Rigidity in Motor Behavior and Brain Functioning in Patients With Schizophrenia and High Levels of Apathy

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The aim of this study was to investigate whether apathy in schizophrenia is associated with rigidity in behavior and brain functioning. To this end, we studied associations between variability in dynamic functional connectivity (DFC) in relevant functional brain networks, apathy, and variability in physical activity in schizophrenia. Thirty-one patients with schizophrenia, scoring high on apathy, were included and wore an actigraph. Activity variability was calculated on the activity counts using the root of the Mean Squared Successive Difference (MSSD). Furthermore, we calculated DFC on resting-state data as phase interactions between blood oxygen-level dependent (BOLD) signals of 270 brain regions per volume. Variability (MSSD) in DFC was calculated for 3 networks, including the default-mode network (DMN), frontoparietal network, and salience-reward network (SRN). Finally, we calculated correlations between these DFC estimates and apathy and activity variability. First, lower activity variability was associated with higher levels of apathy. Second, higher levels of apathy were associated with lower variability in DFC in the DMN and SRN. Third, higher activity variability was associated with higher variability in DFC in the SRN. In conclusion, patients with schizophrenia and more severe levels of apathy showed less variability in their physical activity and more rigid functional brain network behavior in the DMN and SRN. These networks have been shown relevant for self-reflection, mental simulation, and reward processing, processes that are pivotal for self-initiated goal-directed behavior. Functional rigidity of these networks may therefore contribute to reduced goal-directed behavior, which is characteristic for these patients.

Key words: apathy/schizophrenia/dynamic functional connectivity/brain networks/motor behavior/rigidity

Introduction

Flexibility in cognition and behavior is important for psychological health.¹ Individuals, who are more flexible, are better able to modulate behavior to changing environmental demands; possess more characteristic features such as being vital, curious, explorative, and productive; and are more successful in areas such as work and social functioning.^{2,3} In contrast, rigidity in cognition and behavior has been shown to be increased in psychopathology.¹ This may be specifically the case in patients with schizophrenia who suffer from apathy. Apathy is regarded as a core negative symptom of schizophrenia and is associated with a loss of motivation, goal-directed cognitive activity, goal-directed behavior, and emotions.⁴ Often, the days of these patients consist of doing basic tasks and nonproductive activities (eg, lying in bed or watching television), instead of, eg, working, going to school, or undertaking social activities.⁵ Apathy is important to assess because it is burdensome for patients and related to poorer functional outcome.^{6,7} Moreover, adequate treatment options for apathy are lacking, which signifies the need for a deeper understanding of the neurobiological basis of this debilitating symptom.⁸ In this study, we aim to investigate whether apathy in schizophrenia is associated with rigidity in motor behavior and brain functioning.

First, we operationalize rigidity in *motor behavior* as less variable motor activity. Actigraphy can be used to objectively quantify motor activity using a wrist worn motion watch.⁹ This method has multiple advantages, specifically it is well tolerated, feasible, ambulatory, and noninvasive.⁹ A limited number of studies have investigated the association between apathy and activity level in patients with schizophrenia and found a negative correlation between the two variables (eg.^{10–12}). Another study found that activity level at baseline predicts the course of negative symptoms with treatment within a psychotic

episode.⁹ However, no study to date has investigated variability in motor behavior in relation to apathy.

Second, we operationalize rigidity in *brain functioning* as less variable functional connectivity (FC). In the disconnection hypothesis, abnormal FC is suggested to underlie symptomatology in schizophrenia.^{13–15} This hypothesis states that a failure of neuromodulatory mechanisms may lead to the formation of false inferences (eg, hallucinations and delusions) and maladaptive behavior.¹⁶ FC is defined as the temporal relationship between time series of different brain regions across the entire scan duration, thereby assuming stationarity (ie, static functional connections). However recently, it has been shown that the strength and directionality of functional connections changes over the course of minutes or even seconds, suggesting that dynamic functional connectivity (DFC; for a review, see Hutchison et al¹⁷) may be a more accurate measure to capture brain functioning underlying cognition and behavior. From a theoretical perspective, it would be of interest to investigate whether apathy, conceptualized as a rigid state of inactivity (ie, lack of self-initiated goal-directed behavior), is related to less variable DFC.

Although no studies have investigated the association between apathy and DFC, there are a number of studies that have investigated DFC in patients with schizophrenia and supported the suggestion of a dynamically more rigid brain in these patients. First, in patients with schizophrenia compared with healthy controls, less variance was found in DFC-based graph metrics, representing variation in global connectivity strength and functional integration and segregation of information processing.¹⁸ Second, it was observed that patients with schizophrenia, compared with healthy controls, dwell longer in a connectivity state characterized by weaker functional connections between networks and switch less between connectivity states.¹⁹ Third, two studies, using higher dimensional analysis and computational modeling, showed less DFC and weaker coupling between brain regions impacting DFC in patients with schizophrenia compared with healthy controls, respectively.^{20,21} In addition, the former study showed a reduction of DFC in patients with schizophrenia who experience more psychotic symptoms, specifically hallucinations.²¹

Previous research has shown a relationship between variation in brain signals and behavior. Studies have provided preliminary support for an inverted U-shaped curve of brain signal variability across the lifespan (ie, lower variability in infancy and older adulthood and higher variability in young adulthood) and a positive linear relationship between brain signal variability and cognitive performance (for a review, see Garret et al^{22,23}). Furthermore, differences in brain signal variability have been found between individuals with brain disease/injury and healthy controls.^{22,24,25} Thus, there seems to be an optimal level of variability in the brain that facilitates neural efficiency, a greater dynamic range and a greater ability to transition between brain states.^{22,23}

To conclude, we propose that apathy in schizophrenia is related to rigidity in motor behavior and that this is reflected in rigidity in brain functioning of brain networks, which are related to apathy and subserve self-initiated goal-directed behavior. Networks that have been shown to be affected in patients with schizophrenia, scoring higher on apathy, are the default mode network (DMN), frontoparietal network (FPN) and salience-reward network (SRN).^{26–29} To estimate DFC, we used a relatively novel method named phase synchronization, which has a higher temporal resolution than correlation-based sliding window analysis (SWA).³⁰ In this article, we hypothesized to find (1) lower variability in activity and lower variability in DFC in the DMN, FPN, and SRN in patients with schizophrenia scoring higher on apathy, (2) lower variability in activity to be related to lower variability in DFC in the DMN, FPN, and SRN in patients with schizophrenia that score high on apathy.

Methods

Participants

Data were available for 31 patients with schizophrenia, who scored high on apathy (study inclusion criterion: a score of ≥ 27 on the apathy subscale of the Apathy Evaluation Scale [AES]³¹). All patients are part of an ongoing multicenter treatment trial aimed to improve apathy with neurostimulative treatment (trialregister.nl: NTR3805). Participants (in- and outpatients) had a diagnosis of schizophrenia or schizoaffective disorder according to *DSM-IV-TR* criteria and were forwarded by their clinicians. Inclusion criteria were (1) age more than 18 years, (2) Dutch proficiency, (3) stability of antipsychotic medication use for at least 4 weeks before inclusion, and (4) eligibility for magnetic resonance imaging (MRI) and neurostimulative treatment. Exclusion criteria were (1) a history of neurological disorders or head injury, (2) a current diagnosis of an alcohol/substance dependence disorder, and (3) visual and auditory problems that cannot be corrected. All patients gave informed consent after explanation of the experimental procedure. The study was approved by the medical ethics committee of the University Medical Center Groningen and performed according to the Declaration of Helsinki (World Medical Association Inc, 2009). For demographics of the sample, see [table 1](#).

In this study, baseline data were used before start of the neurostimulative treatment (on a Monday). In the week prior to the start of treatment, participants took part in a baseline measurement that consisted of interviews, neuropsychological testing and a functional magnetic resonance imaging (fMRI) session. After these measurements, the actigraph was handed to the participants (mostly on a Thursday or Friday) with the instruction to wear it continuously during the neurostimulative treatment until the post measurement (weekend days before neurostimulative treatment, median = 2, range = 2; weekdays before neurostimulative treatment, median = 2, range = 0–4).

Table 1. Demographics ($n = 31$)

Variables	Mean/distribution	SD	Min	Max
Diagnosis, SZ/SZ-A	22/9			
Age	33.68	8.65	19	54
Sex, M/F	25/6			
BMI	26.39	5.39	17.36	38.20
Handedness ^a	2/28/1			
Education level ^b	0/0/0/5/14/9/3			
Living circumstances ^c	9/1/21			
Number of psychoses	2.77	1.75	1	9
Illness duration	8.19	4.27	2	16
Age at onset	23.61	7.21	11	50
Dopamine equivalent dose, mg	63.98	22.62	0	96.44
AES-C	46.87	6.45	31	60
SANS—apathy	14.42	3.05	7	20
SANS—total	55.74	11.78	29	78
PANSS—positive	13.45	4.86	7	23
PANSS—negative	18.16	3.87	10	24
PANSS—general	34.55	7.72	25	51
PANSS—total	66.16	13.89	43	95
CDSS	4.39	3.22	0	11
Activity variability ^d	744.22	381.61	90.88	2287.33

AES-C, Apathy Evaluation Scale, clinician rated; BMI, body mass index; CDSS, Calgary Depression Scale for Schizophrenia; F, female; M, male; mg, milligram; PANSS, Positive and Negative Syndrome Scale; SANS, Scale for the Assessment of Negative Symptoms; SZ, schizophrenia, SZ-A, schizoaffective disorder.

^aHandedness: left, right, ambidexter.

^bLevel of educational attainment.³² Levels range from 1 to 7 (1 = primary school not finished, 7 = pre-university/university degree).

^cLiving circumstances: sheltered living, admitted, other (independent/with parents)

^d $n = 30$.

Questionnaires

The Mini-International Neuropsychiatry Interview Plus (MINI-Plus) was used to confirm diagnosis of schizophrenia or schizoaffective disorder.³³ Subsequently, the following symptoms were assessed: (1) apathy with the Apathy Evaluation Scale, clinician rated (AES-C³⁴), (2) negative symptoms with the Scale for the Assessment of Negative Symptoms (SANS³⁵), (3) positive, negative and generalized psychopathology with the Positive and Negative Symptom Scale (PANSS³⁶), and (4) depression with the Calgary Depression Scale for Schizophrenia (CDSS³⁷). In case of missing items, which was uncommon (one item on the SANS), a hot-deck imputation was performed.³⁸

Actigraphy

Participants wore an actigraph (Actical Step, FG, FCC version; Respironics, Inc) in their natural environment. The actigraph was continuously worn around the wrist of the nondominant hand. For this study, 2 full weekend days (48 h) were selected for the analyses, because behavior has been shown to be more self-initiated and less externally driven during the weekend by, eg, school, work, supervised daytime activities, or therapy.^{10,39,40} Activity counts were recorded with a 1-min time interval and the data were extracted by means of Actical software (Respironics, Inc; for a technical explanation of the workings of activity

monitors, see John and Freedson⁴¹). To obtain a dynamic measure of activity, we calculated activity variability using the root of the Mean Squared Successive Difference (MSSD; variability measure⁴²). The root was taken for comparability to previous research.⁴³ This measure was calculated on the 10 most active hours per participant per weekend day to take into account that some participants may sleep more than others. Subsequently, a sum was calculated across the 2 weekend days (ie, 20 h in total). One participant was excluded for the analyses including activity variability as a variable, because this individual had been using construction equipment while wearing the actigraph. This resulted in a relatively high MSSD value, which could be designated as an outlier (>5 SD).

Medication

Effects of antipsychotic medication are largely mediated by blockade of dopamine D2-receptors, a neurotransmitter that is—among others—important for motor functioning.⁴⁴ In this study, 30 of 31 patients used antipsychotic medication. To take into account the effect of medication type and dosage, we estimated the dopamine D2-receptor occupancy for each participant (see [Supplementary Information S1](#)). Other types of medication were less frequently used (selective serotonin reuptake inhibitor: 4 patients; tricyclic: 0 patients; tetracyclic: 2 patients; benzodiazepines: 7 patients).

For this reason, we were unable to take into account the effect of medication type and dosage of these latter types of medication.

Image Processing and Time Course Extraction

For the image acquisition parameters, see [Supplementary Information S2](#). Image processing and analysis were performed using SPM12 (v6470; <http://www.fil.ion.ucl.ac.uk>), implemented in MATLAB 7.8.0 (The MathWorks Inc). Preprocessing of the data was performed (see [Supplementary Information S3](#) for details). Furthermore, scrubbing parameters were used to interpolate measurements on time points, which are possibly affected by motion artifacts (see [Supplementary Information S4](#)). Finally, we extracted the regional mean time series of 219 regions of interest (ROIs; [Supplementary Information S5](#)).

Phase Synchronization as a Measure of DFC

Phase synchronization was selected as a measure of DFC, instead of correlation-based SWA, because it has been shown that results based on SWA are dependent on window length and that it gives a poor estimation of the actual underlying correlations between brain areas within a window.⁴⁵ Furthermore, phase synchronization has a higher temporal resolution than SWA.³⁰ Phase synchronization was calculated by applying the Hilbert transform, which is a mathematical transform that is used to obtain the instantaneous phase and amplitude of a narrowband signal per

time point (ie, volume).³⁰ In this analysis, only the instantaneous phase was used and phase differences were calculated for each ROI pair per time point. The first 13 time points were discarded to ensure that at least one cycle has passed to obtain a reliable estimate of the instantaneous phase ($1/0.04$ [lowest frequency of the band-pass filter] = $0.25/2$ TR = 12.5 time points). Phase differences approach zero, when phase synchronization is higher. The end result is a phase difference matrix per time point per subject.

Definition of Brain Networks

A data-driven, iterative module decomposition procedure was applied to achieve an optimal modular structure using a proportional threshold of 1% ([Supplementary Information S6](#)). Input for this procedure was the binarized phase difference adjacency matrix averaged across subjects. First, nodes were partitioned into modules using the algorithm of Blondel et al,⁴⁶ wherein nodes are divided into groups with a maximum number of within-group edges (ie, connections) and a minimum number of between-group edges. Second, the statistic was further optimized by applying the modularity fine-tuning algorithm of Sun et al,⁴⁷ wherein nodes are randomly assigned to other modules until modularity no further improves. The end result is a module decomposition index that provides information on which node belongs to which module. In total, 5 networks were derived: somatosensory-motor network (SMN), DMN, visual network, FPN, and SRN ([figure 1](#)).

Fig. 1. Module decomposition. Nodes could be partitioned in 5 functional brain networks with a maximum number of within-group edges and a minimum number of between-group edges. Colors indicate the different networks that nodes belong to: SMN, somatosensory-motor network (yellow); DMN, default mode network (red); VN, visual network (purple); FPN, frontoparietal network (blue); SRN, salience-reward network (green). Nodes are pasted on a surface template of the human brain using BrainNet Viewer.⁴⁸ Top: lateral view; middle: cerebellum, coronal view; bottom: medial view.

Calculation of DFC Estimates and the Association With Apathy and Activity Variability

First, we calculated a proxy for the level of phase synchrony, based on the order parameter in Ponce-Alvarez et al⁴⁹, across nodes belonging to the DMN, FPN, and SRN separately (using the module decomposition index, see “Definition of Brain Networks”) per time point (see [Supplementary Information S7](#); step 1). Second, we calculated the MSSD on this order parameter to obtain variability of phase synchrony per network, resulting in 3 DFC estimates per subject (step 2). Third, we calculated Spearman correlations between these estimates and (1) apathy scores (AES) and (2) activity variability (1-tailed test, see the last paragraph of the “Introduction” section for the specific hypotheses; step 3). Fourth, to observe whether the associations found in the former step are possibly affected by confounding variables, we calculated Spearman correlations between the DFC estimates, apathy and activity variability, and a number of possible confounding variables, ie, age, Body Mass Index (BMI), illness duration, medication (ie, dopamine equivalent dose), positive symptoms (PANSS), and depression scores (CDSS) (2-tailed test; see [Supplementary Information S8](#)). When (trend) significant associations were found ($P \leq .10$), we calculated semi-partial Spearman correlations to control for the effect of confounding variables using the package `ppcor` in R (v1.1; step 4). A semi-partial correlation is the correlation between 2 variables of interest with variation from a third variable removed only from the second variable.

Results

Associations Between DFC Estimates, Apathy, and Activity Variability

First, a significant negative correlation was found between apathy and activity variability. Second, significant negative correlations were found between apathy and variability in DFC in the DMN and SRN, but not in the FPN. However, the significant negative correlation between apathy and variability in DFC in the DMN became trend significant, after controlling for positive symptoms. Third, a trend significant positive correlation was found between activity variability and variability in DFC in the SRN. Furthermore, a significant positive correlation was found between activity variability and variability in DFC in the DMN after controlling for BMI, but not age. No significant correlations were found between activity variability and variability in DFC in the FPN. See [table 2](#) for the original and corrected correlation values and see [figure 2](#) for scatter plots of the results. As a validity check, we also investigated the association between apathy and activity variability, and variability in DFC between the DMN and SRN. A moderate negative correlation was observed between apathy and

variability in DFC between the DMN and SRN. A weak positive correlation was observed between activity variability and variability in DFC between the DMN and SRN ([Supplementary Information S9](#)). To avoid circular analysis, we refrained from statistical testing in this latter analysis (only). To be able to compare our findings to studies using a static approach, we also calculated associations between the mean level of DFC (mean over time points), apathy, and mean level of activity (mean over hours) ([Supplementary Information S10](#)). Furthermore, because variability in activity is possibly associated with DFC in the SMN, we investigated the association between variability in DFC in the SMN, apathy and activity variability. No significant results were found ([Supplementary Information S11](#)). Moreover, because motor symptoms are possibly associated with our variables of interest (DFC estimates, apathy, and activity variability), we investigated the confounding effect of motor retardation (PANSS item G7) on the current findings. We observed that all found associations remained (trend) significant ([Supplementary Information S12](#)). Finally, we repeated the analyses excluding participants who were scanned with a different echo planar imaging (EPI) sequence. The findings remained significant or became significant ([Supplementary Information S13](#)).

Discussion

The aim of this study was to investigate whether apathy in schizophrenia is associated with rigidity in motor behavior and brain functioning. To this end, we studied, for the first time, associations between variability in DFC in relevant functional brain networks, variability in motor behavior, and apathy in schizophrenia. First, we observed lower variability in activity and lower variability in DFC in the DMN and SRN in patients with schizophrenia scoring higher on apathy. Second, we observed higher variability in DFC in the SRN in patients with schizophrenia, who showed more variability in their activity. The results indeed seem to suggest that flexibility in brain functioning (in particular brain networks) and motor behavior is compromised in patients with schizophrenia and higher levels of apathy, possibly impacting goal directed behavior.

As mentioned earlier, 2 networks seem to play a role in relation to apathy and show lower variability in DFC, ie, the DMN and SRN. However, after controlling for positive symptoms, the relationship with variability in DFC in the DMN became trend significant. This means that, although the relationship with DFC in the DMN is stronger in patients with schizophrenia and apathy, it seems not to be specific for patients with this symptom. The DMN has been reported to be more active during rest and to subserve functions, such as self-reflection, introspection, autobiographical memory, envisioning the future, mental simulation, and emotion regulation.^{50–55}

Fig. 2. Scatter plots of the results (A–D). The images were created using the package ggplot2 in R (Version 0.98.1062). The added line in the scatter plots is based on linear regression, including a 95% confidence region. For r -values and P values, see table 2. AES: Apathy Evaluation Scale; DFC: dynamic functional connectivity; DMN, default mode network; SRN, salience-reward network.

Table 2. Associations Between DFC Estimates and Apathy and Activity Variability

DFC	Apathy ($n = 31$)					Activity variability ($n = 30$)				
	r	$r^\dagger$	P	$P^\dagger$	Confounding variable(s)	r	$r^\dagger$	P	$P^\dagger$	Confounding variable(s)
DMN variability	−.325	−.350 −.294	.037**	.029** .057*	Depression ¹ Positive symptoms ²	.226	.264 .339	.114	.145 .036**	Age BMI
SRN variability	−.386	−.421 −.369 −.446	.016**	.010** .022** .007**	Depression Positive symptoms Illness duration	.222	.375 .266	.119	.051* .082*	Age Illness duration
FPN variability	−.062	−.176 −.123 −.065	.371	.175 .258 .366	Depression Positive symptoms Medication ³	.035	−.003 .075	.426	.493 .349	Age Medication
Activity variability ($n = 30$)	−.359	−.323 −.333	.026**	.044** .039**	Depression Age					

DFC, dynamic functional connectivity; DMN, default mode network; SRN, salience-reward network; FPN, frontoparietal network; r , Spearman correlation value; P , P value.

† Values corrected for confounding variables.

¹As measured with the Calgary Depression Rating Scale (CDSS).

²As measured with the positive symptom scale of the Positive and Negative Symptom Scale (PANSS).

³As measured by the dopamine equivalent dose in milligrams.

* $P \leq .10$.

** $P \leq .05$.

In line with our results, a previous study has shown that DFC between subsystems of the DMN is weaker in patients with schizophrenia compared with healthy controls, specifically in patients reporting more negative symptoms.⁵⁶ Furthermore, decreased variability in DFC in several DMN brain regions was found in patients with schizophrenia compared with healthy controls.⁵⁷ One of the functions of the DMN, which has specifically been mentioned in the literature on goal directed behavior and apathy in schizophrenia, is *episodic future thinking*.^{51–53,58} This process is the ability to mentally simulate possible future events (ie, “pre-experiencing”⁵⁹). The mental simulation of desired future events may benefit goal attainment by increasing expectation of success, motivation and, effort and by facilitating the formation of concrete plans and problem-solving.⁵⁹ It seems that motivation and effort to pursue goals are specifically increased when future-event simulations are related to personal goals.⁶⁰ In line with this, D’Argembeau et al⁶¹ suggest that the function of the DMN comprises the localization of future-event simulations on a continuum of self-relevance, thereby prioritizing future-events that are important for personal goal attainment.^{61,62} Indeed, it has been shown that patients with schizophrenia, who scored higher on apathy, had more difficulties to mentally simulate self-referential information for pleasant future events.⁵⁸ Thus, lower variability in DFC in the DMN in patients with schizophrenia scoring higher on apathy (and those who have more positive symptoms) may be related to impairments in self-reflection and mental simulation while thinking about pleasant future events. However, more research is needed to investigate the role of the DMN in episodic future thinking in patients with schizophrenia and high levels of apathy.

The SRN has been shown to subserve functions related to reinforcement learning and reward processing,^{6,63,64} the identification and appraisal of salient affective stimuli and the production of affective states,^{63,65–67} and the detection of emotional or novel stimuli.^{68–70} In contrast to our results, a previous study has found increased DFC in the SRN and between the DMN and SRN in patients with schizophrenia compared with healthy controls.⁷¹ It is possible that lower variability in DFC in and between these networks is specific for patients with schizophrenia and higher levels of apathy. One of the functions of the SRN, which has specifically been mentioned in the literature on goal directed behavior and apathy in schizophrenia, is *effort-based decision-making*.⁷² This process incorporates how much effort an individual is willing to exert for a given level of reward.⁷³ Effort and motivation are multifaceted constructs that consist of several subprocesses.⁷⁴ Two of these subprocesses have been proposed as correlates of apathy, ie, reward processing (including reward learning, anticipation, and simulation) and effort discounting (ie, the tendency to devalue rewards that require more effort to obtain).⁷² A review of studies investigating

effort-based decision-making in schizophrenia reported that 5 of 8 studies found an association between lower task performance on several effort tasks and higher negative symptoms.⁷³ Brain systems and regions that are part of the SRN and DMN have been related to effort-based decision-making, such as the striatum, amygdala, insula, orbital frontal cortex (OFC), and anterior cingulate cortex.^{73,74} Notably, a recent study has found associations between apathy and activity and FC in and between the striatum and OFC during an effort-based reinforcement task.⁷⁵ Thus, lower variability in DFC in and between the SRN and DMN in patients with schizophrenia and higher levels of apathy may be related to impaired reward processing while making decisions to undertake (pleasant) activities. However, more research is needed to investigate the role of the SRN in effort-based decision-making in patients with schizophrenia and high levels of apathy.

Regarding activity variability, we found lower variability in activity in patients with schizophrenia scoring higher on apathy. As mentioned in the “Introduction” section, this is the first time, to our knowledge, that the association between variability in activity and apathy is investigated. However, there is a study that investigated the association between predictability of movements and negative symptoms and found no relationship.⁷⁶ There are a number of discrepancies between the two studies (Walther et al⁷⁶ vs our report): type of patients (only inpatients vs in- and outpatients; patients with schizophrenia vs patients with schizophrenia and schizoaffective disorder scoring high on apathy), sampling frequency (2 s vs 1 min), total duration of activity monitoring selected for data analysis (two 60-min periods vs 10 most active hours per weekend day), type of time periods (structured time periods wherein individuals undertake single or group activities vs leisure), different methods (partial autocorrelation function vs root of the MSSD; linear regression model vs semi-partial Spearman correlation, including controlling for confounding variables), and different symptom measures (PANSS negative symptom subscale vs AES). Due to these discrepancies, it is difficult to draw conclusions on why the results of the two studies are different. Further research is needed to investigate variability in activity as measured with actigraphy in patients with schizophrenia and negative symptoms.

In this study, we observed that apathy was associated with more rigid motor behavior and DFC as well as that more variability in motor behavior was associated with more flexible DFC. Although we cannot make causal statements, it would be interesting to investigate whether treatments that intervene on the level of behavior (ie, activity variability) or the brain (ie, variability in DFC) have an impact on apathy. For instance, Behavioral Activation Therapy (BAT) in depression (a treatment that is also offered to patients with schizophrenia) has been shown to alter connectivity between brain regions that are part of the DMN and SRN.^{77,78}

Furthermore, neurostimulative treatments, such as transcranial magnetic stimulation and transcranial direct current stimulation, have been shown to modulate oscillatory activity, thereby impacting interactions between brain networks (for a review, see Dayan et al⁷⁹ and Muldoon et al⁸⁰).

Several limitations of our study should be noted. First, we had to use a narrowband signal to obtain the instantaneous phase using the Hilbert transform. However, we selected the frequency band that has the highest functional relevance and is the least affected by noise (eg, cardiac and respiratory effects).³⁰ Second, actigraphy only captures motor behavior and not cognitive behavior, such as reading, studying, or following a lecture. A recent study has investigated actigraphy in combination with ecological momentary assessment in patients with schizophrenia and high levels of apathy to examine whether these patients engage in less daily activities. The authors found a negative association between apathy and motor activity, but no associations between apathy and daily activities. One of the reasons for this null result is that the classification of self-reported behavior in goal-directed and nongoal-directed behavior is very challenging (for further discussion of these findings, see Kluge et al¹²). Third, only patients with schizophrenia and high levels of apathy were investigated in this study. The reason for this is that we investigated baseline measurements of a study exploring the effects of neurostimulative treatment on apathy in schizophrenia, wherein only patients with schizophrenia and clinical levels of apathy were recruited and no healthy controls. Although there was considerable variation in apathy scores and these were approximately normally distributed, future research is necessary to confirm our findings for a larger range of apathy scores and in other populations than patients with schizophrenia. Fourth, we investigated associations between variability in DFC in specific functional brain networks, apathy, and activity variability during resting state. Although brain network functioning during resting state has been shown to exhibit experience-dependent changes over time,⁸¹ it would be interesting to replicate and confirm our findings in a task targeting goal-directed behavior specifically. Notably, it is important that such a task contains lengthy enough trials over which DFC can be properly estimated. Fifth, we performed our analyses based on actigraphy data gathered during the weekend, because behavior has been shown to be more self-initiated and less externally driven during the weekend by, eg, school, work, supervised daytime activities, or therapy. However, it would also be important to replicate and confirm our findings with actigraphy data gathered during weekdays. Possibly, the latter corresponds more to clinically evaluated apathy, specifically in inpatients with schizophrenia.

In conclusion, the aim of this study was to investigate associations between variability in DFC in relevant brain

networks, variability in motor behavior and apathy in patients with schizophrenia. We observed that patients with schizophrenia and severe levels of apathy showed less variability in activity and less variability in DFC in networks involved in self-reflection, mental simulation, and reward processing. This may possibly affect processes such as episodic future thinking and effort-based decision-making. Consequently, this may help to explain the reduction of goal-directed behavior in these patients. Future research should evaluate whether treatments that intervene on the level of behavior or the brain, such as BAT or neurostimulation, may reduce rigidity, thereby facilitating a shift toward more psychological flexibility and a reduction of apathy.

Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin* online.

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Conflict of interest

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

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