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# Aberrant fronto-striatal connectivity and fine motor function in schizophrenia

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ABSTRACT

Abnormal fine motor function is a frequent finding in schizophrenia and has been linked to structural and functional brain alterations. However, whether fine motor function is related to functional alterations within the motor system remains unclear. The aim of this study was to assess whether abnormalities in resting-state functional connectivity are present in schizophrenia patients and to investigate how these abnormalities may be related to fine motor function. We examined 19 schizophrenia patients and 16 healthy controls using resting-state functional connectivity for 11 bilateral regions of interest. Fine motor function was assessed on a set of copying tasks and the Symbol-Digit-Substitution Test. We found significantly reduced functional connectivity between the left caudate nucleus and bilateral dorsolateral prefrontal cortex (DLPFC) and between the left putamen and bilateral supplementary motor area (SMA) proper in patients compared to controls. Altered connectivity from DLPFC to caudate nucleus was related to fine motor tasks, which are sensitive to psychomotor speed, whereas aberrant connectivity between the SMA proper and putamen was associated to both, fine motor task, which are sensitive to psychomotor speed and to speed of information processing. Our findings emphasize the role of fronto-striatal connections in the pathogenesis of fine motor impairments in schizophrenia.

## 1. Introduction

Schizophrenia is characterized by heterogeneous presentation of symptoms and courses. Symptom dimensions include delusions, hallucinations, disorganized speech, negative symptoms and aberrant motor behavior (Heckers et al., 2013; Tandon et al., 2009). The prevalence of psychomotor symptoms in schizophrenia is high and varies from 40 to 80% (Docx et al., 2012; Peralta et al., 2010; Ungvari et al., 2007). In addition to the frequent occurrence, aberrant motor behavior offers a unique window to the pathophysiology of schizophrenia, due to its neurodevelopmental origin and the onset of symptoms long before the first full blown psychotic episodes (Walther, 2015). Indeed, motor symptoms have been reported in unmedicated and medicated patients across all stages of the illness (Docx et al., 2012; Koning et al., 2010; Peralta and Cuesta, 2001, 2010; Walther and Strik, 2012; Wolff and O'Driscoll, 1999). Aberrant motor functioning includes a wide range of symptoms, such as catatonia, neurological soft signs (NSS), extrapyramidal symptoms, abnormal involuntary movements, psychomotor slowing and decreased motor activity (Morrens et al., 2014).

Schizophrenia is associated with altered brain structure in the motor system, in frontal and temporal brain areas, the basal ganglia and the thalamus (Haijma et al., 2013). Furthermore, reduced prefrontal-thalamic and increased motor/somatosensory-thalamic connectivity has been found to be characteristic in schizophrenia patients (Anticevic et al., 2014; Woodward and Heckers, 2016; Woodward et al., 2012) and related to abnormal brain maturation (Woodward et al., 2012). Despite the above mentioned wide range of motor abnormalities and their high prevalence rates, many motor symptoms still remain understudied with neuroimaging methods (Walther, 2015).

Motor abnormalities are considered to be interesting biological

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markers of psychosis risk and may aid screening and staging of schizophrenia spectrum disorders (van Harten et al., 2017). Aberrant fine and gross motor behavior may be assessed by objective means. One possible investigation of gross motor behavior at the behavioral level is the motor activity level, which is assessed with wrist actigraphy. Activity levels in schizophrenia have been associated with aberrant grey matter (GM), white matter (WM) and resting state cerebral blood flow in motor areas or fibers that predominantely belong to the motor system (Bracht et al., 2013; Docx et al., 2017; Farrow et al., 2005; Walther et al., 2011a, b).

Quantification of fine motor behavior includes for example finger-tapping or writing and drawing tasks. Schizophrenia patients show impaired fine motor function, as measured by the Purdue Pegboard Test, Line Copying Task, Figure Copying Task (FCT) or Symbol-Digit-Substitution Test (SDST) (Docx et al., 2013; Morrens et al., 2008a, 2006). Digitized registration of psychomotor performance of writing and copying allows for the disentanglement of the basal cognitive processes involved in the preparation or initiation of single movements on one hand and the actual execution of these movements (Morrens et al., 2008). Previous research demonstrated abnormalities in both aspects in schizophrenia, even for the simplest movements (Bervoets et al., 2014). Some fine motor functions also correlate with NSS, but not all. For example, finger-tapping correlates with sequencing but not with coordination of the neurological evaluation scale (NES) (Docx et al., 2012). Altered motor behavior, particularly NSS has been linked to aberrant brain structure in the precentral and inferior frontal gyrus, inferior parietal lobe, thalamus, caudate nucleus, globus pallidus and the cerebellum and altered activity in the inferior frontal gyrus, superior temporal gyrus, bilateral putamen and cerebellum in patients with schizophrenia (Hirjak et al., 2015, 2014, 2012; Zhao et al., 2014).

Only a few studies investigated neuronal correlates of fine motor functioning or had a focus on fine motor behavior within NSS. Structural and functional abnormalities have been observed in the post- and precentral gyrus and the cerebellum during the finger-tapping task in schizophrenia patients (Singh et al., 2014). In addition, untreated schizophrenia patients revealed during the same task aberrant activation patterns in the basal ganglia and contralateral cerebellum (Muller et al., 2002). Exploring the effect of a fine motor training, a study found less activation in the bilateral premotor area before the beginning of the training and only in the left premotor area after the training in schizophrenia patients compared to controls (Kodama et al., 2001).

In summary, studies report psychomotor slowing of fine motor function in patients with schizophrenia compared to healthy controls (Docx et al., 2013; Morrens et al., 2008a, 2006). In addition, first evidence suggests an association of aberrant functional connectivity as revealed by resting-state functional magnetic resonance imaging (rs-fMRI) in the motor system with gross motor functioning (Walther et al., 2017) as well as a link between task-dependent functional connectivity and some fine motor measures (Kodama et al., 2001; Muller et al., 2002; Singh et al., 2014). However, no study investigated the association of aberrant rs-fMRI of the motor system and processes related to the initiation and execution of fine motor movements in schizophrenia. In this study, we aimed at elucidating this issue and hypothesized (1) aberrant resting state connectivity in the motor system in schizophrenia compared to healthy controls, along with (2) a link between functional dysconnectivity and fine motor function in patients. We selected 22 regions of interest (ROIs) of the motor system and chose a ROI-to-ROI analysis approach. This selection was based on previous studies and literature about the motor system (Mittal et al., 2017; Walther and Mittal, 2017; Walther et al., 2017). Instrumental measures of fine motor function such as drawing and writing tasks and speed of information processing tasks were used.

## 2. Methods

### 2.1. Participants

Nineteen patients with a diagnosis of schizophrenia according to Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR) criteria were included as well as 16 healthy control participants. Patients were recruited from three major in- and outpatient treatment facilities in Belgium (14 inpatients; 5 outpatients). All subjects were right handed. Handedness was categorized according to participants report and validated with the writing task. Eleven patients received atypical antipsychotics, two received typical antipsychotics, and six were administered a combination of atypical and typical antipsychotics. The dosages were calculated as the average chlorpromazine equivalents (CPZ) (Woods, 2003) per day. We assessed the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), NES (Buchanan and Heinrichs, 1989), St. Hans Rating Scale for extrapyramidal motor symptoms (Gerlach et al., 1993), Calgary Depression Scale (CDS) (Addington et al., 1992) and the Salpetriere Retardation Rating Scale (SRRS) (Dantchev and Widlocher, 1998). Patients were in symptomatic remission. The study was performed in accordance with the Declaration of Helsinki. The study was approved by the ethical committee of the University (Hospital) Antwerp. All participants provided written informed consent.

### 2.2. Fine motor tasks

The drawing tasks were performed on a WACOM digitizing tablet with a pressure-sensitive ballpoint pen, both connected to a standard PC (Sabbe et al., 1996). The use of digital measures to assess psychomotor abnormalities offers some advantages, as these assessments are more sensitive and reliable. In addition, they can provide insight as to which subprocesses of psychomotor functioning are impaired (Docx et al., 2013, 2015; Houthoofd et al., 2013). As such, the use of digitized simple copying tasks assessed with a computerized pressure-sensitive pen offers an easy-to-use, accessible and quick objective method to measure quantitative and qualitative motor abnormalities in schizophrenia. Interestingly, it has been demonstrated that clinical observations on the one hand and instrumental objective measurement results on the other hand appear to yield different information that are both important in determining the severity and nature of the psychomotor disorders of the patients (Docx et al., 2012; Janno et al., 2005).

#### 2.2.1. Figure copying task

Stimulus figures ($n = 24$), which were presented on a standard monitor positioned in front of the participant, had to be copied as fast as possible within the confines of the target boxes on a sheet of paper (A4) placed on the digitizer. The stimulus figures were subdivided into three categories of familiarity: letters, familiar figures, and unfamiliar patterns. The variables for the two tasks were initiation time (IT), i.e. the time between the presentation of the stimulus and the initial movement of the pen on the paper, and writing time (WT), i.e. the time needed to draw the stimulus (Morrens et al., 2008a). IT and WT were calculated for all three categories of familiarity (letters, familiar figures, and unfamiliar patterns) separately.

#### 2.2.2. Symbol-digit-substitution test

In the Symbol Digit Substitution Test (SDST), a subtest of the Wechsler Adult Intelligence Scale-Revised (Wechsler, 1981), a series of symbols has to be decoded as fast as possible within a90 s time interval based on a key translating the nine different symbols into the digits 1–9. Completion of the SDST on the digitizer allows to differentiate matching time (MT) and WT, representing the cognitive and sensorimotor component of slowing (Morrens et al., 2008b, 2006).

### 2.3. MRI acquisition

All magnetic resonance (MR) examinations were obtained with a 32-channel phased array head coil on a 3T scanner (Magnetom Trio Tim, Siemens, Erlangen, Germany). High resolution anatomical T1-weighted images were acquired with a magnetization-prepared rapid acquisition gradient echo (MP-RAGE) sequence in the sagittal plane (176 slices; 1 mm isotropic resolution; field-of-view: 256 mm × 192 mm; matrix dimension: 256 × 192; repetition time (TR): 1910 ms; echo time (TE): 3.37 ms; flip angle: 15°). A gradient-echo-planar imaging sequence was used to acquire a time series of 140 T2*weighted BOLD resting-state-fMRI images (50 slices interleaved; 2.5 mm × 2.5 mm × 2.8 mm voxel size; 50 slices per volume; field-of-view: 200 mm × 200 mm; matrix dimension: 80 × 80; TR 3000 ms; TE: 30 ms; flip angle: 90°). Factor 2 GRAPPA acceleration was used. Participants were asked to relax and close their eyes during the acquisition, which lasted 7 min.

### 2.4. ROIs

We defined 11 ROIs for the left and the right hemisphere using the GM Brodmann Area (BA) masks and the automated anatomical labeling (AAL) atlas of the WFU-Pick Atlas software (Maldjian et al., 2003) in the Statistic Parametric Mapping (SPM) 12 (The Wellcome Department of Cognitive Neurology, London, UK, www.fil.ion.ucl.ac.uk/spm). These 11 ROIs are based on previous work on the motor system in psychosis (Bernard et al., 2017; Walther et al., 2017), in line with the new RDoC motor domain, including cortical motor areas, basal ganglia, thalamus, and cerebellum. Furthermore, we added the dorsolateral prefrontal cortex (DLPFC) due to its role in executive function. The DLPFC corresponds to BA 9 and 46, the primary motor cortex (M1) to BA 4 and the cerebellar ROI to lobules V, VI and VIII of the cerebellum as we were interested in motor and somatosensory representations (Stoodley and Schmahmann, 2009). From the AAL we defined the caudate nucleus, pallidum, putamen, thalamus, anterior cingulate cortex (ACC) and the supplementary motor area (SMA). We split the latter two into two areas: the ACC was divided into the dorsal ACC (dACC) and rostral ACC (rACC); the SMA in the preSMA and SMA proper. The rACC comprises all parts of the BA 24 that are located rostral of a vertical section through the genu (Nieuwenhuys and van Huizen, 2008; Vogt, 2009). SMA and preSMA are mainly located at the rostral and caudal parts of the medial premotor cortex (BA6) and are divided through the vertical anterior commissure (Habas, 2010).

### 2.5. Data preprocessing

The data were preprocessed using the Functional Connectivity Toolbox (Conn, version 17.f) (Whitfield-Gabrieli and Nieto-Castanon, 2012) for MATLAB (R2015; MathWorks, Natick, MA, USA). We followed the standard preprocessing pipeline for the first level analysis. This pipeline included multiple steps: functional realignment and unwarping, centering of the structural and functional image to (0,0,0) coordinates, slice-timing correction, segmentation of structural images, structural and functional normalization to MNI space and spatial smoothing using the Gaussian filter Kernel of FWHM = 8 mm. We then processed and regressed out the temporal confounding factors (subject- and session specific time series, e.g. movement parameters) and BOLD signals, that were acquired from subject-specific noise ROIs (CSF and WM masks). After the regression, the fMRI data was band-pass filtered (0.01 – 0.1 Hz) (see (Whitfield-Gabrieli and Nieto-Castanon, 2012) for detailed preprocessing steps).

### 2.6. Functional connectivity analyses

We applied a hypothesis driven approach with analyses of functional connectivity between predefined ROIs (ROI-to-ROI analyses). Functional connectivity maps for each of the 22 ROIs were created for all subjects using Conn. The average BOLD time series was calculated across all voxels within a ROI and entered as a predictor in a multiple regression general linear model.

To explore the connectivity differences between patients and controls, we entered the group variables “patients” and “controls” in the second-level analysis as covariates. Correlation maps of the ROIs were calculated for each connection and compared between groups using *F*-tests at a seed level threshold of $p < 0.05$ false discovery rate (FDR) corrected. We then extracted the values (*p*-FDR corrected) of significant group differences and transformed them into z-values.

### 2.7. Statistical analyses

Statistical analyses were performed using SPSS statistical software package version 24.0 (SPSS, Inc, Chicago, IL). We first compared behavioral and clinical data between groups. Differences between sex and education were explored with chi-squared tests, differences in age were analyzed with *t*-tests and the comparison of NES between groups was tested using a Mann–Whitney-*U test*. Group differences in motor tasks were analyzed with *t*-tests or Mann–Whitney-*U*-tests. In a second step we explored the associations between the behavioral data and the extracted functional connectivity values for each ROI-to-ROI connection, which significantly differed between groups. These measures were z-transformed in SPSS because of the difficulty in interpreting negative functional connectivity values. Correlations between z-scores of the functional connectivity and z-scores of the clinical rating scales were calculated using partial correlations controlling for antipsychotic medication dosages, age, education, akinesia based on the SHRS (SHRS-A) and parkinsonism based on the SHRS (SHRS-P).

## 3. Results

The clinical characteristics of the patients are presented in Table 1. Patients (90% male) and controls (75% male) did not differ in sex ($X^2 = 1.28$, $p > 0.05$) and age (patients: 32.6 ± 8.4; controls: 30.6 ± 6.7; $p > 0.05$). However, patients and controls differed in education, as the majority of the patients did not finish highschool (10 of 19), whereas the majority of the controls finished higher education, for example university (9 of 14). As expected, NES scores were significantly higher in patients (Mean controls = 1.88, mean patients = 7.32, $U = 21$, $p < 0.001$). A comparison of these measures between patients and controls is provided in the supplement (see supplementary Table S1).

**Table 1**
Clinical characteristic of the patients.

| Clinical variables[a] | Patients ($n = 19$) | |
|---|---|---|
| | *M* | *SD* |
| DOI (months) | 110.63 | 67.27 |
| CPZ (mg) | 1615.74 | 1833.63 |
| PANSS-Pos | 11.42 | 3.29 |
| PANSS-Neg | 13.26 | 3.21 |
| PANSS-Total | 49.05 | 8.98 |
| NES | 7.32 | 4.44 |
| SHRS Akathisia[b] | 1.47 | 2.78 |
| SHRS Dyskinesia[b] | 0.26 | 1.15 |
| SHRS Parkinsonism[b] | 5.63 | 4.47 |
| CDS | 1.11 | 1.76 |
| SRRS | 10.26 | 5.54 |

[a] DOI, duration of illness; CPZ, average chlorpromazine equivalents; PANSS, Positive, Negative and Total Syndrome Scale; NES, Neurological Evaluation Scale, SHRS; St. Hans Rating Scale; CDS, Calgary Depression Scale; SRRS, Salpetriere Retardation Rating Scale.

[b] Note, for akathisia only 7 patients had values above 0; for dyskinesia only 1 patient had values above 0; for parkinsonism 14 patients had values above 0.

**Table 2**
Between-subjects contrast.

| Analysis unit | Statistic | *p*-unc | *p*-FDR (seed-level) |
|---|---|---|---|
| Left caudate - left DLPFC | T (33) = 3.12 | 0.004 | 0.040 |
| Left caudate - right DLPFC | T (33) = 3.62 | 0.001 | 0.020 |
| Left putamen - left SMA proper | T (33) = 3.58 | 0.001 | 0.023 |
| Left putamen - right SMA proper | T (33) = 3.30 | 0.002 | 0.024 |

### 3.1. Group differences in the motor tasks

The Mann-Whitney-*U* test revealed significant group differences in the WT of the FCT-letter ($U = 59.5$, $p = 0.002$), FCT-figure ($U = 63$, $p = 0.003$), and FCT-pattern tasks ($U = 82$, $p = 0.020$). On the contrary, patients and controls did not differ significantly in the IT of the FCT-letter, FCT-figure and FCT-pattern task ($p > 0.05$). For the SDST, an independent *t*-test demonstrated differences between the groups in the MT ($t(27) = 2.68$, $p = 0.012$) and WT ($t(27) = 3.91$, $p = 0.001$). All significant results indicated that patients needed more time than controls to complete the tasks (see supplementary Table S2).

### 3.2. Group differences in resting-state functional connectivity

We were interested in the connectivity of 22 ROIs that are important for fine motor behavior. Group differences in rs-fMRI between those ROIs are presented in Table 2 and Fig. 1. Patients had significantly reduced connectivity of cortico-subcortical connections between the left putamen and the bilateral SMA proper and between the left caudate nucleus and bilateral DLPFC.

### 3.3. Partial correlations of aberrant functional connectivity and motor tasks in patients

Next, we examined the relationship between those four connections from the contrast between controls and patients and fine motor tasks within the patient group and controlled all partial correlations for the antipsychotic medication dosage, age, education, akinesia and parkinsonism (see Table 3). Inverse correlations of functional connectivity with the duration of the performance indicate that patients with lower functional connectivity performed the fine motor tasks slower. Partial correlations of functional connectivity and motor tasks for healthy controls as well as across patients with schizophrenia and healthy controls are given in the supplement (see supplementary Table S3 and S4). Differences of correlations between patients with schizophrenia and healthy controls can also be found in the supplement (see supplementary Table S5).

#### 3.3.1. Partial correlations of FCT-letter with functional connectivity

We observed a significant negative correlation between the initiation time of the FCT-Letter and the connectivity between the left caudate and left DLPFC. In addition, we detected significant negative correlations between the writing time of the FCT-Letter and the connectivity between the left putamen and bilateral SMA proper ($p \leq 0.05$).

#### 3.3.2. Partial correlations of FCT-figure with functional connectivity

The initiation and writing time of the FCT-Figure task correlated significantly inverse with the connectivity between the left caudate and left DLPFC ($p \leq 0.05$).

#### 3.3.3. Partial correlations of FCT-pattern with functional connectivity

Our results revealed significant negative associations for the initiation and writing time of the FCT-Pattern task with the connectivity between the left caudate and left DLPFC ($p \leq 0.05$).

#### 3.3.4. Partial correlations of SDST with functional connectivity

The writing time of the SDST and the connectivity between the left putamen and right SMA proper was significantly negative associated ($p \leq 0.05$).

## 4. Discussion

The current study explored the association between fine motor function in schizophrenia with rs-fMRI within the cerebral motor system. We hypothesized reduced cortico-subcortical connectivity in schizophrenia and a link between aberrant connectivity and inferior performance (psychomotor slowing) in fine motor tasks. Results revealed reduced connectivity between the DLPFC and caudate nucleus and between the SMA proper and putamen in patients with schizophrenia compared to healthy controls. In contrast, none of the other connections of the 11 bilateral ROIs demonstrated aberrant resting state connectivity in patients compared to controls. Reduced connectivity at rest was associated with inferior performance on fine motor tasks sensitive to psychomotor speed and speed of information processing.Our

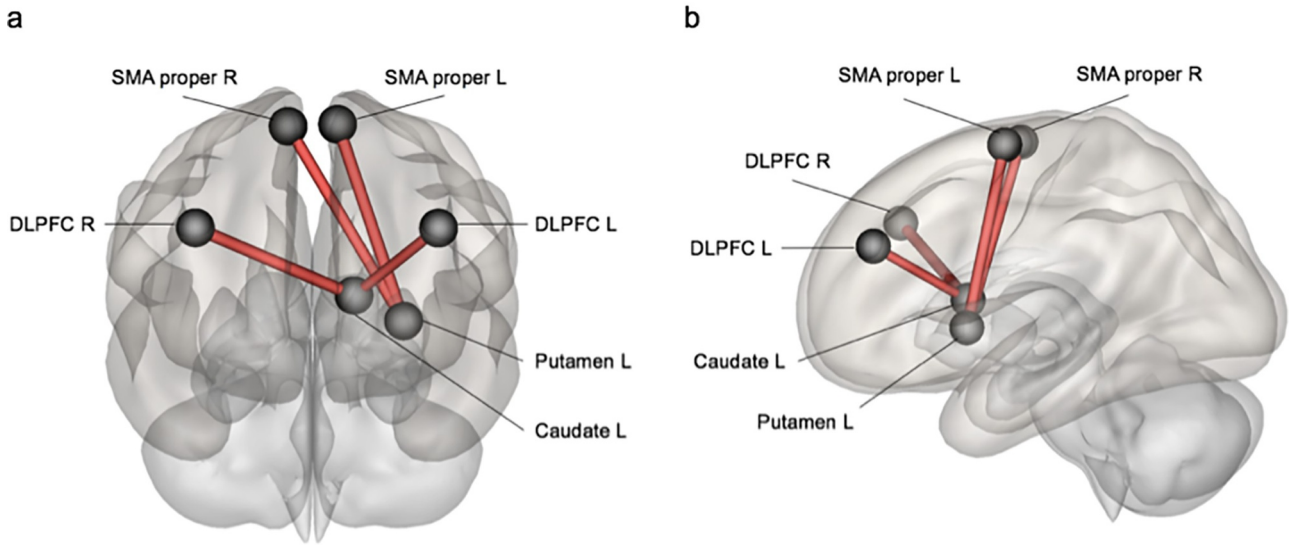


**Fig. 1.** ROI based connectivity maps of group differences in the functional connectivity analysis (FDR seed level corrected, $p < 0.05$). (a) Anterior view and (b) left view.

**Table 3**
Partial correlations of aberrant functional connectivity and motor tasks in patients, controlled for antipsychotic medication dosage, age, education, SHRS-A and SHRS-P.

| Test[a] | Functional connectivity Left caudate-left DLPFC | | Left caudate- right DLPFC | | Left putamen-left SMA proper | | Left putamen right SMA proper | |
|---|---|---|---|---|---|---|---|---|
| | r | *p* | r | *p* | r | *p* | r | *p* |
| FCT-letter IT ($n$ = 19) | −0.505 | **0.027**[b] | 0.091 | 0.711 | 0.130 | 0.595 | −0.013 | 0.958 |
| FCT-letter WT ($n$ = 19) | −0.204 | 0.401 | 0.006 | 0.981 | −0.663 | **0.002** | −0.717 | **0.001** |
| FCT-Figure IT ($n$ = 19) | −0.484 | **0.036** | 0.134 | 0.585 | 0.257 | 0.289 | 0.139 | 0.571 |
| FCT-Figure WT ($n$ = 19) | −0.484 | **0.036** | −0.035 | 0.888 | 0.065 | 0.792 | −0.173 | 0.480 |
| FCT-pattern IT ($n$ = 19) | −0.507 | **0.027** | 0.125 | 0.609 | 0.553 | **0.014**[c] | 0.446 | 0.056 |
| FCT-pattern WT ($n$ = 19) | −0.681 | **0.001** | −0.074 | 0.764 | 0.317 | 0.186 | 0.157 | 0.520 |
| SDST MT ($n$ = 18) | −0.088 | 0.730 | 0.168 | 0.504 | 0.644 | **0.004**[c] | 0.492 | **0.038**[c] |
| SDST WT ($n$ = 18) | −0.194 | 0.439 | −0.051 | 0.842 | −0.440 | 0.067 | −0.493 | **0.037** |

[a] FCT, Figure Copying Task; SDST, Symbol-Digit-Substitution Test; IT, initiation time; WT, writing time; MT, matching time. Number of patients for all tests = 19, except for both SDST $n$ = 18, for all tests $df$ = 15.
[b] **Bold** indicates significant $p$-values at $p < 0.05$ (two-tailed).
[c] Please note that outliers are driving these significant effects. These correlations are not further considered in the results or discussion sections. Scatterplots of all significant correlations are given in the supplement (see Fig. S1).

findings suggest an association of aberrant functional connectivity of fronto-striatal connections with fine motor function at the behavioral level in schizophrenia.

Patients with schizophrenia used more time to complete the Figure Copying Tasks and SDST. The initiation times of all FCT tasks (letter, figure, pattern) correlated inversely with the connection between the left caudate nucleus and left DLPFC. Patients with reduced connectivity to the left DLPFC thus displayed more planning deficits in initiating motor task conditions. Similarly, the writing time of the FCT-Pattern and FCT-Figure task correlated with the connectionbetween the left caudate nucleus and left DLPFC.

The connections between the left putamen and bilateral SMA proper were only associated with writing times, but not with initiation times of our fine motor tasks in patients. Thus, the writing time of the FCT-Letter task correlated inversely with the connections between the left putamen and bilateral SMA proper. In addition, the writing time of the more complex SDST was negatively correlated with the connectivity between the left putamen and right SMA proper. These results suggest, that patients with lower functional connectivity between these brain regions are slower during writing and drawing in simple tasks, which are sensitive to psychomotor speed; likewise, they write slower in complex tasks, which are more sensitive to speed of information processing.

Our rs-fMRI findings are in line with several structural imaging studies, which found associations of NSS with aberrant grey matter of the DLPFC and frontal motor areas (Mouchet-Mages et al., 2011; Thomann et al., 2009) as well as of the putamen and caudate nucleus in first-episode schizophrenia (Dazzan et al., 2004; Hirjak et al., 2012; Thomann et al., 2009). In addition, one study reported reduced activity in the DLPFC and putamen during a stop task performance in schizophrenia patients compared to controls (Rubia et al., 2001). Furthermore, our functional connectivity findings of an association between aberrant resting state connectivity and motor abnormalities at the behavioral level are also in line with a recent report on gross motor function in schizophrenia demonstrating as well aberrant fronto-striatal resting state functional connectivity and an association with a primary motor factor (Walther et al., 2017).

Functional dysconnectivity at rest is already present in subjects at high risk for psychosis, for example between the thalamus or cerebellum and cortical regions (Anticevic, 2017; Bernard et al., 2014). Aberrant striato-thalamo-cortical functional connectivity has also been found in drug-naïve patients with schizophrenia (Martino et al., 2017). In chronic and medicated patients with schizophrenia, aberrant thalamo-cortical, cerebello-cortical and fronto-striatal connections have been reported (Bernard et al., 2017; Walther et al., 2017; Woodward and Heckers, 2016).

The first pair of aberrant connections that we detected in schizophrenia patients is between the left caudate nucleus and bilateral DLPFC. This is in line with a diffusion tensor imaging study which detected in first-episode patients lower fractional anisotropy in tracts linking the prefrontal cortex to the caudate nucleus and this was related to positive symptoms (Molina et al., 2017). In addition, reduced activation of the DLPFC and caudate nucleus and decreased connectivity between them has been found in patients compared to controls and shown to underlie working memory deficits (Bleich-Cohen et al., 2014). Another study revealed a lack of an association between the connectivity of the DLPFC and caudate nucleus with a working memory performance in schizophrenia patients compared to controls (Quide et al., 2013). In contrast, schizophrenia patients showed a negative association between working memory performance and the connectivity between the putamen and ventrolateral prefrontal cortex (Quide et al., 2013). These results reveal that dysfunction of fronto-striatal connectivity is related to information retrieval during working memory performance in patients (Quide et al., 2013).

The second pair of altered connectivity in schizophrenia patients is between the left putamen and the bilateral SMA proper. These findings fit well with a study in Parkinson´s disease, that revealed lower functional connectivity between the preSMA and putamen in patients than controls and an association of low connectivity with the parkinsonism severity score in patients (Wu et al., 2011). In addition, cocaine users showed lower functional connectivity between the SMA and putamen during a finger-tapping task than controls (Hanlon et al., 2011). Other findings point to a lack of connectivity between the SMA and putamen during the same task in cocaine users compared to controls (Lench et al., 2017). Taken together, there is evidence for abnormal fronto-striatal connectivity in patients, and for an involvement of fronto-striatal connections in fine motor function.

In contrast, no significant associations between fine motor tasks and the connectivity between the left caudate and right DLPFC or other functional connectivity arose. However, we focused only on the contrast between the connectivity in patients and controls and correlated it with fine motor tasks within the patient sample. Therefore, functional connectivity between other areas might still be associated with fine motor function. Indeed, additional connections have been implicated in schizophrenia. For example, thalamic circuits have been suggested in schizophrenia neuropathology (Anticevic, 2017; Klingner et al., 2014; Walther et al., 2017; Woodward et al., 2012). Similarly, fronto-temporal connectivity has been associated with cognitive impairments and functioning in patients with schizophrenia (Spoletini et al., 2009; Straube et al., 2014). In addition, cerebellar functional dysconnection has been found in schizophrenia and in individuals at ultra-high risk for

psychosis and plays an important role in the pathophysiology of schizophrenia (Bernard et al., 2014; Chen et al., 2013; Shinn et al., 2015; Walther et al., 2017). In our study, we could not confirm these results, even though groups differed in functional connectivity also in connections including the thalamus and the cerebellum. However, these findings did not survive correction for multiple comparisons (data not shown).

Some limitations should be considered in this study. First, our rather small sample of stable patients in symptomatic remission limits the generalizability of our findings and may reduce the probability of detecting additional associations between impaired fine motor function and functional connectivity in schizophrenia. Second, even though we controlled for antipsychotic medication, it might influence not only motor behavior, but also brain structure and function (Walther, 2015). Patients with schizophrenia show inconsistent motor responses due to antipsychotic medications (Walther, 2015), such as some syndromes remain unchanged, deteriorate or even develop, while others may improve (Morrens et al., 2007; Peralta and Cuesta, 2010). Likewise, antipsychotic medication is also associated with alterations in functional cortico-striatal connections, indicating for example that an improvement of psychosis is linked to a strengthening of connectivity between prefrontal areas and the striatum (Sarpal et al., 2015). However, aberrant functional connectivity in the motor system was also reported in first-episode treatment naïve patients (Martino et al., 2017). Third, fronto-striatal connectivity has been related to working memory performance (Quide et al., 2013). Thus, cognition might modulate the association between fronto-striatal connectivity and fine motor function in our study. However, due to missing data on cognitive functioning, we are not able to disentangle the effect of cognition on our results.

Fourth, to test our hypotheses, we chose a ROI-to-ROI analysis approach. Therefore, we cannot exclude the possibility that other brain areas are of importance for fine motor function. Fifth, the lack of significant group differences in the initiation times of the FCT is in contrast to previous studies (Morrens et al., 2008a). This could be due to selection effects, as our protocol required subjects to rest quietly for several consecutive minutes in the scanner. Thus, we included schizophrenia patients with less severe symptoms, who were able to meet the requirements of the protocol.

In conclusion, our results provide evidence for alterations in fronto-striatal connections in schizophrenia and an association of this dysconnectivity with fine motor function. Fronto-striatal connectivity might therefore contribute to psychomotor slowing in schizophrenia, as assessed by instrumental measures of fine motor tasks. Future studies should test a larger sample of patients, particularly first episode patients or subjects at high clinical risk for psychosis for further validation of our findings of aberrant fronto-striatal connectivity.

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## Conflict of interest

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## Contribution

P.V.V. analyzed the data and wrote the first draft of the manuscript. L.D. contributed in data collection. W.V.H. and P.M.P. were involved in imaging data collection. B.S. provided input on the manuscript. A.F. provided methodological support. S.W. was involved in data analysis and writing the manuscript. M.M. wrote the protocol, designed and supervised the study. All authors approved to the final manuscript.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pscychresns.2019.04.010.

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