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Intrinsic neural network dynamics in catatonia

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Abstract

Catatonia is a transnosologic psychomotor syndrome with high prevalence in schizophrenia spectrum disorders (SSD). There is mounting neuroimaging evidence that catatonia is associated with aberrant frontoparietal, thalamic and cerebellar regions. Large-scale brain network dynamics in catatonia have not been investigated so far. In this study, resting-state fMRI data from 58 right-handed SSD patients were considered. Catatonic symptoms were examined on the Northoff Catatonia Rating Scale (NCRS). Group spatial independent component analysis was carried out with a multiple analysis of covariance (MANCOVA) approach to estimate and test the underlying intrinsic components (ICs) in SSD patients with (NCRS total score ≥ 3; $n = 30$) and without (NCRS total score = 0; $n = 28$) catatonia. Functional network connectivity (FNC) during rest was calculated between pairs of ICs and transient changes in connectivity were estimated using sliding windowing and clustering (to capture both static and dynamic FNC). Catatonic patients showed increased static FNC in cerebellar networks along with decreased low frequency oscillations in basal ganglia (BG) networks. Catatonic patients had reduced state changes and dwelled more in a state characterized by high within-network correlation of the sensorimotor, visual, and default-mode network with respect to noncatatonic patients. Finally, in catatonic patients according to DSM-IV-TR ($n = 44$), there was a significant correlation between increased within FNC in cortico-striatal state and NCRS motor scores. The data support a neuromechanistic model of catatonia that emphasizes a key role of disrupted sensorimotor network control during distinct functional states.

KEYWORDS
catatonia, dynamic functional network connectivity, MRI, sensorimotor neuroscience, static functional network connectivity

1 | INTRODUCTION

Catatonia is a transnosologic psychomotor syndrome with high prevalence in schizophrenia spectrum disorders (SSD). Catatonia is of high clinical relevance, since its acute symptom expression can lead to

Fabio Sambataro and Dusan Hirjak contributed equally to this study.

severe and potentially life-threatening complications as in lethal catatonia (Carroll & Taylor, 1997; Tang, Leung, Ungvari, & Leung, 1995). Understanding the pathogenesis of catatonia is important for both diagnostic refinement and development of novel treatment approaches (Hirjak, Northoff, Taylor, & Wolf, 2020). Over the last 140 years, two seemingly opposing concepts of catatonia emerged: earlier but also some current scientists favor the understanding of catatonia as a purely motor syndrome (Bush, Fink, Petrides, Dowling, & Francis, 1996; Fink, 1994, 2013), while other recent scientists understand catatonia in terms of Kahlbaum (2007, 1874) as a truly psychomotor syndrome (Hirjak, Kubera, Wolf, & Northoff, 2020; Hirjak, Northoff, et al., 2020; Hirjak, Wolf, & Northoff, 2019). In recent years, a number of neuroimaging studies have been devoted to the psychomotor approach of catatonia (for review see Hirjak, Kubera, et al., 2020). Structural and functional differences between SSD patients with and without catatonia have been revealed, predominantly comprising frontoparietal, thalamic and cerebellar regions (Hirjak et al., 2019, 2020). Previous studies suggest that catatonic symptoms are modulated not only by motor regions, but also by brain regions traditionally involved in affect regulation and visuospatial cognition, as a part of the cerebello-thalamo-cortical circuit (CCTCC) which has been suggested to be abnormal in SSD (Bernard & Mittal, 2014; Northoff, Hirjak, Wolf, Magioncalda, & Martino, 2020a). Although the above-mentioned studies shed light on the intersection of sensorimotor, affective and cognitive networks in the pathogenesis of catatonia, they did not take into account the interplay between networks [functional network connectivity (FNC)] along with its recurring patterns of dynamic change over time (i.e., dynamic FNC, "chronnectome"; Allen et al., 2014). Catatonic symptoms may essentially arise from spatiotemporally unstable within and between FNC interactions that eventually could lead to deficient adaption of psychomotor function to constantly changing environmental demands. A viable way to specifically address this issue is by assessing spatiotemporal dynamics of within and between FNC using a well-established multiple analysis of covariance (MANCOVA) approach (Sambataro et al., 2019). Also, chronnectome fingerprints can be measured by using meta-state analysis. Meta-state framework interprets a dFNC state as resulting from the probability of being in several co-existing sets of brain network connectivity patterns at a specific time point, and therefore reflects the global dynamic properties of the brain (Miller et al., 2016).

In this study, we employed resting-state fMRI complemented by multivariate statistical techniques to investigate specifically both static functional network connectivity (sFNC) and dynamic FNC (dFNC) of multiple neural networks related to catatonia symptom expression in SSD. This is important because spatiotemporally stable functional network connectivity (FNC) is crucial for information transfer across remote brain areas, which form networks responsible for affect regulation, visuospatial cognition and the coordination and execution of sensorimotor activities. This work had two main objectives: First, conducting a categorical approach [i.e., comparing SSD patients with and without catatonia according to Northoff Catatonia Rating Scale (NCRS); Hirjak, Thomann, Northoff, Kubera, & Wolf, 2017], we predicted both static and dynamic FNC differences between cortical and subcortical sensorimotor networks and neural systems responsible for affective processing and visuospatial function [i.e., sensorimotor network (SM), basal ganglia (BG), executive (EXE), salience (SAL), and striato-thalamic systems (STH)] between patients with and without catatonia. Second, following a dimensional perspective on catatonia (Heckers, Tandon, & Bustillo, 2010; Ungvari, Caroff, & Gerevich, 2010), we explored relationships between distinct dimensions of catatonia—that is, motor, affective, and behavioral domains—and both static and dynamic FNC. In particular, we hypothesized that patients with catatonia would exhibit altered chronnectome fingerprints and particularly decreased neural dynamism reflecting disrupted SM control during distinct dynamic FNC states.

2 | METHODS

2.1 | Participants

We examined a total of 68 right-handed (Oldfield, 1971) patients satisfying DSM-IV-TR (Sass, Wittchen, Zaudig, & Houben, 2003) criteria for schizophrenia ($n = 63$) or schizoaffective disorder ($n = 3$) (Hirjak, Kubera, et al., 2019; Hirjak, Rashidi, et al., 2020). The inclusion and exclusion criteria are listed in the Appendix S1. 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.

2.2 | Clinical assessment

All patients were recruited and examined within 1 week after partial remission of psychotic symptoms (see Appendix S1). The present study used both a categorical and a dimensional approach to investigate intrinsic neural network dynamics in catatonia (Dazzan et al., 2004). This approach has already been used elsewhere (Hirjak, Kubera, et al., 2019; Hirjak, Rashidi, et al., 2020). 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. Daily doses of antipsychotic medication were converted to olanzapine equivalents (OLZ) according to the classical mean dose method (Leucht et al., 2015). For a detailed assessment of catatonic symptoms we used the German version of the Northoff Catatonia Rating Scale (NCRS; Hirjak et al., 2017). The scale measures the presence and severity of 40 catatonic signs, considering three distinct dimensions of catatonia: motor (13 items), affective (12 items), and behavioral (15 items) symptoms. Northoff et al. (1999) considered a full catatonic syndrome as characterized by the presence of at least one symptom from each dimension, that is, motor, affective, and

behavioral (i.e., hypokinesias and hyperkinesias, affective symptoms, and behavioral alterations), and not solely, for example, motor and/or behavioral. Northoff et al. (1999) developed their own scale based on Kahlbaum's original monograph, historic descriptions and available studies on catatonia. The authors opted for an inclusive approach, because there is no evidence for excluding any catatonic symptoms and they sought to map the complexity of catatonia. Each item can be scored on a 0 to 2 point scale and seeks to be operational. In some items direct quantification is used to estimate symptom severity and in other items specific procedures to elicit the symptom is provided (Northoff et al., 1999).

Therefore, in a first step, we followed a categorical (between-group comparison) approach, using the NCRS criteria (Hirjak et al., 2017) to cover all three categories of catatonia and to identify a clear cut-off to distinguish subjects with (NCRS total score ≥ 3; at least 1 point in the three different symptom categories; i.e., motor, behavioral, and affective) and without (NCRS = 0) catatonia (presence vs. absence). Thirty SSD patients (2 patients with schizoaffective disorder) were operationally defined as having catatonia according to NCRS. The control group which comprised 28 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. This approach allows us to investigate neural underpinnings of catatonia controlling for the effects of SSD (Dazzan et al., 2004; Gay et al., 2013). In a next step, we followed a dimensional (correlative) approach, using the DSM-IV-TR criteria for catatonia [1 motor and at least 1 other symptom (behavioral or affective)] to examine the neurobiological continuum in SSD patients with low and high severity of catatonia (Sass et al., 2003). Forty-four SSD patients (3 patients with schizoaffective disorder) were operationally defined as having catatonia according to DSM-IV-TR (Sass et al., 2003).

2.3 | MRI acquisition

MRI scans were acquired at CIMH on a 3.0 Tesla Magnetom TIM Trio MR scanner (Siemens Medical Systems, Erlangen, Germany) equipped with a 32 channel multiarray head-coil. The scanner protocol included three measurements: a resting-state scan and two structural scans [diffusion-tensor-imaging data and three-dimensional magnetization-prepared rapid gradient-echo (3D-MPRAGE) images]. For rs-fMRI (duration = 6 min), 167 whole-brain echo planar imaging (EPI) volumes were recorded in an axial orientation with the following imaging parameters: repetition time = 1,790 ms, echo time = 28 ms, field of view = 192 × 192 mm, flip angle = 76°, voxel size = 3 × 3 × 3 mm, 34 slices, and slice thickness = 3 mm. The fMRI scans slice acquisition order was sequential. For acquisition of resting-state data, participants were instructed to remain as still as possible, to keep their eyes closed, to not think about anything in particular, and not to fall asleep. Adherence to these instructions was verified by verbal contact immediately after the resting-state scan and as part of a postscanning exit interview. T1-weigthed 3D-MPRAGE data with following parameters were obtained: 176 sagittal slices, field of view = 256 × 256 mm, voxel size = 1 × 1 × 1 mm, TR = 2,530 ms, TE = 3.8 ms, TI = 1,100 ms, and flip angle = 7°.

2.4 | Image processing

Imaging data were preprocessed using Data Processing & Analysis for Brain Imaging version 4.2 (DPABI, Chao-Gan & Yu-Feng, 2010, see Appendix S1). A group of spatial independent component analysis (ICA) was performed on preprocessed fMRI data using the Group ICA of fMRI Toolbox [GIFT4.0b; http://trendscenter.org/software/gift] as described elsewhere (Sambataro et al., 2010; see Appendix S1). Independent components were screened for artifacts and reliability, thus resulting in 33 intrinsic networks (INs) independent components (ICs), which included the following features per each subject: 33 spatial maps (SM), 33 spectra, and one between-functional networks connectivity (FNC) matrix. Spatial maps were thresholded with a *t*-score > mean + 4 standard deviations (Allen et al., 2014). The multitaper method was used to estimate spectra from detrended time courses (TCs) using chronux (http://chronux.org). Detrended TCs after despiking (https://afni.nimh.nih.gov/pub/dist/doc/program_help/3dDespike.html), low-pass filtered (cut-off = 0.15 Hz) detrended TCs were pairwise correlated, and Fisher's *Z*-transformed, thus resulting in a 33 × 33 FNC cross-correlation matrix.

3 | STATIC FUNCTIONAL NETWORK CONNECTIVITY

To test the effects of catatonia on the IC features we used a multivariate model selection approach (MANCOVA) that uses a backward-stepwise selection procedure to test the significance of a reduced model followed by univariate testing. The full model included the following significant covariates (false discovery rate; FDR) approach with $\alpha = 0.05$: diagnostic group (patients with and without catatonia) as predictor, and demographics (age and sex), clinical ratings (PANSS positive, negative and general scores), antipsychotic treatment (Olanzapine equivalents), structural deformation, and motion extent as nuisance variables. All spatial coordinates were reported in the Montreal Neurological Institute (MNI) system.

4 | DYNAMIC FUNCTIONAL NETWORK CONNECTIVITY

The dFNC was performed with a sliding window approach using the dFNC toolbox in GIFT (Damaraju et al., 2014; see Appendix S1). Two statistical approaches were used to estimate dFNC: clustering states that allows the assessment of the frequency and structure of reoccurring dFNC patterns; and assessment of changes of cluster states engagement arranged across time via meta-states, thus allowing the characterization of moving from a meta-state to another in a 5-dimensional space.

4.1 | Cluster states

To identify dFNC states in the native state space, k-means clustering of windowed functional connectivity matrices was repeated 100 times. For each state, an index of dynamic fluidity, mean dwell time, defined as the average time (measured as number of consecutive windows) that subjects remained in the one FC state and the number of transitions were estimated (Allen et al., 2014).

4.2 | Meta-states

Group dFNC was decomposed into maximally independent prototype connectivity patterns using spatial group ICA with a model order of 5, that has been proven to be sufficient to include complex additive effects and keep a richly featured basis pattern in recent literature (Miller et al., 2016). Individual connectivity patterns for group ICA meta-states were calculated using a regression approach of each subject's dFNC data at each time window on the group ICA meta-states. To increase their computational tractability, connectivity patterns were discretized to eight bins following their signed quartile, thus providing a pro-state and an anti-state based on their sign, positive and negative, respectively. A meta-state is defined by a vector of five discretized connectivity patterns, and the trajectories from a meta-state to another within this discrete 5-dimensional state were calculated for each subject and time point. In this framework, a subject could be in more than one meta-state at a specific time point, and the probability of being in one meta-state changes dynamically. These dynamic changes during the whole scan were quantified using the following parameters: dynamic fluidity, including meta-state number, which is the number of meta-states the subjects occupied and meta-state changes, which is the number of switch between meta-states (an estimation of the speed of switches); dynamic range, including the meta-state span, which is the largest L1 distance between two meta-states (an estimation of divergency between states) and meta-state total distance, which is the overall disturbance traveled through the space state (sum of L1 distances between successive meta-states).

4.3 | Group comparisons of dynamic functional connectivity

The primary measures of interest were the state dwell times, indicating for each state the average length of the single time periods that subjects stayed in that FC state, before switching to another state. To test for differences between SSD patients with and without catatonia, a MANOVA was conducted with each state's dwell time as dependent variables, and diagnosis (SSD-Cat versus SSD) as an independent variable. We computed a subject median (computed element-wise) for each partition from the subject windows that were assigned to that partition as a representative connectivity pattern of each subject for that state. To investigate if the observed effects of diagnosis on static FNC (sFNC) are primarily driven by certain dFNC states, we used these subject medians for each state and evaluated the differences using two-sample *t*-tests in a univariate manner. All of the results reported were FDR statistically significant with an $\alpha = 0.05$. We also compared indexes of dynamic fluidity and dynamic range between diagnostic groups using one-tailed two sample *t*-tests.

5 | STATISTICAL ANALYSES

Demographics and clinical features were compared using two-sample *t*-test for continuous variables and χ^2 test for categorical variables, respectively. Partial Pearson's correlation analyses were used to assess the relationship between the static and dynamic connectivity parameters (already adjusted for the variables included in the MANCOVA model) and NCRS scores, considering Neurological Soft Signs (NSS, assessed by means of the Heidelberg NSS Scale; Schroder et al., 1991), dyskinesias [Abnormal Involuntary Movement Scale, AIMS; Guy, 1976; akathisia (Barnes Akathisia Scale, BARS); Barnes, 1989, 2003; and parkinsonism (Simpson Angus Scale, SAS); Simpson & Angus, 1970] as covariates. Statistical significance was assessed using an FDR $\alpha = 0.05$.

The selection of the respective nuisance variables for the categorical and dimensional approaches was based on different hypotheses, the influence of individual covariates on the target variables (FC metrics and catatonic symptoms) (Mamah, Ji, Rutlin, & Shimony, 2019; Payoux et al., 2004), previous MRI studies on motor abnormalities in SSD (Hirjak, Kubera, et al., 2019; Hirjak, Rashidi, et al., 2020; Huttlova et al., 2014; Walther et al., 2017) and the recommendations of the neuroimage community (Barnes et al., 2010; Hyatt et al., 2020) and the European collaboration on movement and sensorimotor/psychomotor functioning in SZ and other psychoses (ECSP) (Walther et al., 2020).

6 | RESULTS

6.1 | Clinical and demographical data

Demographic and clinical data are shown in Table 1. The lowest NCRS total score in the catatonia group ($n = 29$) was three, all other SSD catatonia patients showed a higher NCRS total score [NCRS total score of 4 (3 patients), 5 (4 patients), 6 (7 patients), 7 (5 patients), 8 (3 patients), 9 (1 patient), 10 (1 patient), 11 (2 patients), 12 (1 patient), and 14 (1 patient)].

6.2 | Categorical approach

6.2.1 | Following the categorical (between-group comparison) approach, 33 INs passed quality control

Those INs composed the following brain networks: the basal ganglia (BG: IN4, IN12), the auditory (AUD: IN18), the sensory-motor (SM: IN6, IN7, IN10, IN13, IN15, IN19, and IN22), the visual (VIS: IN1, IN5,

TABLE 1 Clinical and demographic variables in SSD patients with ($n = 30$) and without ($n = 28$) catatonia according to NCRS-dv

	Patients with catatonia ($n = 30$)	Patients without catatonia ($n = 28$)	t[a]	df[a]	Sig. (2-tailed)[a]
Age	39.40 ± 10.49	38.71 ± 10.77	−0.246	56	.807
Gender (M/F)[b]	16/14	13/15	−0.276[b]	1	.599
Education (years)	13.77 ± 2.41	13.25 ± 3.15	0.703	56	.485
Olanzapine equivalents	18.03 ± 9.64	18.82 ± 12.55	−0.27	56	.788
Duration of illness (years)	12.27 ± 11.53	7.57 ± 8.91	1.726	56	.09
PANSS total score	80.27 ± 20.73	56.39 ± 19.69	4.489	56	**<.001**
PANSS positive score	18.93 ± 8.18	13.21 ± 6.24	2.976	56	**.004**
PANSS negative score	21.17 ± 8.63	13.36 ± 6.37	3.895	56	**<.001**
PANSS global score	40.40 ± 11.85	29.93 ± 9.82	3.648	56	**.001**
GAF	57.97 ± 14.96	75.00 ± 15.98	−4.191	56	**<.001**
CGI-S	4.50 ± .90	3.46 ± .69	4.885	56	**<.001**
NCRS motor score	1.87 ± 1.33	0	7.410	56	**<.001**
NCRS affective score	2.80 ± 1.66	0	8.871	56	**<.001**
NCRS behavior score	2.27 ± 1.20	0	9.976	56	**<.001**
NCRS total score	6.90 ± 2.60	0	14.011	56	**<.001**
SAS total score	3.27 ± 2.24	2.14 ± 2.17	1.936	56	**.058**
AIMS total score	1.83 ± 3.05	0.61 ± 1.96	1.804	56	**.077**
BARS global score	1.20 ± 1.51	0.50 ± 1.00	2.058	56	**.044**

Note: Data are mean ± *SD*. Significant results ($p < .05$) are displayed in bold font.
Abbreviations: AIMS, Abnormal involuntary movement scale; BARS, Barnes Akathisia Rating Scale; BPRS, Brief Psychiatric Rating Scale; CGI-S, Clinical Global Impression Scale (Severity); GAF, global assessment of functioning; NCRS, Northoff Catatonia Rating Scale; PANSS, Positive and Negative Symptoms Scale (p, positive, n, negative, g, global); SAS, Simpson and Angus Scale; SSD, Schizophrenia spectrum disorders.
[a]The *F*-values and *p*-values were obtained using an independent samples *t*-test.
[b]The *p*-values for distribution of gender were obtained by chi-square test (Pearson chi-square).

and IN14), the default mode network (DMN, IN3, IN8, IN9, IN21, IN25, IN28, IN32, and IN39), the salience (IN2, IN11, IN33, and IN55), and the executive (EXE: IN20, IN30, IN34, IN35, IN42, IN46, IN52, and IN60) (see Table S1 for further details). Five cluster states were estimated: State 1 characterized by high within-network correlation in SM, VIS, and DMN; State 2 with high within-network correlation in SM; State 3 with moderate within-network correlation in SM and DMN: State 4, with high within network correlation in BG, SM, DMN, and high negative correlation between DMN and EXE, BG, SM, and SAL (Figure 2a).

Effect of catatonia on static connectivity

Multivariate analyses yielded significant differences for the effects of catatonia in the spatial maps, in the spectra but not in static FNC (see Figure S1). In particular, we found an effect of catatonia on the spatial maps of the BG (IN12), the SM (IN7 and IN19; Figure S2), the DMN (IN19), and in the EXE (IN35 and IN46) networks. Stringent univariate analyses confirmed significantly increased IC loadings in the left Inferior Semi-Lunar Lobule/biventer lobule ($x, y, z = -15, -60, -51$, $k = 43$, $T = 6.32$; Figure 1a) within the SM network (IN7; Figure S2) in patients with relative to those without catatonia. The spectra of the BG (IN4), SM (IN13), VIS (IN1), DMN (IN21, IN39), SAL (IN55), and EXE (IN34, IN42) were modulated by catatonia. Univariate analyses indicated reduced very low frequency oscillations (VLFOs) in the 0.009–0.04 Hz frequency in BG (IN4), VIS (IN1), SAL (IN55), and EXE (IN42) in patients with relative to those without catatonia (Figure 1b). In SSD-Cat we found a positive partial correlation between NCRS motor scores and VLFOs in IN55 ($r = .439$, $p = .025$) and between NCRS behavior and VLFOs IN4 ($r = -.399$, $p = .043$).

Effect of catatonia on dynamic connectivity

Cluster states: Catatonia was associated with reduced number of transitions ($t = 1.69$, $p = .048$), along with longer dwelling in state cluster 1 ($t = 2.150$, $p = .036$) and reduced dwelling in state 4 ($t = 1.972$, $p = .05$) in categorical analyses (Figure 2b). *Meta-states*: In SSD-Cat relative to SSD, we found decreased number of state changes ($t = 2.07$; $p = .021$) and total distance ($t = 2.41$; $p = .010$) (Figure 3). None of the NCRS subscales showed significant association with dynamic connectivity measures.

Finally, to exclude that the effects of catatonia on static and dynamic connectivity in SSD patients were unduly driven by a total of two patients with schizoaffective disorders, we rerun univariate analyses with the exclusion of these patients. The analyses confirmed most of our findings although with reduced significance (see Appendix S1).

6.3 | Dimensional approach

Following the dimensional (correlational) approach, 28 INs passed quality control (see Appendix S1). Those INs composed the

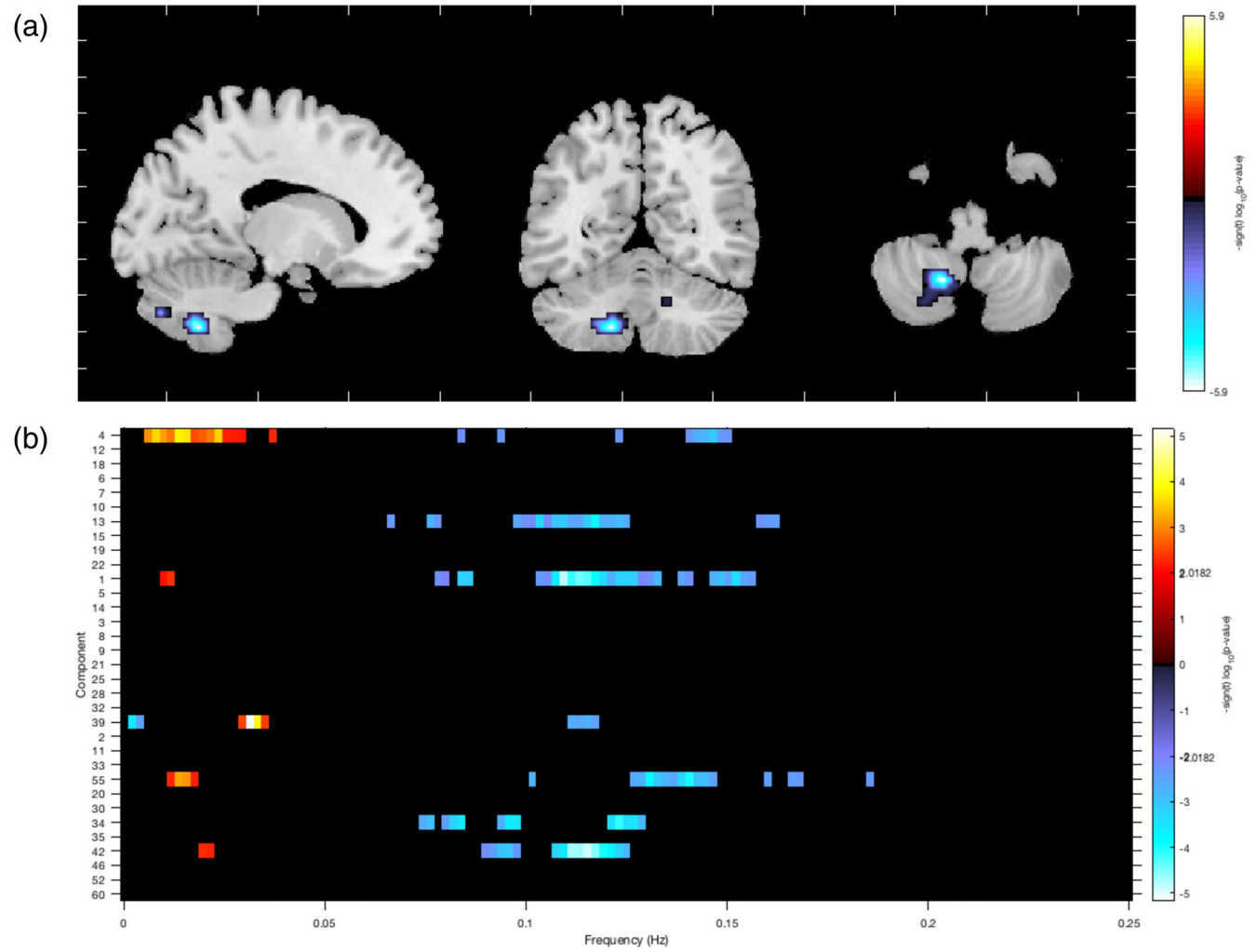

FIGURE 1 Catatonia is associated with altered connectivity of multiple brain networks: (a) Spatial extent of increased connectivity in the left inferior semi-lunar lobule within the sensory motor and cerebellar network (IN7) in SSD-Cat in categorical analyses. (b) SSD-Cat had reduced power in the low frequency spectrum in the basal ganglia (IN4), visual (IN1), default Mode network (IN39), salience (IN55), and executive (IN42) networks relative to SSD. Spatial maps of IN connectivity differences are thresholded at $p = .005$ and corrected for multiple comparisons with $\alpha = 0.05$ and overlaid on the MNI brain template. Color bar indicates $-\text{sign}(t) * \log10(p)$ and t-scores for the SSD > SSD-Cat comparison, respectively. SSD-Cat, schizophrenia spectrum disorders with catatonia; SSD, schizophrenia spectrum disorders; MNI, Montreal Neurological Institute

following brain networks: the basal ganglia (IN35 and IN71), the auditory (IN22), the sensory-motor (IN1, IN8, IN10, IN20, IN32, IN33, and IN37), the visual (IN4, IN7, and IN13), the default mode network (IN5, IN23, IN 27, IN28, and IN53), the salience (IN29, IN39), the executive (IN2, IN15, IN17, IN18, IN31, IN34, IN38, and IN54) see Table S2 for further details. Five cluster states were estimated with State 1 characterized by moderate within-network correlation in SM and VIS and DMN; State 2 that was characterized sparse correlation and underrepresented in the sample and therefore excluded; State 3 with moderate within-network correlation in VIS and DMN: State 4, with high within network correlation in SM, VIS, DMN, and high positive correlation between VIS and AUD and these sensory networks and EXE, BG, SM, and DMN: State 5 where just a modest within network correlation in VIS network was present (Figure S3).

6.3.1 | Association between NCRS scales and static connectivity

Multivariate analyses yielded significant differences for the effects of NCRS subscales in the spatial maps, in the spectra, and in static FNC (see Figure S2). In particular, for the spatial maps we found an association with the affective subscale of NCRS and the VIS (IN7) and the EXE (IN18, IN38); for behavioral subscale of NCRS and the SAL (IN29), EXE (IN31); for motor subscale of NCRS and the SM (IN10). Univariate analyses confirmed a significant association between NCRS motor and the IC loadings of the right Crus1/2 ($x, y, z = 36, -72, -36$, $k = 123$, $T = 6.7616$; Figure 4a), the left Crus 2 ($x, y, z = -15\ -87\ -33$, $k = 21$, $T = 4.0669$; Figure 4a) and the bilateral Crus 2 ($x, y, z = 6\ -81\ -30$, $k = 8$, $T = 3.4099$; Figure 4a) clusters within the sensory motor network (IN10). NCRS behavior scores were associated with the IC

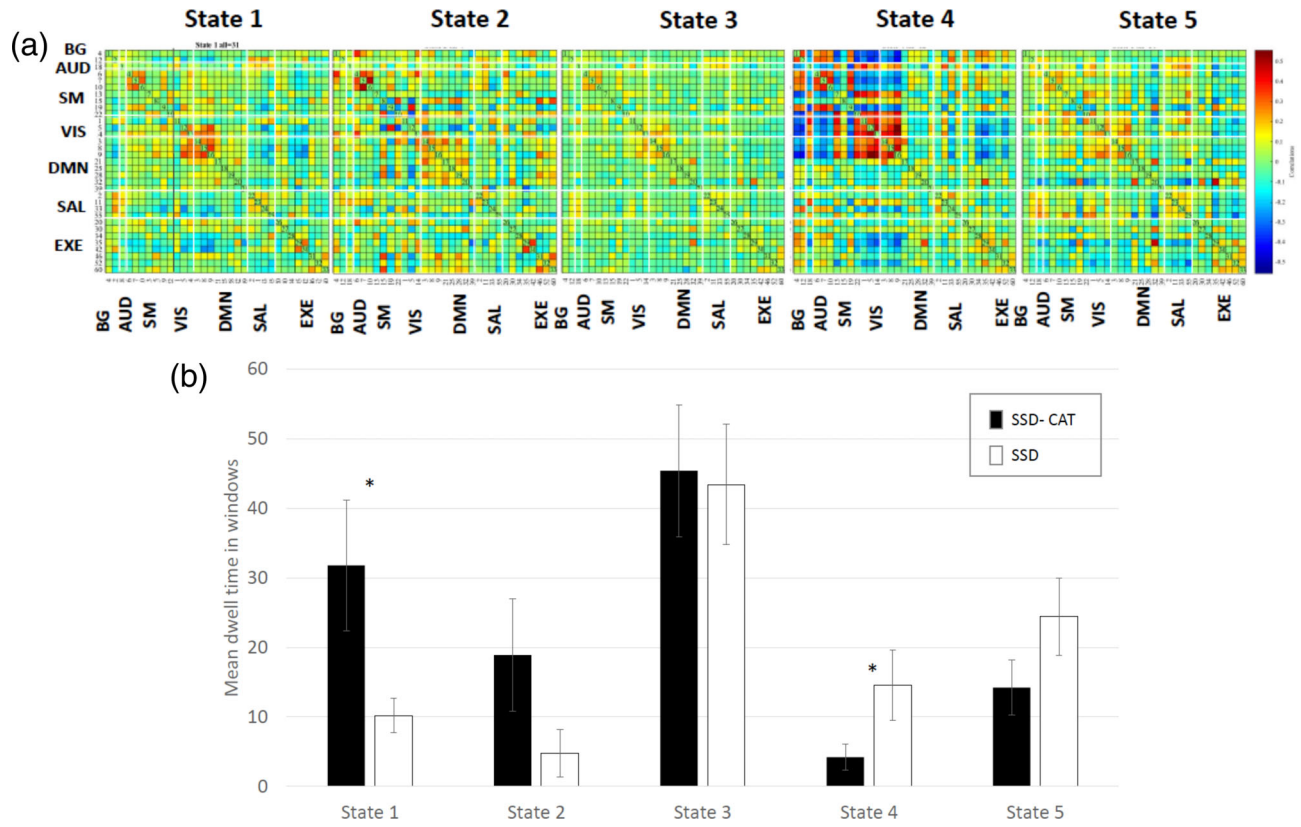

FIGURE 2 Catatonia is associated with increased persistence in states with low network interplay. (a) The cluster states resulting from the dynamic functional network connectivity (dFNC) analysis identified by k-means clustering on the whole-group level. Median cluster centroids in the correlation matrices (among the 33 considered network components) for each of the five dFNC States are reported. Color bar indicates the magnitude of each correlation. (b) Dwell times (and SEM) in the different State clusters per SSD sample. SSD-Cat are indicated in black and SSD in white. Dwell times are given in number of TR windows (1 window = 2 s). Significant differences in dwell times are marked with * for the SSD vs. SSD-Cat contrast with $p < .05$. SSD-Cat, schizophrenia spectrum disorders with catatonia; SSD, schizophrenia spectrum disorders; TR, repetition time

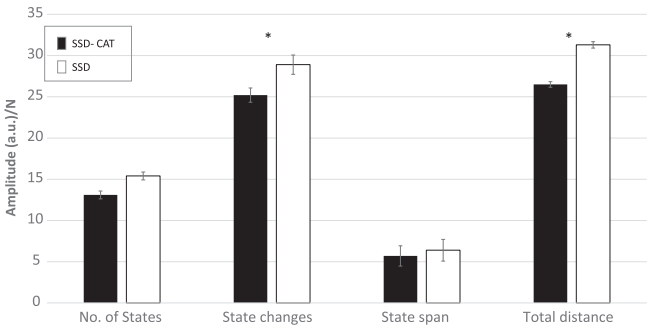

FIGURE 3 Catatonia is associated with reduced fluidity of meta-states. Bar plots indicate number of meta-states, number of state changes, state span, and total distance per each SSD sample, respectively. Significant differences for the SSD > SSD-Cat contrast are marked with * for $p = .05$. SSD-Cat, schizophrenia spectrum disorders with catatonia; SSD, schizophrenia spectrum disorders

loadings of the left superior frontal gyrus ($x, y, z = -36, 18, 57$, $k = 7$, $T = 5.8304$; Figure 4b) within the EXE (IN31). For the spectral analyses, we found an association with the affective subscale of NCRS and the LOFs SAL (IN29); for behavioral subscale of NCRS and the DMN (IN28), respectively. None of these associations were confirmed by univariate analyses.

6.3.2 | Association between NCRS scales and dynamic connectivity

Cluster states: We did not find any correlation with NCRS scores. *Meta-states*: We found a partial correlation between the number of meta-states and NCRS affective scores ($\rho = 0.331$, $p = .037$), and between the state span and NCRS behavioral scores and NCRS total ($\rho = 0.408$, $p = .009$ and $\rho = 0.347$, $p = .028$, respectively).

Finally, to exclude that the association between NCRS scales and static and dynamic connectivity in SSD patients were unduly driven by a total of three patients with schizoaffective disorders, we rerun univariate analyses with the exclusion of these patients. The analyses confirmed most of our findings although with reduced significance (see Appendix S1).

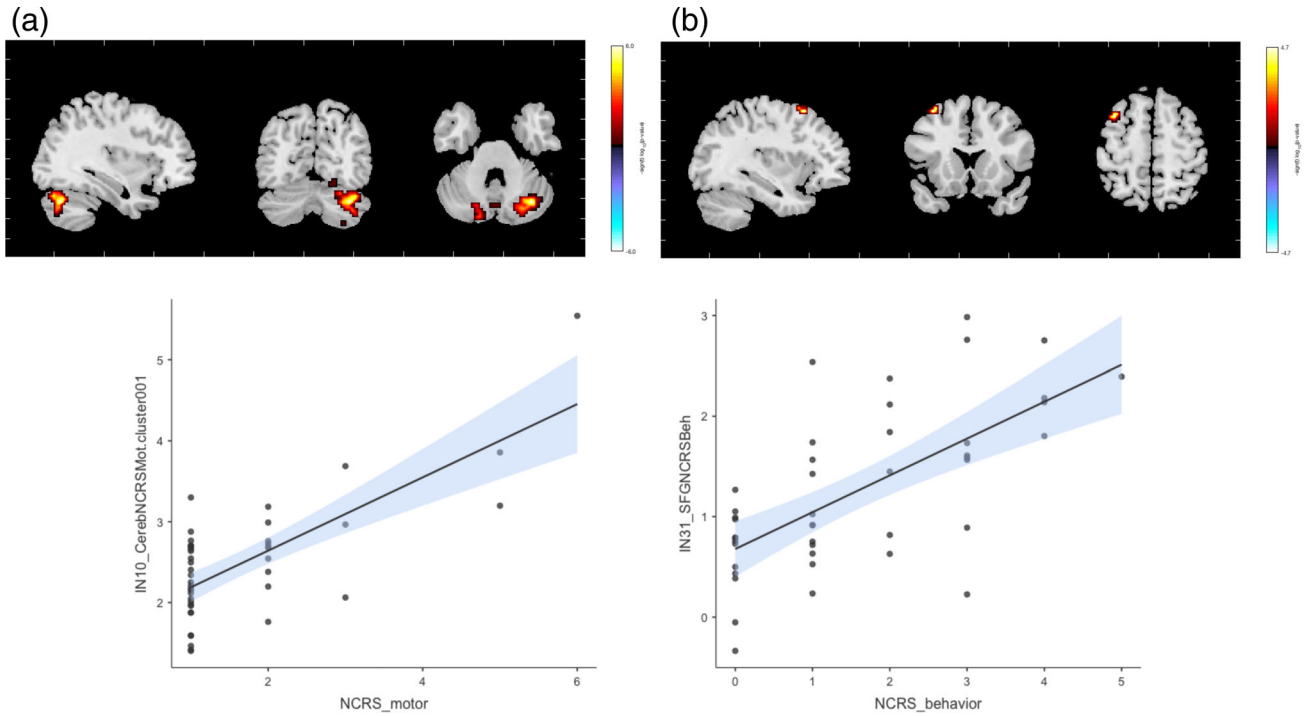

FIGURE 4 Catatonia severity is associated with increased connectivity in somatomotor and executive networks. (a) Increased connectivity in bilateral cerebellum within the sensory motor network (IN10) was associated with NCRS motor scores. (b) Increased connectivity in the left superior frontal gyrus within the executive network (IN31) was associated with NCRS behavior scores. Top rows: spatial maps of IN connectivity differences are thresholded at $p = .005$ and corrected for multiple comparisons with $\alpha = 0.05$ and overlaid on the MNI brain template. Lower rows: scatterplots of IN loadings and NCRS subscales are displayed with linear best fit lines. Color bar indicates $-\text{sign}(t) * \log10(p)$ and for NCRS motor and behavior scales, respectively. NCRS, Northoff Catatonia Rating Scale; MNI, Montreal Neurological Institute

7 | DISCUSSION

The major aim of this study was to examine intrinsic neural network dynamics in catatonia. Three main findings emerged: First, SSD patients with catatonia showed increased sFNC in cerebellar networks along with decreased low frequency oscillations in BG, SAL, DMN, EXE, and VIS networks when compared with noncatatonic patients. Second, patients with catatonia had reduced state changes and total distance of the meta-states and dwelled more in a state characterized by high within-network correlation of the SM, VIS, and DMN, and less time in a state characterized by the interplay between BG, SM, and SAL networks with respect to patients without catatonia. Finally, distinct NCRS subdomains were associated with SM and EXE network sFNC.

7.1 | Static functional network connectivity

Catatonia can be conceptualized as a truly psychomotor syndrome, which is characterized by unique spatiotemporal dynamics of within and between FNC. First, we found increased sFNC in cerebellar regions within the SM network along with decreased low frequency oscillations in BG in catatonic patients. This finding is in line with congruent evidence generated by diverse MRI methods in the last 2 years that pointed to the role of cortical and subcortical networks (e.g., BG mediated by dopamine) as well as aberrant higher-order frontoparietal networks [e.g., SM insufficiently modulated by (GABA)-ergic and glutamatergic transmission] as modulators of catatonic symptoms in SSD patients (Hirjak, Kubera, et al., 2020; Hirjak, Rashidi, et al., 2020; Northoff, Hirjak, et al., 2020a). In particular, the increased sFNC in the left inferior semi-lunar lobule/biventer lobule within the SM is in accordance with recently introduced concept of psychomotor mechanisms in psychiatric disorders (Northoff, Hirjak, et al., 2020a) that postulates a strong interconnection of cerebellar circuits with BG and limbic regions as well as with multiple motor and nonmotor regions of the cortex (Bostan & Strick, 2018). This said, SM cortical regions, BG, and cerebellum form an integrated network with dense multitransmitter modulated interconnections between their respective motor, affective (limbic), and cognitive territories (Bostan & Strick, 2018). More precisely, cerebellum is responsible for the temporal coordination of motor, affective, and cognitive functioning (Moussa-Tooks et al., 2019; Northoff, Hirjak, Wolf, Magioncalda, & Martino, 2020b). Decreased low frequency oscillations in BG and increased sFNC in cerebellar regions might lead to aberrant temporal map, disinhibition, and hyperactivity of cortical SM regions such as M1 resulting in development of psychomotor abnormalities (Caligiore, Mannella, Arbib, & Baldassarre, 2017). Additionally, it is likely that both increase and decrease of a neurotransmitter within the SM, BG and cerebellar networks will influence psychomotor activity (Northoff, Hirjak, et al., 2020a). In particular, imbalance between the

individual neurotransmitters within the motor, affective, and cognitive parts of the cerebellum might lead to psychomotor dysfunction (i.e., motor, affective, and cognitive dysmetria) in catatonia. The present findings of increased sFNC corroborate another report on static FC in the sensorimotor system by Walther et al., who reported bilaterally increased connectivity from thalamus to primary motor cortex to be correlated with catatonic symptoms in schizophrenia (Walther et al., 2017). A similar relationship between subcortical–sensorimotor connectivity and psychopathological symptoms was also detected by Martino and colleagues (Martino et al., 2018). Interestingly, our findings also corroborate a recent study that combined activation likelihood estimate (ALE) meta-analysis with meta-analytic functional connectivity modeling (Chase et al., 2018). Chase et al. (2018) revealed interconnections between ventral striatum and sensorimotor regions, particularly presupplementary area, midbrain, and cerebellum. This study suggests that reward and sensorimotor systems are intricately linked in the pathophysiology of psychotic disorders. Furthermore, catatonic patients showed decreased FNC between SM and DMN as well as EXE. Contributions of DMN to catatonia are noteworthy given that this system essentially integrates internal and external stimuli to a coherent self-model (Metzinger, 2008) that is capable to distinguish between self-generated activity and extraneous processes (Ebisch & Aleman, 2016). Decoupling of language networks and DMN has been recently shown in patients with auditory verbal hallucinations, where DMN dysfunction could explain the lacking sense of agency while experiencing voices in the absence of a corresponding external stimulus (Broyd et al., 2009; Buckner & DiNicola, 2019; Kubera et al., 2019; Kubera et al., 2020). Similarly, reduced connectivity between SM and DMN may lead to spatiotemporal disintegration and subsequent difficulties in coordinating movements and behavior. SM–DMN-decoupling, as shown here for the first time in catatonia, may reflect a pathological mechanism underlying catatonia that has been so far not been highlighted by previous research.

7.2 | Dynamic functional network connectivity

In most of the dFNC states identified in our current study, the SM network was disrupted. In particular, in catatonia increased sFNC in the SM network was found along with the predominance of a dynamic network state with decreased FNC between BG and SM, BG, and SAL, suggesting that catatonia is characterized by aberrant temporal and spatial structuring and organization of FNC between SM, BG, and SAL. Our results unveil nuanced information about how catatonia is related to lost temporal coordination of affective, motor and behavioral functioning (Northoff, Hirjak, et al., 2020b). In keeping with this, chronnectome fingerprint analysis shows a reduced dynamic range and decreased dynamic fluidity for a brain network connectivity in catatonia. These changes reflect an overall impairment of the flexibility of the brain not only at the level of specific states, where patients with catatonia tend to dwell in states with reduced network interplay, but also at a global level with reduced overall dynamics of the brain as already showed in schizophrenia (Miller et al., 2016). This type of aberrant FNC could present clinically as akinesia, rigidity, posturing, and mutism. This notion receives support from the cerebellar findings of this study that emphasize the crucial role of the cerebellum in the temporal coordination of cerebral motor activity and bodily movements (Moussa-Tooks et al., 2019). Even though the involvement of cerebellar regions in the pathophysiology of catatonia has been postulated in very early imaging studies (Joseph, Anderson, & O'Leary, 1985; Wilcox, 1991), more recent MRI studies on psychiatric disorders did not identify significant association between cerebellum and catatonic symptoms (Dean et al., 2020; Hirjak, Rashidi, et al., 2020; Walther, Schappi, et al., 2017). Finally, the correlations between increased sFNC in bilateral cerebellum within the SM network and NCRS motor scores as well as between increased sFNC in the left superior frontal gyrus within the EXE network and NCRS behavioral scores corroborate our previous study that showed a significant relationship between cortical thickness in superior frontal cortex and NCRS behavior scores (Hirjak, Kubera, et al., 2019). Furthermore, the association between number of meta-states and meta-state span and NCRS affective and behavior score support the idea of altered dynamic connectivity underlying different catatonia symptom domains. Overall, the present results fit well with the idea of spatio-temporal psychopathology (Northoff, 2018; Northoff & Stanghellini, 2016; Northoff, Wainio-Theberge, & Evers, 2020): distinct symptom dimensions of catatonia are here assumed to be primarily based on changes in the brain's spatiotemporal dynamics as like abnormal dwelling times of specific states and abnormal low-frequency fluctuations over various networks. Together, these findings mark catatonia a truly global spatiotemporal disorder of the brain's dynamics which can well account for its literally psycho-motor rather than purely motor character (Northoff, Hirjak, et al., 2020b).

7.3 | Strengths and limitations

The study sample size, well-matched study groups, and the use of comprehensive set of sophisticated functional connectivity measures are the strengths of our rsfMRI study. However, some methodological aspects limit the generalizability of our results: First, the antipsychotic medication might have confounded the connectivity measures. Second, no statement can be made regarding the periodic course of catatonia. Future studies should longitudinally monitor catatonic symptoms, preferably using electronic wearables. Third, out of concern that some positive and negative symptoms might be misinterpreted as catatonic features, thus inflating NCRS scores, and because we found a significant difference in PANSS total scores between SSD-Cat and SSD patients, PANSS total score was included as a covariate in the between-group analyses. The phenomenon that psychopathological symptoms can exacerbate sensorimotor abnormalities including catatonia reflects the daily clinical practice. From a clinical perspective, psychopathological symptoms may also modulate the sensorimotor domain, especially when patients suffer from anxiety,

mania, impulsivity, anhedonia, or psychomotor slowing. Often catatonic symptoms can be confused or misclassified. Basically, the question arises what can be the concrete cause (e.g., negative symptoms, depression, or catatonia) of akinesia or hyperkinesia. Fourth, the lack of healthy controls may be a potential limitation of this study. Still, the examination of two homogeneous groups (catatonic and noncatatonic patients) allowed us to investigate neural underpinnings of catatonia controlling for the effects of SSD (Dazzan et al., 2004; Gay et al., 2013). Finally, we studied catatonic symptoms in SSD patients only, so that any inference on putative transdiagnostic mechanisms is premature at this stage. This said, we strongly advocate transdiagnostic MRI studies using instrumental assessments on catatonia.

8 | CONCLUSION

This study provides first evidence for both static and dynamic FNC changes in SSD patients with catatonia. The data suggest that catatonia is associated with distinct spatial and temporal dynamics of intrinsic neural network function. Importantly, dynamic changes of cerebellar and frontal regions are in-line with current transnosologic models of psychomotor dysfunction.

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CONFLICT OF INTEREST

The authors declare that no competing financial interests exist.

AUTHOR CONTRIBUTIONS

Fabio Sambataro: Data analysis, Interpretation of results, writing and manuscript revision. **Dusan Hirjak:** Design of the study, Data collection, Interpretation of the results, writing and manuscript revision. **Stefan Fritze:** Data collection. **Katharina M. Kubera:** Design of the study and Interpretation of results. **Georg Northoff:** Interpretation of the results, writing, and manuscript revision. **Vince D. Calhoun:** Data analysis. **Andreas Meyer-Lindenberg:** Interpretation of the results, writing and manuscript revision. **Robert C. Wolf:** Design of the study, data analysis, Interpretation of the results, writing and manuscript revision.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

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