including the cingulate motor area, which is important for action planning and action selection. This is in line with results from our previous study in a smaller sample of acute catatonia (no overlap with the current report)(Walther et al., 2017) and findings of aberrant orbitofrontal activity in akinetic catatonia (Northoff et al., 2004; Richter et al., 2010). Similarly, in the Mannheim sample reduced volumes of the amygdala have been detected in catatonia (Fritze et al., 2022). But our findings also extend previous work by demonstrating reduced grey matter volume in catatonia compared to healthy controls in the thalamus, orbitofrontal cortex, parietal cortex, and insula. These areas clearly extend the core motor system, supporting catatonia as a truly psychomotor syndrome. Similar as affective and behavioral experiences may shape motor behavior in Parkinson's disease, motor behavior in catatonia is associated with affective and behavioral states (Hirjak et al., 2020; Obeso et al., 2014; Walther et al., 2019). Importantly, we found these associations in patients with catatonia irrespective of the applied rating scale, challenging the hypothesis of Hirjak et al. (2020), who suggested that the NCRS was more sensitive to psychomotor features than the BFCRS thought to focus on “pure” motor abnormalities. In contrast, our data suggest that differences in brain-behavior associations in the catatonia literature probably result from differences in sample characteristics, such as sample size, timing of neuroimaging in relation to catatonia symptoms, or acute vs. chronic forms. And finally, the current results clearly support the association of the psychomotor syndrome of catatonia with structural alterations in brain areas of the motor circuitry and further areas of higher-order motor, behavioral, and emotional control.

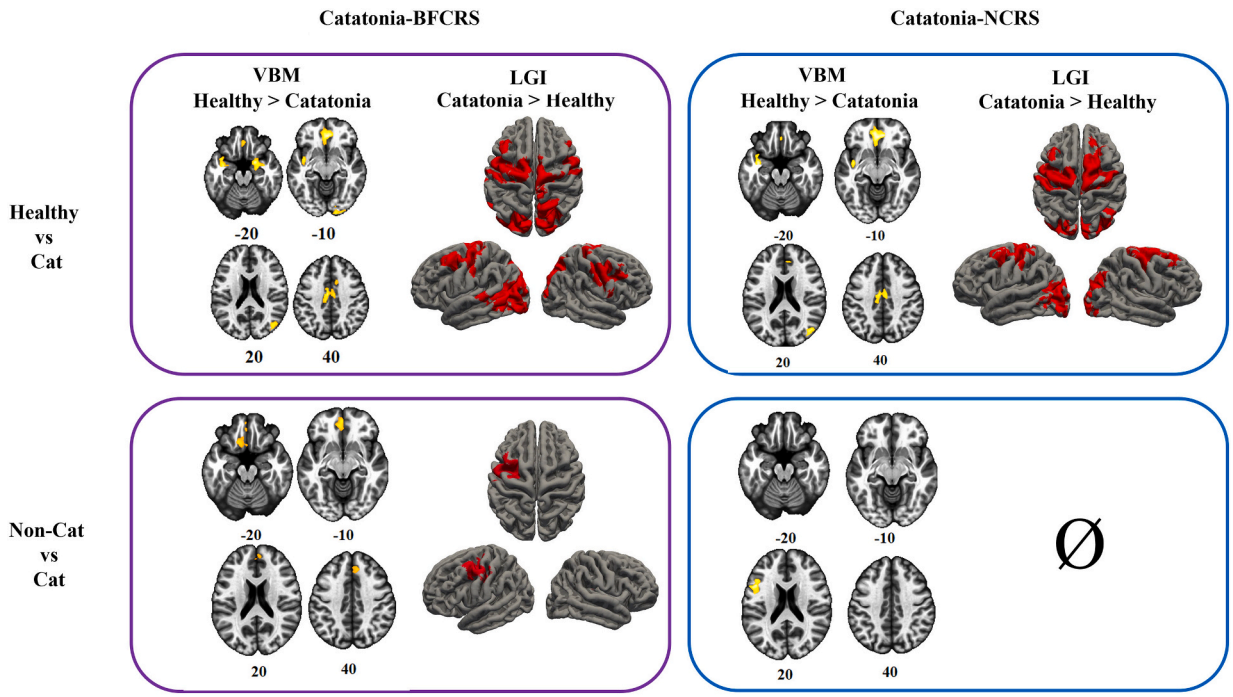

Fig. 3. Catatonia MRI substrates. VBM and LGI difference between HC (n = 42), patients with (n = 59) and without catatonia (n = 39) using the Catatonia-BFCRS classification (left panel) and patients with (n = 47) and without catatonia (n = 51) using the Catatonia-NCRS classification (right panel). NCRS: Northoff catatonia rating scale; BFCRS: Bush Francis catatonia rating scale; Cat: Catatonia; Non-Cat: non-catatonia; VBM: voxel-based morphometry; LGI:local gyrification index. Numbers indicate the z position in MNI space.

This study demonstrates the remarkable consistency of findings using structural brain imaging in a novel sample of SSD patients. Both NCRS and BFCRS identified catatonia patients differed from healthy controls in similar brain areas, including core motor regions but also limbic-affective brain areas. In addition, the BFCRS classification identified brain alterations in which patients with and patients without catatonia differ, e.g. lower volumes of Broca's area and higher gyrification in premotor and primary motor cortex in catatonia. The lack of association between the structural markers and the severity of catatonia using both scales is also a strongly consistent finding, which suggests that the specific structural changes are state-related (i.e., being catatonic). However, dimensional severity analyses would need larger sample size given the heterogeneity of catatonia symptoms.

We found distinct associations with catatonia using three markers of grey matter structure. Although locally reduced cortical thickness is a frequent finding across all stages of SSD (Zhao et al., 2022), we failed to detect any group difference in catatonia, which is in line with the sample from Mannheim (Hirjak et al., 2019). Since cortical thickness is susceptible to multiple factors during lifetime such as training, normative decline, or medication, the catatonia syndrome may have limited effect sizes (Hogstrom et al., 2013; Nelson et al., 2020; Norbom et al., 2021; van Haren et al., 2011). In contrast, we found robust effects of catatonia on grey matter volume, which is frequently altered in SSD (Guo et al., 2015; Haijma et al., 2013). Grey matter volume and cortical thickness have been discussed as offering complementary information in neuropsychiatric disorders (Goto et al., 2022). The dissociation of group differences in our sample is thus not overly surprising. Finally, aberrant gyrification has been suggested as an endophenotype of schizophrenia, as it was reported to be highly heritable and unrelated to the use of antipsychotic medication in a large sample (Nanda et al., 2014). In fact, gyrification in psychosis seems to be altered before the onset of the illness. For example, Damme et al. found hypogyrification in bilateral anterior and posterior cingulate cortex in subjects at clinical high risk for psychosis without any changes at one year follow-up (Damme et al., 2019). Similarly, a study in first episode patients without medication detected hypogyrification of cingulate cortex, pre- and postcentral gyrus, and insula among others without any change following six weeks of antipsychotic treatment (Nelson et al., 2020). Thus, gyrification in schizophrenia seems to be a marker of aberrant neurodevelopment, suggested to result from perinatal insults. However, some studies also reported frontal areas with hypergyrification in SSD, which was related to executive dysfunction (Sasabayashi et al., 2017; Takayanagi et al., 2019). Likewise, a previous study from Mannheim found local increases of gyrification in the anterior cingulate cortex in catatonia compared to patients without catatonia (Hirjak et al., 2019). Our study found increased LGI in catatonia patients compared to healthy controls in premotor, motor, and parietal cortices. In addition, the patients with catatonia according to BFCRS also had increased LGI in the premotor/motor cortex compared to SSD patients without catatonia. Thus, while hypogyrification appears to be a frequent finding in adult SSD, SSD patients with catatonia show specifically increased LGI in core motor cortex areas. While this novel finding calls for replication in other samples, results of this study suggest that aberrant folding in the motor cortex during critical neurodevelopmental periods may specifically give rise to the catatonia syndrome in SSD. If this assumption was true, it might explain phenomena such as reduced GABA-A receptor density or increased resting state perfusion in premotor and motor cortex (Foucher et al., 2018; Northoff et al., 1999b; Walther et al., 2017). Finally, it is worth noting that with more permissive statistical thresholds, LGI in catatonia is altered in the entire motor cortex and not only in some "representations" of the body as suggested by the current analyses.

This study acquired structural brain imaging in a large sample of SSD patients enriched with subjects with psychomotor slowing. Catatonia was ascertained with the two most frequently applied rating scales. Group comparisons of grey matter indices were corrected for age, TIV, current antipsychotic medication, and for multiple comparisons. However, some limitations also require discussion. First, we focused exclusively on catatonia in SSD patients who agreed to be enrolled in a clinical trial, rendering interpretations on potential mechanisms in catatonia due to other mental illness dubious. Second, while the presence of

catatonia was carefully established and prior history could be considered, researchers struggle to exclude the history of catatonia episodes from patient recall or even case files due to poor coverage of catatonia in standard documentation (Dean et al., 2020). Third, all patients were on antipsychotic medication, which could not be controlled in the comparisons with HC. Still, we covaried for current medication dosage in the comparisons between patient groups, although lifetime exposure to antipsychotics would be important it was unavailable information to us. Fourth, while patient groups were comparable in age, sex, medication, and positive symptom severity, the catatonia groups had more negative symptoms, total PANSS scores, and higher scores on parkinsonism. Due to expected multicollinearity, we decided against adding all of these features as covariates.

In sum, this study demonstrates good agreement between NCRS and BFCRS when classifying catatonia. Furthermore, findings suggest similar group differences in brain structure alterations for both catatonia rating scales. Finally, the study shows first accounts of aberrant increased gyrification in the motor cortices and higher order cortical areas in catatonia, suggesting early neurodevelopmental insult.

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CRediT authorship contribution statement

SW designed the study, acquired funding, wrote the protocol, supervised data acquisition and analysis and wrote the first draft of the manuscript. NN and MN recruited patients and conducted measurements. AK and FW provided clinical ratings and data checks. SL conducted all analyses and prepared figures and tables. All authors discussed and edited the final manuscript.

Declaration of competing interest

Sebastian Walther received honoraria from Lundbeck, Mepha, and Neurolite unrelated to this work. All other others report no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2022.10.004.

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