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# Association between functional and structural connectivity of the corticostriatal network in people with schizophrenia and unaffected first-degree relatives

## *Supplemental information*

### 1. Supplementary Methods and Materials

#### 1.1. Participant Inclusion and Exclusion Criteria

Subjects were interviewed with the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, text revision (DSM-IV-TR) axis I disorders (SCID-I/P, SCID-I/NP Chinese version). Based on interviews and reviews of clinical history, **individual** who met the DSM-IV-TR criteria for schizophrenia were included in the study. All relatives included in this study were free of Axis I disorder in order to study familial alterations unrelated to illness manifestation and were not taking any psychoactive medications. Furthermore, **non-clinical** controls **were free of Axis I disorder** and had no family history of schizophrenia or any other psychotic disorder. The following exclusion criteria were applied to all groups: (a) < 18 or > 45 years of age; (b) left handedness; (c) history of brain trauma with loss of consciousness, neurological diseases or serious physical diseases (respiratory disorders, cardiovascular disease and so on); (d) diagnosis of alcohol/substance abuse within 12 months before participation; and (e) contraindications for MRI scan.

#### 1.2. Medication Data

Medication histories were initially recorded based on self-reports, and then verified either by their psychiatrists or chart review. Eighteen of 47 **people with schizophrenia** during the imaging were free of antipsychotic medication (medication naïve: n=1; off antipsychotic medications for at least 2 weeks: n=17), and all other **people with schizophrenia** received mono- or dual therapy with antipsychotic medication. One **people with schizophrenia** were treated with first-generation antipsychotic agents (haloperidol) alone, 25 **people with schizophrenia** were treated with second-generation antipsychotic agents alone (risperidone n=9; olanzapine n=6; aripiprazole n=4; paliperidone n=3; clozapine n=1;

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quetiapine n=1; blonanserin n=1), 2 **people with schizophrenia** were treated with haloperidol and a second-generation agent (olanzapine and haloperidol n=1; aripiprazole and haloperidol n=1), and 1 **people with schizophrenia** were treated with two second-generation agents (olanzapine and quetiapine). Antipsychotic medication was converted to chlorpromazine (CPZ) equivalent doses.

1.3. Resting State fMRI Data Preprocessing

The preprocessing was performed with Statistical Parametric Mapping (SPM8) software (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/), the Analysis of Functional NeuroImage (AFNI, http://afni.nimh.nih.gov/afni), and the FMRIB Software Library (FSL, http://fsl.fmrib.ox.ac.uk/fsl). The first 10 volumes of the functional images, collected before equilibrium magnetization was reached, were discarded. Then, images were slice-time corrected, and motion-corrected. Each fMRI scan was intensity scaled to yield a whole brain mean value of 10000. Temporal band-pass filtering (0.01–0.08 Hz) was performed to reduce the effects of low-frequency drifts and high-frequency noise, and 6 affine motion parameters were also regressed out of the data. Removal of linear and quadratic trends was also implemented. The single-subject images were spatially normalized to the Montreal Neurological Institute (MNI) space using DARTEL of SPM8, resampled to $2\times2\times2mm^3$ during the normalization, and smoothed with a 6-mm full-width at half-maximum (FWHM) Gaussian kernel. Head movement parameters were examined for each subject. We did not use scrubbing to remove time points based on framewise head motion since the scrubbing may make rs-fMRI scans of subjects to have different numbers of time points. Instead, we excluded subjects if their head motion greater than 2mm in translation or 2° in rotation or mean framewise displacement greater than 0.5mm. One-way ANOVA did not reveal any significant differences in movement parameters among groups (Frame-wise displacement p=0.891).

1.4. DTI Data Preprocessing

The DTI data was pre-processed using the following steps: For each subject, DTI data were corrected for eddy currents and head motion by affine registration to the non-weighted image (b0

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image); subsequently the skull from the data was removed; fractional anisotropy (FA) was calculated based on the skull removed data for group analysis; structural connection between two regions was identified using probabilistic tractography. All these steps were performed using FSL (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/). The structural connectivity strength of a connection was defined as the mean FA values of voxels on the structural connection identified using the probabilistic tractography.

**2. Supplementary Results**

2.1. Group Differences in the Corticostriatal Functional Connectivity

Ventral Striatum

Group differences in functional connectivity between the ventral striatum and the cortex are summarized in Table S1 and shown in Figure S1. Compared with the **non-clinical** controls, the people with schizophrenia had decreased functional connectivity between the ventral striatum and the orbital prefrontal cortex (BA11 and BA47) and the anterior cingulate cortex (ACC, BA32). We also found that the first-degree relatives had significant decreases in functional connectivity between the right ventral striatum and the orbital prefrontal cortex extending into ACC, compared with the **non-clinical** controls. No regions exhibited higher ventral striatum functional connectivity in the people with schizophrenia and the first-degree relatives than the **non-clinical** controls.

Compared with the first-degree relatives, the **people with schizophrenia** had lower functional connectivity between the ventral striatum and the orbital prefrontal cortex, the ACC, the amygdala, and the temporal pole region, accompanied by increased functional connectivity between the left ventral striatum and the right medial prefrontal cortex.

Executive Striatum

As shown in Table S2 and Figure S1, significant group differences in the executive striatal functional connectivity were observed. Compared the non-clinical controls, the **people with schizophrenia** showed weaker functional connectivity between the executive striatum and cortex

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regions including the supplemental motor area, the superior frontal gyrus, the ACC, and the bilateral thalamus; the first-degree relatives had significantly weaker functional connectivity between the executive striatum and the left thalamus.

Compared with the relatives, the **people with schizophrenia** had decreased functional connectivity between the left executive striatum and the left medial prefrontal cortex. However, no significant difference was observed in functional connectivity of the right executive striatum.

Sensorimotor Striatum

As shown in Table S3 and Figure S1, significant group differences were observed in the sensorimotor striatal connectivity. Compared with the non-clinical controls, the **people with schizophrenia** had weaker functional connectivity between the sensorimotor striatum and the supplemental motor area, the superior frontal gyrus, the transverse temporal gyrus, the insular, bilateral thalamus and the putamen. Compared with the relatives, the **people with schizophrenia** showed weaker connectivity between the left sensorimotor striatum and the inferior frontal gyrus extending into left insular. The relatives had weaker functional connectivity between the sensorimotor striatum and the Cingulate Cortex.

2.2. Group Differences in the Corticostriatal Structural Connectivity

Ventral Striatum

No significant difference was observed in connectivity maps of the bilateral ventral striatum between the **people with schizophrenia** and the non-clinical controls ($p < 0.05$, corrected for FWE). Compared with the **non-clinical** controls, the relatives had significant increases in structural connectivity between the ventral striatum and the orbitofrontal (OFC) of the ipsilateral hemisphere. Compared with the relatives, the **people with schizophrenia** showed significantly decreased structural connectivity between the right ventral striatum and the right orbitofrontal OFC and increased structural connectivity between the left ventral striatum and the left middle frontal gyrus (Figure S2).

Executive Striatum

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Compared with the **non-clinical** controls, the **people with schizophrenia** and the relatives showed reduced structural connectivity between the left executive striatum and the left superior frontal gyrus (Figure S2). We observed a significant decrease in structural connectivity between the right executive striatum and the bilateral superior frontal gyrus in the **people with schizophrenia** compared with the **non-clinical** controls.

Compared with the **non-clinical** controls, the relatives exhibited increased structural connectivity between the right executive striatum and the right superior frontal gyrus and middle frontal gyrus, orbital part. Compared with the **people with schizophrenia**, the relatives had increased structural connectivity between the right executive striatum and the right superior and middle frontal gyrus.

Sensorimotor Striatum

The **people with schizophrenia** had decreased structural connectivity between the left sensorimotor striatum and the left inferior parietal lobule (IPL), as well as increased connectivity between the left sensorimotor striatum and the left precentral gyrus compared with the **non-clinical** controls. The relatives showed no significant difference in connectivity between the left sensorimotor striatum compared with both the **people with schizophrenia** and **non-clinical** controls. Compared with the relatives, the **people with schizophrenia** had stronger connectivity between the left sensorimotor striatum and the left precentral gyrus. We found a similar difference pattern in the right sensorimotor striatal connectivity, but more extensive cortex regions were involved, including the parietal lobe, the temporal lobe, and the insular. Both the **people with schizophrenia** and the relatives showed increased connectivity between the right sensorimotor striatum and the right insular, the IPL, and the precentral gyrus, compared with the **non-clinical** controls, and the **people with schizophrenia** had stronger connectivity on these connections than the relatives.

Compared with the **non-clinical** controls, the **people with schizophrenia** had decreased structural connectivity between the right sensorimotor striatum and the right inferior frontal cortex.

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Compared with the relatives, the **people with schizophrenia** had decreased structural connectivity between the right sensorimotor striatum and the right insular, the right transverse temporal gyrus and the right inferior frontal cortex (Figure S2).

## 3. Supplemental Tables

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Table S1. Regions with Significant Differences in Functional Connectivity with the Ventral Striatum across Groups.

| Seed Region | Regions of Difference (Brodmann Area) | Side | Cluster Size (Voxels) | MNI Coordinate | | | Peak Intensity (t) |
|---|---|---|---|---|---|---|---|
| | | | | **X** | **Y** | **Z** | |
| Right Ventral Striatum | SZ<NC | | | | | | |
| | Orbitofrontal Cortex (BA47/11) | Right | 492 | 24 | 44 | -16 | 5.15 |
| | Anterior cingulate cortex (BA32/24) | Right | 265 | 14 | 32 | 18 | 4.37 |
| | subcallosal gyrus (BA25) | Right | | 6 | 22 | -14 | 4.21 |
| | REL<NC | | | | | | |
| | Anterior cingulate cortex (BA32/24) | Left | 742 | -8 | 36 | 22 | 4.18 |
| | Medial Cingulate Gyrus | Right | | 4 | 28 | 34 | 4.05 |
| | Anterior cingulate cortex (BA32/24) | Right | | 12 | 32 | 18 | 3.68 |
| | REL>SZ | | | | | | |
| | Orbitofrontal Cortex(bA11) | Right | 1887 | 12 | 50 | -12 | 4.64 |
| | Anterior cingulate cortex (BA32/24) | Right | | 4 | 40 | -4 | |
| | Temporal pole | Left | 513 | -34 | 8 | -28 | 4.04 |
| | REL<SZ | | | | | | |
| | Caudate | Right | 607 | 20 | 16 | 12 | 5.37 |
| | Putamen | Left | 555 | -18 | 16 | 4 | 5.40 |
| Left Ventral Striatum | SZ<NC | | | | | | |
| | Orbitofrontal Cortex (BA47/11) | Right | 492 | 22 | 42 | -16 | 4.77 |
| | Anterior cingulate cortex (BA32/24) | Left | 265 | -8 | 32 | 18 | 3.85 |
| | REL<SZ | | | | | | |

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| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Medial prefrontal cortex | Right | 222 | 18 | 48 | -20 | 4.68 |
| | Middle frontal cortex | Right | | 14 | 34 | -10 | 4.21 |

SZ: people with schizophrenia; REL: unaffected first-degree relatives of people with schizophrenia; NC: non-clinical controls; MNI: Montreal Neurological Institute.

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Table S2. Regions with Significant Differences in Functional Connectivity with the Executive Striatum across Groups.

| Seed Region | Regions of Difference (Brodmann Area) | Side | Cluster Size (Voxels) | MNI Coordinate | | | Peak Intensity (t) |
|---|---|---|---|---|---|---|---|
| | | | | **X** | **Y** | **Z** | |
| Right Executive Striatum | SZ<NC | | | | | | |
| | Anterior cingulate cortex (BA32/24) | Right | 2783 | 8 | 24 | 34 | 4.61 |
| | Supplementary motor area | Right | 1153 | 4 | 14 | 56 | 3.99 |
| | Cerebellum | Left | 929 | -40 | -58 | -48 | 5.36 |
| | REL<NC | | | | | | |
| | Pallidum | Right | 2169 | -24 | -12 | -2 | 4.73 |
| | Cerebellum | Left | 635 | -28 | -42 | -40 | 3.81 |
| Left Executive Striatum | SZ<NC | | | | | | |
| | Superior frontal gyrus | Left | 743 | -28 | 48 | 20 | 4.20 |
| | Anterior cingulate cortex (BA32/24) | Right | 2710 | 12 | 32 | 14 | 4.46 |
| | Thalamus | Left | 2691 | -10 | -18 | 6 | 5.48 |
| | Supplementary motor area | Right | | 2 | 16 | 53 | |
| | REL<NC | | | | | | |
| | Thalamus | Left | 808 | -16 | -26 | -6 | 4.26 |
| | REL>SZ | | | | | | |
| | Medial prefrontal cortex | Left | 2188 | -8 | 26 | 56 | 4.06 |

SZ: people with schizophrenia; REL: unaffected first-degree relatives of people with schizophrenia; NC: non-clinical controls; MNI: Montreal Neurological Institute.

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Table S3. Regions with Significant Differences in Functional Connectivity with the Sensorimotor Striatum across Groups.

| Seed Region | Regions of Difference (Brodmann Area) | Side | Cluster Size (Voxels) | MNI Coordinate | | | Peak Intensity (t) |
|---|---|---|---|---|---|---|---|
| | | | | **X** | **Y** | **Z** | |
| Right Sensorimotor Striatum | SZ<NC | | | | | | |
| | Medial Superior Frontal Gyrus | Left | 1759 | -2 | -4 | 58 | 4.16 |
| | Cerebellum | | 1603 | 0 | -58 | -2 | 4.74 |
| | Insular | Left | 755 | -28 | 16 | 12 | 4.34 |
| | Thalamus | Right | 2280 | 14 | -18 | 6 | 6.10 |
| | Thalamus | Left | 1354 | -12 | -18 | 0 | 4.60 |
| | REL<NC | | | | | | |
| | Cingulate Cortex (BA32) | Left | 1171 | -2 | 8 | 42 | 4.12 |
| | Pallidum | Right | 1130 | 24 | -10 | 4 | 6.04 |
| | Pallidum | Left | 995 | -24 | -12 | 0 | 5.62 |
| Left Sensorimotor Striatum | SZ<NC | | | | | | |
| | Transverse Temporal Gyrus | Right | 447 | 34 | -32 | 12 | 4.45 |
| | Supplementary Motor Cortex | Left | 1213 | -4 | 4 | 54 | 4.53 |
| | Inferior frontal gyrus, opercular part | Right | 965 | 54 | -12 | 14 | 4.78 |
| | Thalamus | Left | 2409 | -14 | -20 | -2 | 4.42 |
| | REL<NC | | | | | | |
| | Pallidum | Right | 689 | 24 | -10 | 4 | 5.45 |
| | REL> SZ | | | | | | |

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| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Inferior Frontal Gyrus | Left | 1123 | -54 | 22 | 2 | 3.89 |
| | Insular | Left | | -34 | 10 | 6 | 3.46 |

SZ: people with schizophrenia; REL: unaffected first-degree relatives of people with schizophrenia; NC: non-clinical controls; MNI: Montreal Neurological Institute.

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**4. Supplemental Figures**

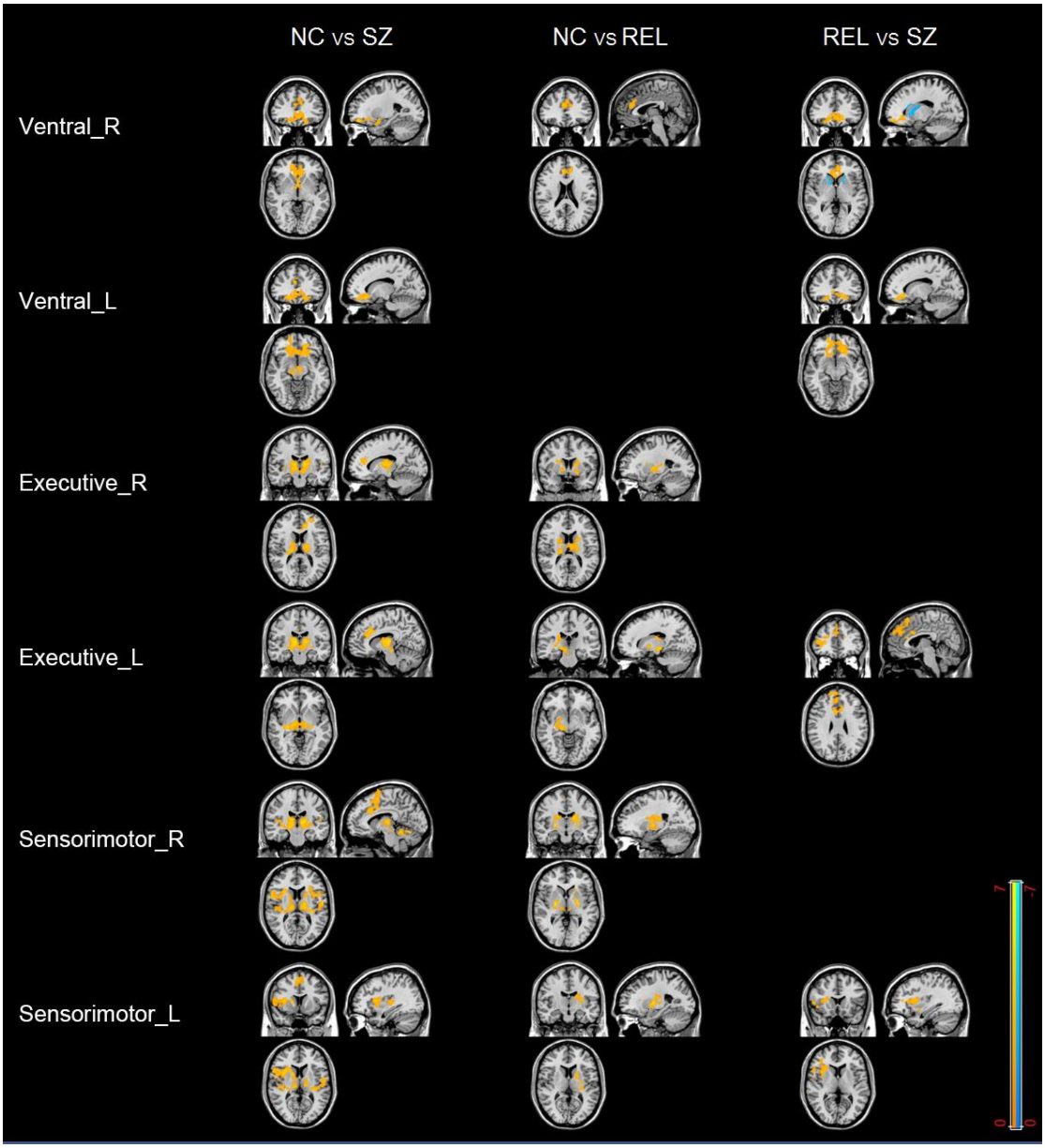


Figure S1. Differences in the corticostriatal functional connectivity between the groups under study, with the increased functional connection (NC>SZ, NC>REL, REL>SZ) shown in yellow and the decreased (NC<SZ, NC<REL, REL<SZ) shown in blue. NC: non-clinical controls, SZ: people with schizophrenia, REL: unaffected relatives, R: right hemisphere; L: left hemisphere. Results are displayed at $p< 0.05$, FWE corrected.

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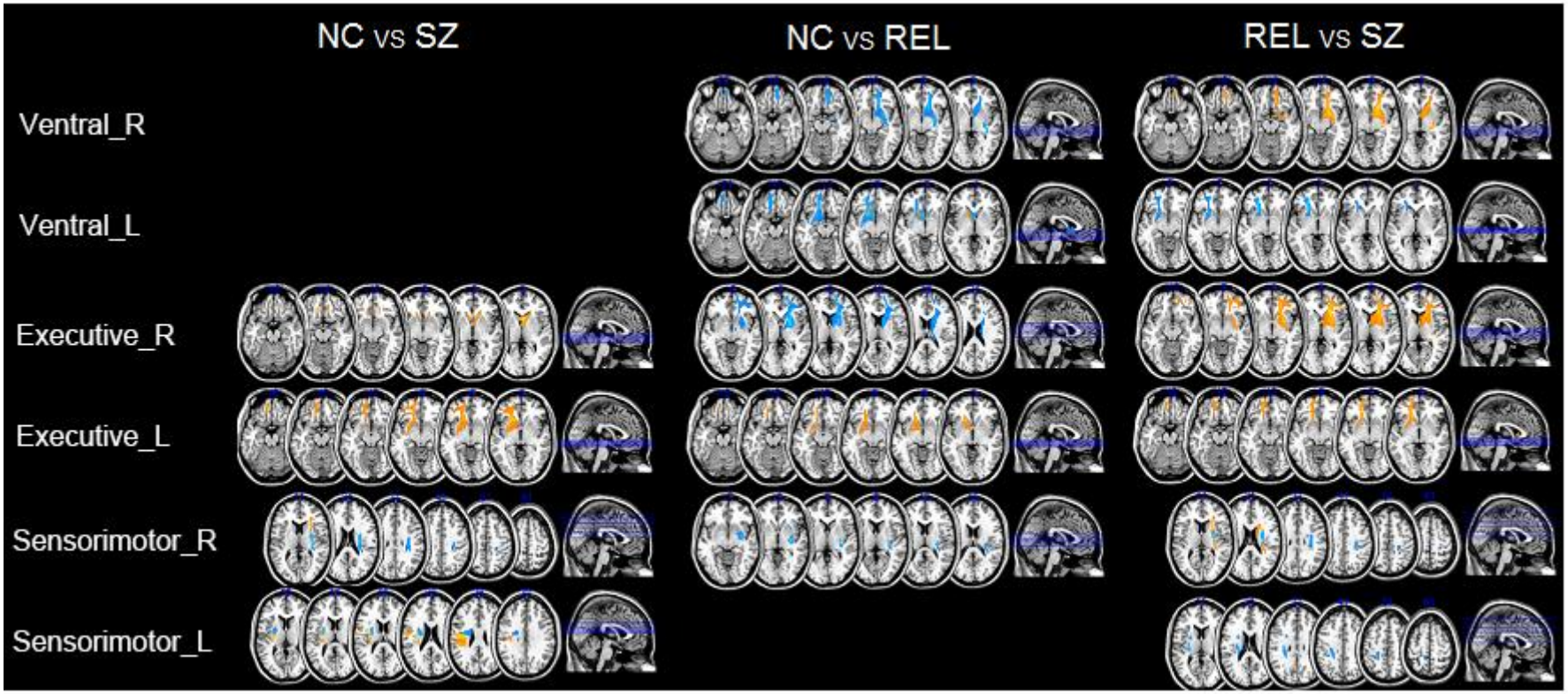

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Figure S2. Differences in structural connectivity among the groups, with the increased structural connection (NC>SZ, NC>REL, REL>SZ) shown in yellow and the decreased (NC<SZ, NC<REL, REL<SZ) shown in blue. NC: non-clinical controls, SZ: people with schizophrenia, REL: unaffected relatives, R: right hemisphere; L: left hemisphere. Results are displayed at $p < 0.05$, FWE corrected.