Differential Resting-State Connectivity Patterns of the Right Anterior and Posterior Dorsolateral Prefrontal Cortices (DLPFC) in Schizophrenia

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In schizophrenia (SCZ), dysfunction of the dorsolateral prefrontal cortex (DLPFC) has been linked to the deficits in executive functions and attention. It has been suggested that, instead of considering the right DLPFC as a cohesive functional entity, it can be divided into two parts (anterior and posterior) based on its whole-brain connectivity patterns. Given these two subregions’ differential association with cognitive processes, we investigated the functional connectivity (FC) profile of both subregions through resting-state data to determine whether they are differentially affected in SCZ. Resting-state magnetic resonance imaging (MRI) scans were obtained from 120 patients and 172 healthy controls (HC) at 6 different MRI sites. The results showed differential FC patterns for the anterior and posterior parts of the right executive control-related DLPFC in SCZ with the parietal, the temporal and the cerebellar regions, along with a convergent reduction of connectivity with the striatum and the occipital cortex. An increased psychopathology level was linked to a higher difference in posterior vs. anterior FC for the left IFG/anterior insula, regions involved in higher-order cognitive processes. In sum, the current analysis demonstrated that even between two neighboring clusters connectivity could be differentially disrupted in SCZ. Lacking the necessary anatomical specificity, such notions may in fact be detrimental to a proper understanding of SCZ pathophysiology.

Keywords: fMRI neuroimaging, Schizophrenia, DLPFC, resting-state fMRI, parcellation
INTRODUCTION

In neuroimaging, the most widely used method of characterizing functional neuroanatomy is based on the integration of larger anatomical brain regions. Based on this methodology, the DLPFC is frequently treated as a unified region controlling function through a top-down modulation of task-relevant information processing in the premotor and posterior parietal associative cortices (1, 2).

The DLPFC is reciprocally interconnected with motor areas in the medial frontal lobe, the rostral cingulate cortex, the premotor cortices as well as the cerebellum and the superior colliculus (3–6). While there is consensus regarding the role of the DLPFC in executive control, the varied results with respect to the location and extent of activation sites [e.g., (7–9)] beg the question of whether this variability is due to the region’s functional heterogeneity.

Deficits in executive function, working memory, and attention in schizophrenia [stable and common symptoms observed during the lifespan of schizophrenia patients (10–12) are thought to be linked to reduced activity in the bilateral] DLPFC and the dorsal parietal cortex (13). However, findings pertaining to DLPFC involvement in schizophrenia are not consistent with studies that do not reveal any differences in the DLPFC between HC (14) and others despite reporting patterns of hyperactivation (15). Moreover, there is considerable variability in terms of the location and extent of DLPFC impairment across functional neuroimaging experiments investigating executive functions in both healthy controls (16, 17) and patients (13, 18, 19). For instance, when healthy controls showed involvement of the BA44 and BA 40 in response to working memory challenge (17) the differences between patients with schizophrenia and healthy controls during working memory task were seen more posterior (BA 45, BA 46, BA 47) (18).

The inconclusive results of the studies mentioned above may be due not only to the variations in the experimental context but also to the lack of an understanding of the functional heterogeneity of the DLPFC region. This most likely indicates that the executive control of behavior relies on distinct DLPFC subregions involved in differentiable neural networks and cognitive functions.

The results of our previous parcellation study involving data from healthy individuals suggest that a single region of interest within the right DLPFC is not a functional entity but is organized hierarchically with one anterior ventral and one posterior dorsal DLPFC sub-region (Figure 1) (16). Our previous study showed an increased connectivity between the posterior (vs. anterior) DLPFC and the posterior parietal cortex, thereby indicating a possible network for cognitive control related to stimulus processing and selection of behavior-relevant information. In contrast, for the anterior (vs. posterior) DLPFC cluster, an increased functional connectivity with the ACC was seen. This resonates well with the results from a range of fMRI studies investigating cognitive control, suggesting that the DLPFC and the ACC (BAs 24 and 32) are specifically activated with an increase in demands for cognitive control and monitoring due to conflict in information processing and competing response plans (20–22). Thus, while the posterior cluster of the region is likely changed to be more strongly involved in action control processes, depending on the interaction with stimulus processing and working changed memory, the anterior region is likely responsible for higher-order control processes such as motor response monitoring and action inhibition (16).

Based on these observations, we sought to explore whether SCZ is linked to a differential connectivity disruption in the right anterior and posterior DLPFC (aDLPFC/pDLPFC) sub-regions, hypothesizing that a connectivity imbalance in the DLPFC sub-regions is part of the SCZ pathophysiology.

METHODS

Definition of Volume of Interest (VOI)

The DLPFC VOIs were based on previous work (16), separating the right DLPFC region into two clusters by using hierarchical cluster analysis: a more anterior-ventral (center of gravity MNI coordinates: 30/43/23) one and a more posterior-dorsal one (center of gravity MNI coordinates: 37/33/32) (Figure 1). Henceforth, for the sake of simplicity, the regions will be referred to as anterior and posterior seeds or sub-regions. In the study by Cieslik et al. (16), volume of Interest was defined by merging the DLPFC activation sites from 4 previous studies investigating motor control. The first 3 studies (23–25) used manual stimulus–response tasks requiring a speeded response to a visual stimulus by a button press with either the left or right index finger, whereas the fourth study (26) used a manual sequence reproduction task. All 4 studies, which differed in the specific demands for executive motor control, showed activation in the right DLPFC with partially overlapping but slightly different locations. Following thresholding at $P < 0.05$ (cluster-level family-wise
error [FWE]-corrected) of the individual contrasts, the ensuing 4 DLPFC clusters were combined into a single VOI (cluster size: 674 voxels). That is, every single voxel in the VOI region showed activation in at least one of the 4 studies. Subsequently, it was assessed whether this seed region could be divided into subregions based on similarities and differences between co-activation patterns of the individual seed voxels across neuroimaging experiments.

**Sample Description**

We investigated resting-state functional connectivity of the two right DLPFC sub-regions in 120 patients with a clinical diagnosis of schizophrenia [recruited at six sites: Aachen, Alberquerque (COBRE), Göttingen, Groningen, Lille, and Utrecht] and 172 healthy controls, with patients and controls not differing with respect to age Symptom severity was assessed by use of the Positive and Negative Syndrome Scale [PANSS, (27)] (for detailed demographic and clinical characteristics, please refer to Table 1 and Supporting Information Table S1).

The diagnosis was ascertained by clinical examination of the attending psychiatrist according to the International Classification of Diseases (28) or the Diagnostic and Statistical Manual of Mental Disorders (29) criteria.

At the time of scanning, all patients were under antipsychotic medications, except for 6 (7%), who were not on any medication. Chlorpromazine-equivalents (CPZ-equivalents) were estimated as described in (Table 2) (30).

All subjects provided written informed consent to participate in the study prior to inclusion as approved by the ethics committees of the participating universities. Joint re-analysis was approved by the ethics committee at the Heinrich-Heine University Düsseldorf.

**Resting State fMRI Data: Imaging and Preprocessing**

For each subject resting state EPI (echo-planar-imaging) images were acquired using standard blood-oxygen-level-dependent (BOLD) contrast [gradient-echo EPI pulse sequence] (Please see Table S2 for details on EPI sequence for each site).

Prior to further processing (using SPM8, www.fil.ion.ucl.ac.uk/spm) the first four images were discarded allowing for magnetic field saturation. The EPI images were corrected for head movement by affine registration in a two-pass procedure realigning EPI volumes to its mean image. The mean EPI image for each subject was spatially normalized to the MNI ICBM-152 subject template using the “unified segmentation” approach (31). The ensuing deformation field was applied to the individual EPI volumes and smoothed with a 5-mm FWHM Gaussian kernel.

Neither the patient and control subsamples (sites) nor the overall disease cohorts showed group differences (t-tests with $p > 0.2$) in the three movement parameters (DVARs, FD, and RMD), indicating reasonably similar head motion during the scanning process (32).

To minimize spurious correlations between BOLD time courses through confounds such as physiological noise and motion, any variance that could be explained by the following nuisance variables was removed from each voxel's time series: (i) the six motion parameters derived from image realignment and (ii) their first derivative. According to published evaluations, motion regressors entered the model as first- and second-order terms resulting in 24 movement regressors (33) Given the evidence of group comparisons being distorted by correcting for the global mean signal (34, 35), the whole-brain resting-state functional connectivity of each of the two seeds (for all subjects) was calculated without Global Signal regression.

Finally, the data were band-pass filtered preserving BOLD frequencies between 0.01 and 0.08 Hz (36).

**Individual and Group Level Analyses**

For each subject and VOI the first eigenvariate of the VOIs time-series were calculated separately for each DLPFC seed and supplied to further whole-brain functional connectivity analysis. Linear (Pearson) correlation coefficients between the time series of the seed regions and those of all other gray-matter voxels in the brain were computed to quantify resting-state functional connectivity. These voxel-wise correlation coefficients were then transformed into Fisher's z-scores and then fed into a second-level analysis of variance (ANOVA).

**TABLE 1 | Demographic and clinical characteristics.**

|                | Controls ($n = 172$) | Patients ($n = 120$) |
|----------------|----------------------|----------------------|
| Age (years)    | 33.55 ± 10.74        | 32.11 ± 9.37         |
| Male/Female (%)| 105/67               | 87/33                |
| Duration of illness (years) | 10.16 ± 9.51       | 9.51 ± 8.07          |
| POS (PANSS, positive) | 15.08 ± 5.33        | 14.68 ± 5.39         |
| NEG (PANSS, negative) | 28.48 ± 8.07        | 28.48 ± 8.07         |
| PANSS (total)   | 58.32 ± 15.58        | 58.12 ± 15.58        |

**TABLE 2 | Information on how many of the patients were medicated or unmedicated at time of measurement and mean medication (CPZ-equivalents) per site.**

| Site     | Unmedicated ($n$) | Medicated ($n$) | Antidepressant** ($n$) | Mean CPZ-equivalents (SD) |
|----------|-------------------|-----------------|------------------------|---------------------------|
| Site 1   | 0                 | 9               | 2                      | 572.22 (255.71)           |
| Site 2   | 0                 | 41              | 12                     | 700.44 (386.29)           |
| Site 3   | 0                 | 20              | 4                      | n.a*                      |
| Site 4   | 0                 | 9               | 2                      | 731.44 (617.83)           |
| Site 5   | 1                 | 9               | 5                      | 820.44 (576.68)           |
| Site 6   | 2                 | 26              | 9                      | 785.19 (493.64)           |

Total     | 6                 | 114             | 34                     | 795.63 (462.4)            |

Site 1, Aachen; Site 2, COBRE; Site 3, Groningen; Site 4, Lille; Site 5, Utrecht; Site 6, Göttingen.

*Only statements regarding the nature of the drugs (irrespective of dose details) can be made here.

**All individuals taking antidepressants (combination of two or only one).
Next, any variances from each voxel of the two seeds of the resting state functional connectivity (RSFC) data, which could be explained by age, gender, site and amount of within-scanner movement, were removed. To do so, voxel-wise effects of age, gender, site, and amount of within-scanner movement were included as predictors in a regression model based on only the HC data. This model was then used to adjust the FC data of each patient into relative scores. Therefore, these scores reflect hyper- or hypoconnectivity at each voxel relative to what would have been expected based on those covariates in HC. Thus, the deviations from the expected value calculated on the basis of HC values was used to express hyper- or hypoconnectivity of the DLPFC seeds in patients. The main problem that arises when estimating the coefficients for confounder adjustment from the entire group of subjects (i.e., patients and controls) is the potential multi-collinearity between socio-demographic confounders (age, gender as well as measurement site) and clinical characteristics and hence the neurobiological features of schizophrenia. Thus, the estimated effects of the confounders also include pathological features that are likely to introduce a bias to the estimation. In view of this, we resorted to the use of cFWE correction was on account of the fact that no significant clusters were left after FWE correction on the voxel level. The significant effects of the interaction were tested with t-tests. The results of the t-test were p < 0.05 family-wise error (FWE)-corrected on the voxel level.

Finally, we assessed seed × group interactions to reveal a specific disconnectivity of both DLPFC sub-regions. We tested for the regions showing a relatively increased positive RSFC with the posterior DLPFC cluster (and relatively decreased positive RSFC with the anterior cluster), and then visa-versa.

Results of the interaction were regarded as significant if they passed the threshold of a cluster-level FWE (cFWE) rate of p < 0.05 (cluster-forming threshold at voxel level: p < 0.001). The use of cFWE correction was on account of the fact that no significant clusters were left after FWE correction on the voxel level. The significant effects of the interaction were tested with t-tests. The results of the t-test were p < 0.05 family-wise error (FWE)-corrected on the voxel level.

Correlations Between Functional Connectivity and Clinical Parameters
At the next step we analyzed the relationship between the relative RSFC shifts between both seed regions and psychopathology in the schizophrenic sample. To this extend, the differences of adjusted RSFC between the anterior and posterior DLPFC seeds were calculated (pDLPFC > aDLPFC) in the SCZ sample. For this reason, positive differential values indicate a RSFC shift from the anterior (and toward the posterior) seed, while negative differential values indicate a RSFC shift from the posterior (and toward the anterior) seed. The calculated amount of differential disconnectivity was then correlated with the Positive and Negative Syndrome Scale (PANSS) total scores and all individual subscales. Again, the results were cFWE-corrected at p < 0.05 (Figures S1, S2, cluster-forming threshold at voxel level: p < 0.001). No significant clusters were left following additional Bonferroni correction. For exploratory reasons, results prior to Bonferroni correction have been provided.

Anatomical Allocation of Results
Brain regions were anatomically allocated to probabilistic cytoarchitectonic maps using v2.0 of the SPM Anatomy Toolbox [http://www.fz-juelich.de/ime/spm_anatomy_toolbox; (38, 39)].

RESULTS
Resting-State Functional Connectivity in HC
In HC, a significantly stronger RSFC of the posterior (compared to the anterior) seed was found with the left homotopoe
(geometrically corresponding) region (peak MNI: −28/56/16; $T = 9.48$; 1,578 voxels), the bilateral IPS (peak MNI: 56, −34, 46/−44, −42, 42; areas hIP1, hIP2, and hIP3), the right inferior temporal gyrus (peak MNI: 60/−54/−16; $T = 6.20$; 123 voxels) and the left precentral gyrus (BA 44; peak MNI: −46/6/32; $T = 6.90$; 88 voxels). Conversely, significantly stronger RSFC of the anterior (compared to the posterior) seed was observed with the left homotope region (MNI-coordinates: −28/56/16 $T = 9.48$; 1,578 voxels), the left ACC (MNI-coordinates: −2/30/20; $T = 7.18$; 87 voxels), the left PCC (MNI-coordinates: −8/−46/28; $T = 5.44$; 66 voxels), the right inferior frontal gyrus (p. orbitalis, MNI-coordinates: 30/18/−22; $T = 6.03$; 64 voxels) and the right frontopolar region (Area Fp1, MNI-coordinates: 32/50/18; $T = 40.58$; 1,067 voxels).

Taken together, in a new sample of healthy controls we could replicate our previous results (16).

**Group Differences in Resting-State Functional Connectivity: Conjunction Analysis**

Compared to the HC, SCZ patients showed significantly reduced RSFC of the two seed regions (conjunction analysis) with the bilateral caudate, the right putamen, bilateral inferior occipital gyrus (V4) extending into middle occipital gyrus (Figure 2). For further details, please refer to Table 3.

Results of the individual contrasts [$p < 0.05$ family-wise error (FWE)-corrected on the voxel level] of SCZ-related reduction in RSFC with the anterior and posterior clusters respectively are presented in Tables S3, S4. Please also refer to Table S5 which shows for exploratory reasons the conjunction analysis results after cFWE correction. In contrast with these marked reductions, no significant RSFC increases were observed for either seed in SCZ patients relative to HC.

**Group Differences in Resting-State Functional Connectivity: Group x Seed Interaction**

Seed (aDLPFC/pDLPFC) × diagnostic group (SCZ/HC) interactions indicated sub-regional DLPFC disconnectivity with the right inferior parietal lobule (IPL) (peak MNI: 50/−54/42; $T = 3.74$; 239 voxels) and the left cerebellum (peak MNI: −46/−58/−40; $T = 4.62$; 134 voxels) in patients (Figures 3A,D).

According to the parameter estimates (Figure 3B), the IPL of both groups had a weaker connectivity with the aDLPFC compared to the pDLPFC, although the difference was significant only in the patient group (peak MNI: 54/−34/60; $T = 6.27$) (Figure 3C).

In the second cluster located in the cerebellum, HC showed stronger FC in the anterior DLPFC compared to the posterior DLPFC, while a reverse pattern was observed in patients (Figure 3E). The group difference in parameter estimates (Figure 3F) indicated a shift of the cerebellum’s RSFC away from the anterior (toward the posterior) DLPFC subregion among patients. None of the group comparisons revealed any significant differences in the region (Figure 3E).

The reverse interaction indicated further subregional DLPFC disconnectivity with the right precentral gyrus (Area 4a, peak MNI: 38/−22/56; $T = 4.31$; 127 voxels) and the right middle temporal gyrus (peak MNI: 50/−32/−6; $T = 4.45$; 115 voxels) (Figures 4A,D).

In HC, a significantly increased positive RSFC with the posterior DLPFC cluster (and decreased RSFC with the anterior cluster) was observed in Area 4a (peak MNI: 38/−22/56; $T = 4.31$; 127 voxels) and a reverse non-significant relationship (relatively decreased positive RSFC with the posterior cluster and an increased RSFC with the anterior cluster) was observed in SCZ (Figure 4B).
The group difference in parameter estimates (Figure 4C) revealed an RSFC shift in patients from Area 4a toward the anterior and away from the posterior DLPFC subregion.

In the cluster located in the right middle temporal gyrus (Figure 4E), the SCZ group showed a relatively decreased positive RSFC with the posterior DLPFC cluster (and relatively increased positive RSFC with the anterior cluster), with these subregional differences in RSFC being statistically significant (peak MNI: 52/−30/−10; T = 7.23). The group difference in terms of parameter estimates (Figures 4E,F) revealed a significantly reduced positive RSFC between the right middle temporal gyrus and the posterior DLPFC (peak MNI: 48/−32/−6; T = 5.45; 20 voxels) in patients as compared to controls.

Correlation With Clinical Parameters
With increasing symptom severity, several cortical regions showed a relatively decreased RSFC with the anterior DLPFC sub-region, paralleled by a relatively increased RSFC with the posterior sub-region.

An increase in the difference in adjusted RSFC (calculated as pDLPFC > aDLPFC) in the left IFG/anterior insula lobe (MNI: −34/22/12; T = 4.35; 161 voxels) was found to go along with higher total PANSS scores (Figure 5A), while in the left operculum (MNI: −44/−6/18; T = 4.31; 124 voxels) a stronger difference was related to higher general psychopathology PANSS scores (Figure 5B).

The correlation analysis with the total negative symptoms scale and the age of onset did not reveal any significant effects.

DISCUSSION
We investigated RSFC in HC and patients with SCZ, targeting the connectivity for the right anterior and posterior executive control-related DLPFC sub-regions (16). In SCZ patients, those two neighboring sub-regions demonstrated diametrically altered functional connectivity affecting the right IPL, the left cerebellum, the right precentral gyrus and the right middle temporal gyrus. Correlation analysis indicated furthermore that the connectivity imbalance of the DLPFC sub-regions with the left IFG/anterior insula and the left operculum may be linked to symptom severity.

We believe that such small, albeit not well understood, effects have an enormous impact on the results (and their interpretation) of neuroimaging studies. The common practice of studying the DLPFC region as a whole obfuscates the differential effects, thus stymieing the progress of our understanding of DLPFC functions and their pathological effects in patient collectives.

Reduction of RSFC With the Striatum and the Occipital Cortex in Both DLPFC Sub-regions
Reduced corticostriatal connectivity, common among patients with chronic and adolescent-onset schizophrenia ([40, 41]) as well as patients with first-episode psychosis (42) and their relatives (43), is not only a trait characteristic, but also, as indicated by an improvement of psychosis symptoms with increased RSFC between the right striatum and the right DLPFC (44), a state characteristic of psychosis (44).

Reduced RSFC with the bilateral striatum in SCZ patients (compared to HC) was found for both DLPFC seeds. As corticostriatal dysconnectivity accounts for psychotic symptoms of SZC, it is not surprising that it likely affects rather large areas of the right DLPFC.

A reduced RSFC between the DLPFC and the bilateral V4 (a region crucial for visual object recognition and visual attention (45) is a less common finding in schizophrenia patients and is

### TABLE 3 | Regions with significantly decreased functional connectivity with both DLPFC seeds.

| Cluster | Voxel | Macro | Cyto | t-score | MNI Coordinates |
|---------|-------|-------|------|---------|-----------------|
| 1       | 317   | R rectal gyrus |     | 6.36    |          |
|         |       | R caudate nucleus |   | 6.23    |          |
|         |       | R caudate nucleus |   | 5.63    |          |
|         |       | R rectal gyrus |     | 5.53    |          |
|         |       | R rectal gyrus |     | 5.62    |          |
|         |       | R putamen |     | 5.40    |          |
| 2       | 198   | R middle occipital gyrus extending to the inferior occipital gyrus | hOc4v [V4(v)] | 6.15 | 36 | −80 | 8 |
| 3       | 117   | R putamen |     | 5.93    |          |
| 4       | 89    | L caudate nucleus |   | 5.95    |          |
| 5       | 67    | L inferior occipital gyrus extending to the middle occipital gyrus | hOc4v [V4(v)] | 5.96 | −36 | −88 | −6 |
| 6       | 65    | R inferior frontal gyrus | | 5.89 | 56 | 20 | 24 |
| 7       | 44    | L cerebellum |     | 5.29    |          |
| 8       | 43    | R inferior temporal gyrus | | 5.65 | 52 | −54 | −20 |
| 9       | 33    | L middle occipital gyrus | | 5.36 | −30 | −90 | 8 |
| 10      | 13    | R precuneus | 7A | 5.20 | 10 | −68 | 62 |
likely to be linked to disruptions in the visual attention network (46, 47).

**Attention and Action Inhibition: Connectivity Shifts From the Anterior (Toward the Posterior) DLPFC Subregion**

Among patients, we observed a subregional DLPFC dysconnectivity with the right IPL and the left cerebellum. As previously shown by our group, the anterior DLPFC subregion in particular is likely involved in higher-order control processes of motor behavior such as attention and subsequent behavioral adjustments (16). As part of the frontoparietal executive-control network, the IPL is strongly interconnected with the DLPFC (48) and is also involved in attentional selection of sensory contents (49) and sustained attention (50). Our research (the presented work as well as the previous study by Cieslik et al. (16) has consistently shown an increased connectivity between the posterior (vs. anterior) DLPFC and the IPL in HC. In the present study, the IPL-aDLPFC connectivity was found to be weaker in patients compared to HC, and, only in patients, the IPL showed a significantly weaker connectivity to the aDLPFC compared

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**FIGURE 3** | Regions showing an SCZ-related (relative) decreased functional connectivity with the anterior DLPFC compared to the posterior seed were (A) the right IPL (Area PGa) and (D) the left cerebellum. Contrast estimates for the effect in the respective region (B,E) and the difference (SCZ—HC) in RSFC between HC and SCZ for the posterior and anterior DLPFC seeds respectively (C,F) are demonstrated below. *indicates the significant effects of the interaction assessed with t-tests (p < 0.05 family-wise error (FWE)-corrected on the voxel level).
to the pDLPFC. Apart from being linked to thought disorder and disruption of sensory integration, the reduced connection between the DLPFC (in particular the anterior DLPFC seed) and the IPL likely underlies the pronounced deficits in attention and other executive functions seen in psychosis (51). In addition, the connectivity shift from the anterior (toward the posterior) DLPFC region may underlie particular deficits in attentive stimulus processing and selection of behavior-relevant information. The connectivity shift may also explain why the involvement of the parietal cortex in SCZ strongly depends on the chosen task. For instance, compared to controls, patients with childhood-onset schizophrenia have shown significantly lower activation in the posterior parietal cortices along with decreased frontoparietal functional connectivity during a working-memory task (52). The link is underscored by the fact that selective attention plays a central role in working memory (53).

With cerebellar hypoactivation being commonplace in SCZ (54, 55), a few studies also indicate changes in the RSFC between the cerebellum and the DLPFC in SCZ (56, 57). The cerebellum, which has been known to be linked to the motor system, is also likely involved in attention, cognitive learning, and multisensory integration (58). It has also been seen to have a lower activation level during working-memory tasks in patients with childhood-onset schizophrenia (52). Habas et al. (59) have shown that the cerebellum, as part of cortico-cerebellar loops, is involved in executive control and salience detection. Our findings are also consistent with the notion of a misconnection in the cortico-cerebellar-thalamo-cortical (CCTC) network (60) underlying the pathophysiology of schizophrenia.
Taken together, our observations suggest that the cortico-cerebellar and cortico-parietal RSFC dysfunction in SCZ may not only be network-specific (61), but also strongly dependent on the exact localization of the DLPFC clusters. Given the involvement of the anterior DLPFC seed in higher-order control processes of motor behavior and attention (16), these findings can help broaden our understanding with respect to the task-based aberrant activity patterns in those regions.

**Action Execution: Connectivity Shifts From the Posterior (Toward the Anterior) DLPFC Subregion**

Here, we observed effects in the patients' primary motor cortex (Area 4a) and the right MTG.

The right DLPFC has been seen to be strongly interconnected with the motor cortex (4, 61, 62), modulating its activity during selection, planning, and execution of motor behavior (63). In HC, we saw a significantly increased positive RSFC with the posterior DLPFC cluster (and decreased RSFC with the anterior cluster) in Area 4a. This effect, likely associated in HC with a stronger emphasis of the posterior DLPFC cluster in action execution (16), was missing in patients. Connectivity shifts from the posterior (toward the anterior) DLPFC subregion and the Area 4a may be a correlate of reduced capacities in action execution (64) and prolonged motor planning and execution (65) seen in schizophrenia. The primary motor cortex, which is activated not only during execution (66, 67) but also during observation of others' actions (68), the latter putatively reflecting mirror neuron activity (69), is linked to a wide range of important social behaviors, from speech to imitation and empathy (69) and is reduced in schizophrenia (70, 71). The activation of the primary motor cortex is also closely linked to automatic motor potentiation: e.g., the viewing of a right-facing cup handle activates the left hemispheric motor areas (72), triggering potentiation of the right hand (73). The regulatory relationship...
between the frontal and primary motor cortices is also evident in what is known as “utilization behavior” (74), which is believed to be linked to intrusive, disruptive, and inappropriate motor behaviors seen in individuals with frontal system damage or dysfunction (e.g., dementias, schizophrenia, depressive disorders, attention deficit hyperactivity disorder) (75).

In the cluster located in the right MTG, only patients showed a connectivity shift from the posterior (toward the anterior) DLPFC. That this effect was not seen in HC, indicates its association with functional aberrations. Thus, the right MTG is linked to the perception of biological motion [movements generated by living beings; (76)] as well as different aspects of face perception (77, 78). In SCZ, deficits in face perception (79) and biological motion perception (80), processes crucial to the interpretation of social information, have already been elucidated (81). As demonstrated by our results, deficits in action execution in schizophrenia may be related in particular to the disturbed RSFC between the right DLPFC subregion and the primary motor cortices. Specifically, given the involvement of the posterior DLPFC seed in action execution (16), a connectivity shift from the posterior (toward the anterior) DLPFC may underlie impairments (in SCZ) with respect to prolonged motor planning and execution, or utilization behavior.

The Link Between Pathophysiology and Psychopathology

The correlation analysis with psychopathology indicated that the sub-regional DLPFC connectivity with the left IFG/anterior insula and the left operculum correlated positively with increasing total PANSS and general psychopathology scores.

The ACC, the DLPFC, the insula and the posterior parietal cortex form a regulatory network for high-level cognitive control and attentional processes (82, 83). In particular, decreased gray matter in the anterior insula has been linked to executive function deficits observed in e.g., schizophrenia, bipolar disorder, and depression (84).

Patients with schizophrenia also experience difficulties in appropriately attributing self-generated sensory stimuli. The anterior insula/IFC region and the adjoining frontal operculum have been suggested to be involved in the processing of self-generated sensory stimuli (81). The regulatory influence of the right DLPFC on the anterior insula has been observed during the regulation of pain intensity (85) as well as visual and auditory awareness of the moment (81). Taken together, our findings suggest that symptoms linked to misperception of the self as a distinct entity, and also deficits in high-level cognitive control and attentional processes, are likely to be dependent on symptom severity.

LIMITATIONS

Despite its careful design, and the fact that it reached its goal, the study had a few limitations that ought to be mentioned. First, the data were collected from 6 different sites, and thus the heterogeneity of scanners and sequences might potentially have affected the results. Second, given that the diagnosis was based (depending on the site where the subjects were recruited) on the DSM-5 or ICD-10 criteria, the procedure, despite the overlap in diagnostic criteria, could have led to diagnostic inconsistencies. Third, at the time of assessment, most patients (93%) were under psychopharmacological treatment, with about 69% (n = 83) of the patient's group taking multiple compounds and no more than six having the same combination of drugs. Therefore, the potential effect of medication on the results cannot be ruled out. Finally, another limitation of the study is the lack of neuropsychological assessment of patients, owing to which the examination of the DLPFC subregions in relation to executive functions was rendered impossible.

CONCLUSION

As summarized, the current analysis involving a large, representative sample of SCZ patients has demonstrated that even the connectivity of two neighboring clusters identified by advanced in-vivo mapping may be differentially disrupted in SCZ. Thus, we conclude that the imbalanced connectivity of the sub-regions (anterior and posterior DLPFC seeds), rather than that of the DLPFC as a whole, characterizes the connectional disruption of the DLPFC in SCZ. We would also argue that prevalent concepts such as “prefrontal dysfunction” may be far too broad to help explain the apparently region-specific disturbances in SCZ.

AUTHOR CONTRIBUTIONS

NC and SE: substantial contributions to the conception or design of the work; TN-J, BD, BK, AA, RJ, IS and OG: the acquisition of data for the work; NC, SE, EC, and VM: analysis and interpretation of data for the work; NC, SE, EC, and VM: drafting the work; NC, SE, EC, VM, TN-J, BD, BK, AA, RJ, IS, and OG: revising it critically for important intellectual content; NC, SE, EC, VM, TN-J, BD, BK, AA, RJ, IS, and OG: agreement to be accountable for all aspects of the work.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2018.00211/full#supplementary-material
REFERENCES

1. Koecchin E, Ody C, Kouniheir F. The architecture of cognitive control in the human prefrontal cortex. Science (2003) 302:1181–5. doi: 10.1126/science.1086445

2. MacDonald GM, Gervais BR, Snyder JA, Tarasov GA, Borisova OK. Radiocarbon dated Pinus sylvestris L. wood from beyond tree-line on the Kola Peninsula, Russia. Holocene (2000) 10:143–7. doi: 10.1191/095953800667807510

3. Bates JE, Goldman-Rakic PS. Prefrontal connections of medial motor areas in the rhesus monkey. J Comp Neurol (1993) 336:211–28. doi: 10.1002/cne.9303360205

4. Lu MT, Preston JB, Strick PL. Interconnections between the prefrontal cortex and the premotor areas in the frontal lobe. J Comp Neurol (1994) 341:375–92. doi: 10.1002/cne.9303410308

5. Schmahmann JD, Pandya DN. The cerebrocerebellar system. Int Rev Neurobiol. (1997) 41:31–60. doi: 10.1016/S0074-7742(08)60346-3

6. Petrides M, Pandya DN. Dorosoral prefrontal cortex: comparative cytoarchitectonic analysis in the human and the macaque brain and corticocortical connection patterns. Eur J Neurosci. (1999) 11:1011–36. doi: 10.1046/j.1460-9568.1999.00518.x

7. Nee DE, Jonides J, Berman MG. Neural mechanisms of proactive interference-resolution. Neuroimage (2007) 38:70–751. doi: 10.1016/j.neuroimage.2007.07.066

8. Vogt P, Rittgers KH, Estraguel G, Korak J, Wade TG, Wickham JD. Mapping spatial patterns with morphological image processing. Landsc Ecol. (2007) 22:171–77. doi: 10.1007/s10888-006-9013-2

9. Yamaguchi S, Zheng D, Oka T, Bokura H. The key locus of common response inhibition network for no-go and stop signals. J Cogn Neurosci. (2008) 20:1434–42. doi: 10.1162/jocn.2008.20100

10. Birkett P, Brindley A, Norman P, Harrison G, Baddeley A. Control of attention in schizophrenia. J Psychiatr Res. (2006) 40:579–88. doi: 10.1016/j.jpsychires.2005.11.001

11. Everett J, Laplante L, Thomas J. The selective attention deficit in schizophrenia. Limited resources or cognitive fatigue? J Neurol Med Dis. (1989) 177:735–8. doi: 10.1007/BF00950535-1989-12000-00004

12. Orellana G, Slachevsky A, Peña M. Executive attention impairment in first episode schizophrenia. BMC Psychiatry (2012) 12:154. doi: 10.1186/1471-244X-12-154

13. Barch DM, Ceaser A. Cognition in schizophrenia: core psychological and neural mechanisms. Trends Cogn Sci. (2012) 16:27–34. doi: 10.1016/j.tics.2011.11.015

14. Guillouzet-Bongaarts AL, Hyde TM, Dalley RA, Hawrylucz MJ, Henry A, Hof PR, et al. Altered gene expression in the dorsolateral prefrontal cortex of individuals with schizophrenia. Mol Psychiatry (2014) 19:478–87. doi: 10.1038/mp.2013.30

15. Callcott JH, Bertolino A, Mattay VS, Langheim FJP, Duyn J, Coppola R, et al. Physiological dysfunction of the dorsolateral prefrontal cortex in schizophrenia revisited. Cereb Cortex (2000) 10:1078–92. doi: 10.1093/cercor/10.11.1078

16. Cieslik EC, Zilles K, Caspers S, Roski C, Kellermann TS, Jakobs O, et al. Dissociating bottom up and top-down processes in a manual stimulus–response compatibility task. J Neurophysiol. (2010) 104:1472–83. doi: 10.1152/jn.00261.2010

17. Jakobs O, Pomjasinski W, Jakobs K, Zilles K, Langner R. Neural correlates of developing and adapting behavioral biases in speeded choice actions—An fMRI study on predictive motor coding. Cereb Cortex (2011) 21:1178–91. doi: 10.1093/cercor/bhq188

18. Lembcke C, Zilles K, Kurth F, Eickhoff SB. Dissociating bottom up and top-down control in the human prefrontal cortex. Schizophr Bull. (2012) 17:263–73. doi: 10.1093/schbul/bss010

19. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull. (1987) 13:261–76. doi: 10.1093/schbul/13.2.261

20. Dilling H, Freyberger HJ. (2016). Taschenführer zur ICD-10-Klassifikation Psychischer Störungen. Bern: Hogrefe.

21. American Psychiatric Association (2013). Diagnostic and Statistical Manual of Mental Disorders 5th Edn. Washington, DC: American Psychiatric Association.

22. Andreasen NC, Plessor M, Nopoulos P, Miller D, Ho BC. Antipsychotic dose equivalents and dose-years: a standardized method for comparing exposure to different drugs. Biol Psychiatry (2010) 67:255–62. doi: 10.1016/j.biopsych.2009.08.040

23. Ashburner J, Friston KJ. Unified segmentation. Neuroimage (2005) 26:839–51. doi: 10.1016/j.neuroimage.2005.02.018

24. Van Dijk KRA, Sabuncu MR, Buckner RL. The influence of head motion on intrinsic functional connectivity MRI. Neuroimage (2012) 59:431–8. doi: 10.1016/j.neuroimage.2011.07.044

25. Satterthwaite TD, Elliott MA, Gerraity RT, Ruparel K, Loughead J, Calkins ME et al. An improved framework for confound regression and filtering for control of motion artifact in the preprocessing of resting-state functional connectivity data. Neuroimage (2015) 64:240–56. doi: 10.1016/j.neuroimage.2012.08.052

26. Gotts SJ, Saad ZS, Jo HJ, Wallace GL, Cox RW, Martin A. The perils of global signal regression for group comparisons: a case study of Autism Spectrum Disorders. Front Hum Neurosci. (2013) 7:356. doi: 10.3389/fnhum.2013.00356

27. Saad ZS, Gotts SJ, Murphy K, Chen G, Hang JJ, Martin A et al. Trouble at rest: how correlation patterns and group differences become distorted after global signal regression. Brain Connect. (2012) 2:25–32. doi: 10.1089/brain.2012.0080

28. Fox MD, Raichle ME. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat Rev Neurosci. (2007) 8:700–11. doi: 10.1038/nrn2201

29. Roszycka M, Satterthwaite TD, Koutsouleris N, Ersus G, Doshi J, Wolf DH, et al. Multisite machine learning analysis provides a robust structural imaging signature of schizophrenia detectable across diverse patient populations and within individuals. Schizophr Bull. (2017). doi: 10.1093/schbul/sbx137. [Epub ahead of print].

30. Eickhoff SB, Greffkes C, Zilles K, Fink GR. The somatotopic organization of cytoarchitectonic areas on the human parietal operculum. Cereb Cortex (2007) 17:1800–11. doi: 10.1093/cercor/bhh090

31. Eickhoff SB, Stephan KE, Mohlberg C, Greffkes C, Gereon RF, Amunts K, et al. A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. Neuroimage (2005) 25:1325–35. doi: 10.1016/j.neuroimage.2004.12.034

32. Peters H, Riedl V, Manoloi A, Scherr M, Schwerthöffer D, Zimmer C, et al. Changes in extra-striatal functional connectivity in patients with schizophrenia in a psychotic episode. Br J Psychiatry (2017) 210:75–82. doi: 10.1192/bjp.bp.114.151928
41. James A, Joyce E, Lunn D, Hough M, Kenny L, Ghaetaorhe R, et al. Abnormal frontostriatal connectivity in adolescent-onset schizophrenia and its relationship to cognitive functioning. *Eur Psychiatry* (2016) 35:32–8. doi: 10.1016/j.eurpsy.2016.01.2426

42. Zhou Y, Liang M, Jiang T, Tian L, Liu Y, Liu Z, et al. Functional dysconnectivity of dorsolateral prefrontal cortex in first-episode schizophrenia using resting-state fMRI. *Neurosci Lett.* (2007) 417:297–302. doi: 10.1016/j.neulet.2007.02.081

43. Fornito A, Harrison BJ, Goodby E, Dean A, Ooi C, Nathan RJ, et al. Functional dysconnectivity of corticostriatal circuitry as a risk phenotype for psychosis. *JAMA Psychiatry* (2013) 70:1143. doi: 10.1001/jamapsychiatry.2013.1976

44. Sarpal DK, Robinson DG, Lencz T, Argyelan M, Ikuta T, Karlsgodt K, et al. Antipsychotic treatment and functional connectivity of the striatum in first episode schizophrenia. *JAMA Psychiatry* (2015) 72:5. doi: 10.1001/jamapsychiatry.2014.1734

45. Rogelj D, Chelazzi L, Connor CE, Conway BR, Fujita I, Gallant JL, et al. Toward a unified theory of visual area V4. *Neuron* (2012) 74:12–29. doi: 10.1016/j.neuron.2012.03.011

46. Potts GF, O’Donnell BF, Hirayasu Y, McCarley RW. Disruption of neural systems of visual attention in schizophrenia. *Arch Gen Psychiatry* (2002) 59:418–24. doi: 10.1001/archpsyc.59.5.418

47. Wood SM, Potts GF, Martin LE, Kothmann D, Hall JF, Ulanday JB. Disruption of auditory and visual attention in schizophrenia. *Psychiatry Res.* (2007) 156:105–16. doi: 10.1016/j.psychres.2007.04.014

48. Sooley WW, Menon V, Schatzberg AF, Keller J, Gary HG, Kenna H, et al. Dissociable intrinsic connectivity networks for salience processing and executive control. *J Neurosci.* (2007) 27:2349–56. doi: 10.1523/JNEUROSCI.5587-06.2007

49. Ptak R. The frontoparietal attention network of the human brain: action, saliency, and a priority map of the environment. *Neuroscientist* (2012) 18:502–15. doi: 10.1177/1073858411409051

50. Singh-Curry V, Husain M. The functional role of the inferior parietal lobe in the dorsal and ventral stream dichotomy. *Neuropsychologia* (2009) 47:1434–48. doi: 10.1016/j.neuropsychologia.2008.11.033

51. Torrey EF. Schizophrenia and the inferior parietal lobule. *Schizophr Res.* (2009) 10:117–30. doi: 10.1016/j.schres.2014.10.040

52. Trimble D, Young AB, Miron R, Almqvist B, Okuda T, Mechanic S, et al. Dissociable intrinsic connectivity networks for salience, and a priority map of the environment. *Neuroscientist* (2013) 19:231–6. doi: 10.1177/1073858411409051

53. Mothersill O, Knee-Zaska C, Donohoe G. Emotion and theory of mind in schizophrenia: a mirror neuron deficit? *Aesthet Creativ Arts* (2013) 77:588. doi: 10.3389/fnhum.2014.00588

54. Chen YL, Tu PC, Lee YC, Chen YS, Li CT, Su TP. Resting-state fMRI mode network in schizophrenia. *Schizophr Bull.* (2013) 39:797–806. doi: 10.1093/schbul/sbr193

55. Mothersill O, Knee-Zaska C, Donohoe G. Emotion and theory of mind in schizophrenia: investigating the role of the cerebellum. *J Am Acad Child Adolesc Psychiatry* (2018) 57:166–74. doi: 10.1016/j.jaac.2017.12.009

56. Vandreverdonck A. Symbiosis of executive and selective attention in working memory. *Front Hum Neurosci.* (2014) 8:588. doi: 10.3389/fnhum.2014.00588

57. Lungu O, Barakat M, Laventure S, Debas K, Proulx S, Luck D, et al. The incidence and nature of cerebellar findings in schizophrenia: a quantitative review of fMRI literature. *Schizophr Bull.* (2013) 39:797–806. doi: 10.1093/schbul/sbr193

58. Moosbrugger H, Bahnke I, Teufel T. Abnormal frontostriatal connectivity in adolescent-onset schizophrenia. *J Am Acad Child Adolesc Psychiatry* (2018) 57:166–74. doi: 10.1016/j.jaac.2017.12.009

59. Kordos J, Dosenbach NU, Fair DA, Sepulcre J, Nystrom LE, Vincent JL, et al. Dissociable intrinsic connectivity networks for salience, and a priority map of the environment. *Neuroscientist* (2014) 20:160–9. doi: 10.1177/1073858414542236

60. Proctor RN, Kiebel SJ, Wager TD, Ollinger JM, Ugurbil K, Smith SM. Dissociable intrinsic connectivity networks for salience, and a priority map of the environment. *Neuroscientist* (2004) 10:345–54. doi: 10.1177/1073858404265361

61. Craig AD. How do you feel - now? The anterior insula and human awareness. *Philos Trans R Soc B* (2002) 357:117–30. doi: 10.1098/rstb.2001.1602
82. Menon V, Uddin LQ. Saliency, switching, attention and control: a network model of insula function. *Brain Struct Funct.* (2010) **214**:655–67. doi: 10.1007/s00429-010-0262-0

83. Goodkind M, Eickhoff SB, Oathes DJ, Jiang Y, Chang A, Jones-Hagata LB, et al. Identification of a common neurobiological substrate for mental illness. *JAMA Psychiatry* (2015) **72**:305. doi: 10.1001/jamapsychiatry.2014.2206

84. Wylie KP, Tregellas JR. The role of the insula in schizophrenia. *Schizophr Res.* (2010) **123**:93–104. doi: 10.1016/j.schres.2010.08.027

85. Lorenz J, Minoshima S, Casey KL. Keeping pain out of mind: the role of the dorsolateral prefrontal cortex in pain modulation. *Brain* (2003) **126**:1079–91. doi: 10.1093/brain/awg102

**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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