Supplementary material

**Neurological Soft Signs are associated with altered white matter**

**in patients with schizophrenia**

Petra Verena Viher1, Katharina Stegmayer1, Tobias Bracht1, Andrea Federspiel1, Stephan Bohlhalter2,3, Werner Strik1, Roland Wiest4, Sebastian Walther1

Author affiliations:

1Translational Research Center, University Hospital of Psychiatry and Psychotherapy, University of Bern, Switzerland;

2Department of Clinical Research, University Hospital, Inselspital, Bern, Switzerland;

3Neurocenter, Luzerner Kantonsspital, Switzerland;

4Support Center of Advanced Neuroimaging, Institute of Neuroradiology, University of Bern, Switzerland

Corresponding author:
Petra V. Viher
Translational Research Center
University Hospital of Psychiatry and Psychotherapy
University of Bern
Bolligenstrasse 111, 3000 Bern 60, Switzerland
petra.viher@upd.unibe.ch
Phone: +41 31 930 97 57
Fax: +41 31 930 94 04

Table of Contents

[1. Tractography 3](#_Toc74743590)

[2. Motor rating scales 3](#_Toc74743591)

[3. Correlations of NES scores with demographic and clinical characteristics 4](#_Toc74743592)

[4. Group comparison of white matter microstructure (WM) between patients and controls 4](#_Toc74743593)

[4.1 Group comparison of fractional anisotropy (FA) 4](#_Toc74743594)

[4.2 Group comparison of mean diffusivity (MD) 5](#_Toc74743595)

[4.3 Group comparison of radial diffusivity (RD) 5](#_Toc74743596)

[5. Results for the association of NES subscales with DTI parameters in patients with schizophrenia 6](#_Toc74743597)

[5.1 Results for the association of NES subscale motor coordination with DTI parameters in patients with schizophrenia 6](#_Toc74743598)

[5.2 Results for the association of NES subscale sensory integration with DTI parameters in patients with schizophrenia 9](#_Toc74743599)

[5.3 Results for the association of NES subscale sequence of complex motor tasks with DTI parameters in patients with schizophrenia 12](#_Toc74743600)

[6. Results for the partial correlations between the NES scores and three motor fiber tracts 13](#_Toc74743601)

[References 14](#_Toc74743602)

## 1. Tractography

DTI data was first pre-processed using the software ExploreDTI (version 5.8.3.) for tractography 1. We corrected for motion artefacts and eddy current distortions applying a B-Matrix rotation 2, and for field inhomogeneities 3. We then used an echo planar imaging (EPI) correction in order to warp the diffusion images to the anatomical images, which resulted in a resolution of 1x1x1 mm3. Quantitative parameters such as FA was calculated by fitting a single diffusion tensor model to the diffusion data 4. Then, we started tractography analyses with ExploreDTI, and used an algorithm similar to that of Basser et al. (1994) 4. We chose as termination criteria for the tractography an angle threshold > 45° and FA < 0.2. We reconstructed tracts based on anatomical landmarks. For the corticospinal tract, the first ROI was defined on a horizontal section surrounding the precentral gyrus and the second ROI was drawn on a horizontal section at the height of the pons, where the corticospinal tract descends 5, 6. For the superior longitudinal fascicle, we placed two ROIs in the green triangular-shaped SLF in the coronal plane, similar to Szeszko et al. 2018 7. The two ROIs for the aslant tract were placed on the anatomical image around the superior frontal gyrus, supplementary motor area (SMA) and pre-SMA, and another ROI at the inferior frontal gyrus, including pars opercularis and triangularis 8-10. Finally, we extracted the mean FA values across the entire tracts for each subject.

## 2. Motor rating scales

We used three different scales to test for motor abnormalities. We applied the Abnormal Involuntary Movement Scale (AIMS)11 to assess signs of dyskinesia in orofacial muscles, extremities and trunk. The motor part of the Unified Parkinson’s Disease Rating Scale (UPDRS III)12 was used to test for parkinsonism and the Bush-Francis Catatonia Rating Scale (BFCRS)13 to assess catatonic behaviour. One rater (K.S.) performed all ratings and has prior been trained to achieve κ > 0.8 by the principal investigator (S.W.). The ratings were completed within one examination session and assessed according to the original description of the instruments.

**Table S1.** Motor rating scales in 41 patients with schizophrenia

|  |  |
| --- | --- |
| Rating scalea | Mean (SD) |
| AIMS | 2.1 (3.6) |
| UPDRS-III | 6.5 (7.1) |
| BFCRS | 1.1 (2.7) |

a AIMS, Abnormal Involuntary Movement Scale; UPDRS, Unified Parkinson’s disease rating scale; BFCRS, Bush-Francis Catatonia Rating Scale.

## 3. Correlations of NES scores with demographic and clinical characteristics

**Table S2.** Correlations (Spearman) of NES scales with demographic and clinical characteristics.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Variablesa | Age | CPZ  | DOI  | AIMS | UPDRS | BFCRS | PANSS total | PANSS pos. | PANSS neg. |
|  | r | *p* | r | *p* | r | *p* | r | *p* | r | *p* | r | *p* | r | *p* | r | *p* | r | *p* |
| NES total | .33 | **.04** | .33 | **.03** | .49 | **.01** | .37 | **.02** | .59 | **.01** | .43 | **.01** | .29 | .06 | .17 | .29 | .34 | **.03** |
| Sensory integration | .33 | **.04** | .29 | .06 | .44 | **.01** | .25 | .11 | .36 | **.02** | .29 | .06 | .20 | .20 | .10 | .55 | .23 | .15 |
| Motor coordination | .51 | **.01** | .23 | .16 | .55 | **.01** | .31 | **.05** | .63 | **.01** | .51 | **.01** | .21 | .20 | -.01 | .94 | .29 | .07 |
| Sequencing of complex motor acts | .32 | **.04** | .20 | .22 | .35 | **.03** | .16 | .32 | .35 | **.02** | .48 | **.01** | .17 | .29 | .01 | .95 | .26 | .11 |

a The number of subjects for all variables is N=41. NES, Neurological Evaluation Scale; CPZ, average chlorpromazine equivalents; DOI, duration of illness (months); AIMS, Abnormal Involuntary Movement Scale; UPDRS, Unified Parkinson’s Disease Rating Scale; BFCRS, Bush-Francis Catatonia Rating Scale; PANSS, Positive and Negative Syndrome Scale (total, positive, negative). Please note, that none of the p-values would survive Bonferroni correction for multiple comparisons.

## 4. Group comparison of white matter microstructure (WM) between patients and controls

### 4.1 Group comparison of fractional anisotropy (FA)

**Table S3.** Location of significant higher **FA** values for healthy controls compared to patients with schizophrenia.

|  |  |  |  |
| --- | --- | --- | --- |
|  | Center of Gravity (mm coordinates) | Cluster size | *P(FWE-corr)* |
|  | X | Y | Z |  |  |
| **JHU WM labels atlas** |  |  |  |  |  |
| Genu of corpus callosum | 0.0 | 27.7 | 9.1 | 1416 | 0.012 |
| Body of corpus callosum | 0.2 | -6.0 | 27.8 | 2231 | 0.013 |
| Splenium of corpus callosum | 2.3 | -43.9 | 21.9 | 759 | 0.027 |
| Anterior limb of internal capsule R | 19.8 | 14.0 | 7.1 | 296 | 0.016 |
| Anterior limb of internal capsule L | -18.0 | 14.2 | 5.2 | 263 | 0.018 |
| Anterior corona radiata R | 21.5 | 31.2 | 5.2 | 834 | 0.015 |
| Anterior corona radiata L | -20.1 | 28.2 | 5.9 | 754 | 0.017 |
| Superior corona radiata R | 20.0 | -15.0 | 37.9 | 295 | 0.013 |
| Superior corona radiata L | -18.9 | -10.5 | 37.3 | 291 | 0.014 |
| Posterior corona radiata R | 23.5 | -42.1 | 30.7 | 275 | 0.022 |
| Posterior corona radiata L | -23.9 | -40.9 | 29.4 | 332 | 0.021 |
| Posterior thalamic radiation R | 32.7 | -60.6 | 7.8 | 540 | 0.039 |
| Posterior thalamic radiation L | -32.6 | -56.9 | 7.7 | 686 | 0.020 |
| Sagittal stratum L | -39.7 | -42.8 | -5.3 | 53 | 0.026 |
|  |  |  |  |  |  |
| **JHU WM tractography atlas** |   |   |   |  |  |
| Anterior thalamic radiation L | -19.2 | 15.6 | 6.6 | 298 | 0.018 |
| Anterior thalamic radiation R | 20.7 | 19.0 | 8.1 | 308 | 0.018 |
| Corticospinal tract L | -22.0 | -24.9 | 41.5 | 139 | 0.019 |
| Corticospinal tract R | 22.6 | -22.7 | 40.7 | 116 | 0.020 |
| Inferior fronto-occipital fasciculus L | -30.0 | -13.5 | 2.6 | 532 | 0.019 |
| Inferior fronto-occipital fasciculus R | 30.1 | -10.8 | 4.1 | 526 | 0.027 |
| Inferior longitudinal fasciculus L | -35.4 | -54.5 | 3.9 | 157 | 0.021 |
| Inferior longitudinal fasciculus R | 35.5 | -59.6 | -2.1 | 132 | 0.040 |
| Superior longitudinal fasciculus L | -39.8 | -38.5 | 26.9 | 79 | 0.028 |
| Superior longitudinal fasciculus R | 38.0 | -41.0 | 28.5 | 119 | 0.045 |

### 4.2 Group comparison of mean diffusivity (MD)

**Table S4.** Location of significant higher **MD** values for patients with schizophrenia compared to healthy controls.

|  |  |  |  |
| --- | --- | --- | --- |
|  | Center of Gravity (mm coordinates) | Cluster size | *P(FWE-corr)* |
|  | X | Y | Z |  |  |
| **JHU WM labels atlas** |  |  |  |  |  |
| Genu of corpus callosum | -0.7 | 27.7 | 9.6 | 875 | 0.030 |
| Body of corpus callosum | -4.9 | 13.9 | 23.9 | 231 | 0.036 |
| Anterior limb of internal capsule R | 20.8 | 19.0 | 4.3 | 81 | 0.029 |
| Anterior corona radiata R | 22.3 | 28.8 | 8.1 | 870 | 0.030 |
| Anterior corona radiata L | -21.2 | 28.8 | 9.7 | 1052 | 0.029 |
| Superior corona radiata R | 25.8 | 7.6 | 25.0 | 97 | 0.031 |
| Superior corona radiata L | -22.8 | 3.9 | 32.3 | 200 | 0.043 |
| External capsule R | 27.0 | 13.3 | -2.4 | 97 | 0.035 |
| Superior longitudinal fasciculus R | 34.0 | 0.0 | 20.9 | 62 | 0.046 |
|  |  |  |  |  |  |
| **JHU WM tractography atlas** |   |   |   |  |  |
| Anterior thalamic radiation L | -23.1 | 29.1 | 10.5 | 192 | 0.028 |
| Anterior thalamic radiation R | 22.2 | 26.9 | 9.0 | 155 | 0.029 |
| Inferior fronto-occipital fasciculus L | -26.4 | 31.0 | 4.9 | 348 | 0.027 |
| Inferior fronto-occipital fasciculus R | 28.4 | 31.3 | 4.4 | 382 | 0.030 |

### 4.3 Group comparison of radial diffusivity (RD)

**Table S5.** Location of significant higher **RD** values for patients with schizophrenia compared to healthy controls.

|  |  |  |  |
| --- | --- | --- | --- |
|  | Center of Gravity (mm coordinates) | Cluster size | *P(FWE-corr)* |
|  | X | Y | Z |  |  |
| **JHU WM labels atlas** |  |  |  |  |  |
| Genu of corpus callosum | 0.2 | 27.6 | 9.2 | 1362 | 0.010 |
| Body of corpus callosum | -0.3 | -5.1 | 27.6 | 2080 | 0.013 |
| Splenium of corpus callosum | 2.5 | -43.2 | 21.6 | 854 | 0.018 |
| Anterior limb of internal capsule R | 20.4 | 15.3 | 7.0 | 212 | 0.011 |
| Anterior limb of internal capsule L | -18.3 | 14.8 | 5.2 | 188 | 0.014 |
| Anterior corona radiata R | 21.9 | 29.7 | 7.2 | 1162 | 0.012 |
| Anterior corona radiata L | -20.6 | 28.5 | 9.3 | 1305 | 0.012 |
| Superior corona radiata R | 19.5 | -8.8 | 37.1 | 265 | 0.014 |
| Superior corona radiata L | -19.1 | -6.6 | 36.6 | 280 | 0.014 |
| Posterior corona radiata R | 23.8 | -42.0 | 30.2 | 337 | 0.016 |
| Posterior corona radiata L | -23.8 | -40.1 | 28.6 | 344 | 0.017 |
| Posterior thalamic radiation R | 33.2 | -57.2 | 8.6 | 621 | 0.018 |
| Posterior thalamic radiation L | -32.7 | -56.4 | 7.9 | 663 | 0.019 |
| Sagittal stratum L | -39.6 | -42.8 | -6.0 | 82 | 0.034 |
| External capsule R | 27.3 | 12.8 | -4.6 | 146 | 0.016 |
| External capsule L | -25.7 | 12.9 | -4.3 | 148 | 0.029 |
|  |  |  |  |  |  |
| **JHU WM tractography atlas** |   |   |   |  |  |
|  |  |  |  |  |  |
| Anterior thalamic radiation L | -20.6 | 21.0 | 8.3 | 327 | 0.014 |
| Anterior thalamic radiation R | 21.8 | 23.5 | 9.0 | 294 | 0.012 |
| Corticospinal tract L | -21.8 | -25.2 | 42.8 | 165 | 0.018 |
| Corticospinal tract R | 22.2 | -26.2 | 43.6 | 79 | 0.018 |
| Inferior fronto-occipital fasciculus L | -29.7 | -3.3 | 2.7 | 646 | 0.016 |
| Inferior fronto-occipital fasciculus R | 29.7 | -0.1 | 3.8 | 685 | 0.014 |
| Inferior longitudinal fasciculus L | -35.8 | -54.5 | -0.2 | 237 | 0.025 |
| Inferior longitudinal fasciculus R | 36.2 | -57.7 | -1.0 | 104 | 0.017 |
| Superior longitudinal fasciculus L | -40.3 | -29.7 | 26.6 | 388 | 0.023 |
| Superior longitudinal fasciculus R | 39.9 | -32.2 | 28.0 | 244 | 0.022 |

## 5. Results for the association of NES subscales with DTI parameters in patients with schizophrenia

Here, we tested four WM parameters and their voxel-wise linear association with three NES subscales. Each test was FWE-corrected using TFCE. We decided to omit further correction for multiple comparisons, as this was a set of exploratory analyses. But please note that stringent Bonferroni correction would require *p*-values of *p* < .0042 (0.05/12).

### 5.1 Results for the association of NES subscale motor coordination with DTI parameters in patients with schizophrenia

#### 5.1.1 Association between axial diffusivity (AD) and NES subscale motor coordination

**Table S6**. Location of significant correlations between **motor coordination** and white matter microstructure (**AD**) in patients with schizophrenia.

|  |  |  |  |
| --- | --- | --- | --- |
|  | Center of Gravity (mm coordinates) | Cluster size | *P(FWE-corr)* |
|  | X | Y | Z |  |  |
| **JHU WM labels atlas** |  |  |  |  |  |
| Genu of corpus callosum | 1.0 | 27.9 | 8.3 | 1388 | 0.007 |
| Body of corpus callosum | -0.1 | -1.9 | 26.0 | 1870 | 0.010 |
| Splenium of corpus callosum | 1.5 | -41.3 | 18.9 | 1172 | 0.014 |
| Fornix (column and body of fornix) | 0.2 | -6.6 | 14.5 | 103 | 0.018 |
| Cerebral peduncle R | 14.2 | -18.2 | -12.1 | 133 | 0.022 |
| Cerebral peduncle L | -17.4 | -14.1 | -6.5 | 75 | 0.038 |
| Anterior limb of internal capsule R | 18.9 | 8.7 | 9.1 | 306 | 0.020 |
| Anterior limb of internal capsule L | -17.7 | 8.9 | 8.6 | 259 | 0.029 |
| Posterior limb of internal capsule R | 22.6 | -13.9 | 6.8 | 363 | 0.017 |
| Posterior limb of internal capsule L | -21.3 | -14.0 | 5.7 | 310 | 0.037 |
| Retrolenticular part of internal capsule R | 30.8 | -30.4 | 9.8 | 214 | 0.019 |
| Retrolenticular part of internal capsule L | -30.7 | -29.7 | 7.6 | 319 | 0.020 |
| Anterior corona radiata R | 23.8 | 25.1 | 9.2 | 843 | 0.012 |
| Anterior corona radiata L | -22.2 | 23.5 | 12.2 | 683 | 0.014 |
| Superior corona radiata R | 25.1 | -6.6 | 30.6 | 689 | 0.012 |
| Superior corona radiata L | -24.0 | -2.7 | 29.8 | 762 | 0.011 |
| Posterior corona radiata R | 25.8 | -38.2 | 26.6 | 415 | 0.018 |
| Posterior corona radiata L | -26.2 | -38.2 | 24.9 | 298 | 0.016 |
| Posterior thalamic radiation R | 32.2 | -49.3 | 15.6 | 131 | 0.017 |
| Posterior thalamic radiation L | -30.7 | -55.5 | 14.4 | 64 | 0.020 |
| Sagittal stratum L | -38.7 | -19.8 | -9.7 | 89 | 0.019 |
| External capsule R | 30.2 | -1.0 | 12.6 | 85 | 0.037 |
| External capsule L | -31.1 | -7.7 | 4.2 | 351 | 0.020 |
| Fornix / Stria terminalis L | -27.6 | -25.6 | -3.5 | 134 | 0.032 |
| Superior fronto-occipital fasciculus R | 22.2 | 5.8 | 21.1 | 66 | 0.012 |
|  |  |  |  |  |  |
| **JHU WM tractography atlas** |   |   |   |  |  |
| Anterior thalamic radiation L | -15.3 | 4.0 | 10.7 | 590 | 0.022 |
| Anterior thalamic radiation R | 10.5 | -3.9 | 6.7 | 627 | 0.021 |
| Corticospinal tract L | -22.5 | -20.4 | 21.8 | 425 | 0.027 |
| Corticospinal tract R | 21.9 | -20.6 | 16.8 | 505 | 0.021 |
| Inferior fronto-occipital fasciculus L | -30.9 | 5.5 | -1.0 | 423 | 0.016 |
| Inferior fronto-occipital fasciculus R | 26.6 | 28.8 | 4.4 | 320 | 0.014 |
| Inferior longitudinal fasciculus L | -42.8 | -21.2 | -9.1 | 112 | 0.017 |
| Superior longitudinal fasciculus R | 37.8 | -24.7 | 30.7 | 247 | 0.045 |

#### 5.1.2 Association between mean diffusivity (MD) and NES subscale motor coordination

**Table S7.** Location of significant correlations between **motor coordination** and white matter microstructure (**MD**) in patients with schizophrenia.

|  |  |  |  |
| --- | --- | --- | --- |
|  | Center of Gravity (mm coordinates) | Cluster size | *P(FWE-corr)* |
|  | X | Y | Z |  |  |
| **JHU WM labels atlas** |  |  |  |  |  |
| Genu of corpus callosum | 0.8 | 27.6 | 8.4 | 1565 | 0.007 |
| Body of corpus callosum | -0.1 | -1.6 | 27.0 | 2180 | 0.013 |
| Splenium of corpus callosum | 2.2 | -41.3 | 21.1 | 928 | 0.025 |
| Fornix | 0.2 | -6.5 | 14.4 | 107 | 0.025 |
| Cerebral peduncle R | 16.6 | -14.2 | -7.8 | 93 | 0.034 |
| Cerebral peduncle L | -16.1 | -17.5 | -8.9 | 184 | 0.046 |
| Anterior limb of internal capsule R | 19.2 | 9.4 | 9.1 | 397 | 0.017 |
| Anterior limb of internal capsule L | -18.0 | 9.0 | 8.6 | 397 | 0.018 |
| Posterior limb of internal capsule R | 20.9 | -11.5 | 3.9 | 186 | 0.032 |
| Posterior limb of internal capsule L | -20.5 | -13.4 | 3.5 | 192 | 0.043 |
| Retrolenticular part of internal capsule R | 31.9 | -27.4 | 4.9 | 126 | 0.039 |
| Retrolenticular part of internal capsule L | -33.3 | -27.0 | 0.9 | 151 | 0.022 |
| Anterior corona radiata R | 22.1 | 26.4 | 11.7 | 1110 | 0.015 |
| Anterior corona radiata L | -20.8 | 27.9 | 10.5 | 1107 | 0.015 |
| Superior corona radiata R | 23.4 | -1.3 | 32.2 | 610 | 0.015 |
| Superior corona radiata L | -22.6 | -1.4 | 31.4 | 643 | 0.014 |
| Posterior corona radiata R | 25.1 | -38.4 | 27.9 | 292 | 0.037 |
| Posterior thalamic radiation R | 31.8 | -53.5 | 14.8 | 188 | 0.040 |
| Posterior thalamic radiation L | -29.6 | -59.2 | 13.9 | 140 | 0.035 |
| Sagittal stratum R | 39.9 | -27.8 | -9.4 | 199 | 0.042 |
| Sagittal stratum L | -39.6 | -29.8 | -9.4 | 263 | 0.028 |
| External capsule R | 31.1 | -0.3 | -2.2 | 548 | 0.025 |
| External capsule L | -29.9 | 1.4 | -0.7 | 790 | 0.017 |
| Fornix / Stria terminalis R | 28.6 | -24.8 | -4.1 | 151 | 0.032 |
| Fornix / Stria terminalis L | -27.6 | -26.3 | -3.5 | 167 | 0.023 |
| Superior fronto-occipital fasciculus R | 22.2 | 5.5 | 21.0 | 72 | 0.010 |
| Superior fronto-occipital fasciculus L | -21.1 | 4.4 | 20.5 | 66 | 0.018 |
|  |  |  |  |  |  |
| **JHU WM tractography atlas** |   |   |   |  |  |
|  |  |  |  |  |  |
| Anterior thalamic radiation L | -15.6 | 5.4 | 10.3 | 784 | 0.023 |
| Anterior thalamic radiation R | 11.6 | -0.6 | 6.6 | 788 | 0.024 |
| Corticospinal tract L | -19.4 | -19.4 | 12.3 | 342 | 0.037 |
| Corticospinal tract R | 21.2 | -21.0 | 19.0 | 201 | 0.036 |
| Inferior fronto-occipital fasciculus L | -31.5 | 3.3 | -1.7 | 705 | 0.018 |
| Inferior fronto-occipital fasciculus R | 31.5 | 7.5 | -0.4 | 703 | 0.024 |
| Inferior longitudinal fasciculus L | -42.0 | -30.2 | -9.2 | 263 | 0.029 |
| Inferior longitudinal fasciculus R | 41.5 | -26.6 | -13.0 | 116 | 0.043 |
| Superior longitudinal fasciculus L | -37.4 | -27.6 | 27.4 | 783 | 0.028 |
| Superior longitudinal fasciculus R | 37.2 | -20.7 | 30.5 | 412 | 0.041 |
| Uncinate fasciculus L | -28.5 | 10.6 | -7.9 | 134 | 0.015 |
| Uncinate fasciculus R | 30.5 | 8.8 | -9.6 | 91 | 0.016 |

####  5.1.3 Association between radial diffusivity (RD) and NES subscale motor coordination

**Table S8.** Location of significant correlations between **motor coordination** and white matter microstructure (**RD**) in patients with schizophrenia.

|  |  |  |  |
| --- | --- | --- | --- |
|  | Center of Gravity (mm coordinates) | Cluster size | *P(FWE-corr)* |
|  | X | Y | Z |  |  |
| **JHU WM labels atlas** |  |  |  |  |  |
|  |  |  |  |  |  |
| Genu of corpus callosum | 0.6 | 27.7 | 8.0 | 1421 | 0.019 |
| Body of corpus callosum | -0.6 | 0.5 | 27.5 | 1527 | 0.026 |
| Fornix  | 0.1 | -6.4 | 14.7 | 84 | 0.042 |
| Anterior corona radiata R | 20.5 | 29.5 | 12.0 | 709 | 0.030 |
| Anterior corona radiata L | -19.7 | 30.2 | 10.1 | 969 | 0.022 |
| Superior corona radiata R | 18.7 | 8.8 | 35.1 | 142 | 0.024 |
| Superior corona radiata L | -19.0 | -2.6 | 36.5 | 280 | 0.024 |
| External capsule R | 28.1 | 12.5 | -9.0 | 97 | 0.049 |
| External capsule L | -27.9 | 12.1 | -5.1 | 448 | 0.024 |
|  |  |  |  |  |  |
| **JHU WM tractography atlas** |   |   |   |  |  |
|  |  |  |  |  |  |
| Anterior thalamic radiation L | -14.6 | 5.0 | 12.4 | 219 | 0.036 |
| Anterior thalamic radiation R | 9.0 | -3.7 | 6.0 | 388 | 0.044 |
| Inferior fronto-occipital fasciculus L | -27.3 | 23.5 | 2.1 | 285 | 0.024 |
| Inferior fronto-occipital fasciculus R | 28.4 | 31.3 | 6.5 | 195 | 0.036 |
| Uncinate fasciculus L | -28.9 | 10.0 | -8.0 | 143 | 0.023 |

### 5.2. Results for the association of NES subscale sensory integration with DTI parameters in patients with schizophrenia

#### 5.2.1 Association between axial diffusivity (AD) and NES subscale sensory integration

**Table S9.** Location of significant linear relationship between **sensory integration** and white matter microstructure (**AD**) in patients with schizophrenia.

|  |  |  |  |
| --- | --- | --- | --- |
|  | Center of Gravity (mm coordinates) | Cluster size | *P(FWE-corr)* |
|  | X | Y | Z |  |  |
| **JHU WM labels atlas** |  |  |  |  |  |
|  |  |  |  |  |  |
| Genu of corpus callosum | 3.1 | 28.1 | 8.5 | 1026 | 0.031 |
| Body of corpus callosum | 3.0 | 1.2 | 25.8 | 981 | 0.036 |
| Splenium of corpus callosum | -2.3 | -40.0 | 19.9 | 287 | 0.039 |
| Anterior limb of internal capsule R | 19.1 | 8.4 | 9.2 | 407 | 0.025 |
| Anterior limb of internal capsule L | -19.2 | 7.7 | 10.9 | 261 | 0.032 |
| Posterior limb of internal capsule R | 23.7 | -13.4 | 10.0 | 308 | 0.027 |
| Posterior limb of internal capsule L | -18.0 | -3.7 | 8.9 | 63 | 0.034 |
| Retrolenticular part of internal capsule R | 26.5 | -23.0 | 7.5 | 58 | 0.029 |
| Retrolenticular part of internal capsule L | -31.4 | -30.7 | 8.0 | 197 | 0.038 |
| Anterior corona radiata R | 23.0 | 25.7 | 11.0 | 902 | 0.025 |
| Anterior corona radiata L | -22.7 | 21.8 | 18.6 | 450 | 0.033 |
| Superior corona radiata R | 24.4 | -7.8 | 31.6 | 868 | 0.021 |
| Superior corona radiata L | -24.2 | -5.3 | 30.6 | 669 | 0.031 |
| Posterior corona radiata R | 24.4 | -27.8 | 29.3 | 140 | 0.029 |
| Posterior corona radiata L | -26.1 | -36.9 | 25.8 | 207 | 0.035 |
| External capsule R | 28.7 | 1.4 | 10.3 | 79 | 0.030 |
| External capsule L | -31.5 | -8.8 | 5.7 | 249 | 0.042 |
| Superior fronto-occipital fasciculus R | 22.2 | 6.1 | 21.0 | 61 | 0.017 |
|  |  |  |  |  |  |
| **JHU WM tractography atlas** |   |   |   |  |  |
|  |  |  |  |  |  |
| Anterior thalamic radiation L | -20.7 | 15.2 | 11.3 | 307 | 0.034 |
| Anterior thalamic radiation R | 19.0 | 13.1 | 8.5 | 289 | 0.024 |
| Corticospinal tract L | -23.5 | -22.8 | 37.4 | 244 | 0.032 |
| Corticospinal tract R | 24.1 | -20.8 | 26.6 | 417 | 0.025 |
| Inferior fronto-occipital fasciculus L | -28.9 | 21.4 | 5.0 | 195 | 0.038 |
| Inferior fronto-occipital fasciculus R | 27.6 | 31.0 | 5.1 | 348 | 0.024 |
| Superior longitudinal fasciculus R | 35.9 | -24.8 | 31.5 | 313 | 0.032 |

#### 5.2.2 Association between fractional anisotropy (FA) and NES subscale sensory integration

**Table S10**. Location of significant linear relationship between **sensory integration** and white matter microstructure (**FA**) in patients with schizophrenia.

|  |  |  |  |
| --- | --- | --- | --- |
|  | Center of Gravity (mm coordinates) | Cluster size | *P(FWE-corr)* |
|  | X | Y | Z |  |  |
| **JHU WM labels atlas** |  |  |  |  |  |
|  |  |  |  |  |  |
| Genu of corpus callosum | -8.1 | 29.2 | 9.4 | 364 | 0.044 |
| Anterior corona radiata L | -18.3 | 35.5 | 12.2 | 188 | 0.043 |

#### 5.2.3 Association between mean diffusivity (MD) and NES subscale sensory integration

**Table S11.** Location of significant linear relationship between **sensory integration** and white matter microstructure (**MD**) in patients with schizophrenia.

|  |  |  |  |
| --- | --- | --- | --- |
|  | Center of Gravity (mm coordinates) | Cluster size | *P(FWE-corr)* |
|  | X | Y | Z |  |  |
| **JHU WM labels atlas** |  |  |  |  |  |
| Genu of corpus callosum | 1.2 | 27.9 | 8.4 | 1404 | 0.010 |
| Body of corpus callosum | -0.1 | -0.2 | 27.8 | 1607 | 0.021 |
| Splenium of corpus callosum | -1.9 | -40.0 | 20.6 | 444 | 0.039 |
| Anterior limb of internal capsule R | 19.7 | 9.5 | 9.4 | 410 | 0.015 |
| Anterior limb of internal capsule L | -18.4 | 8.8 | 9.3 | 423 | 0.017 |
| Posterior limb of internal capsule R | 24.1 | -13.4 | 11.2 | 190 | 0.035 |
| Posterior limb of internal capsule L | -18.7 | -4.4 | 9.5 | 71 | 0.024 |
| Retrolenticular part of internal capsule R | 32.7 | -24.9 | 2.2 | 152 | 0.043 |
| Retrolenticular part of internal capsule L | -31.8 | -30.3 | 6.8 | 209 | 0.032 |
| Anterior corona radiata R | 22.0 | 26.9 | 11.1 | 1299 | 0.012 |
| Anterior corona radiata L | -20.6 | 27.6 | 10.9 | 1120 | 0.014 |
| Superior corona radiata R | 23.6 | -3.7 | 31.9 | 780 | 0.017 |
| Superior corona radiata L | -22.7 | -4.4 | 31.9 | 678 | 0.016 |
| Posterior corona radiata R | 22.3 | -31.4 | 33.0 | 159 | 0.043 |
| Posterior corona radiata L | -24.5 | -37.8 | 27.9 | 237 | 0.033 |
| Posterior thalamic radiation L | -30.8 | -55.6 | 13.7 | 236 | 0.033 |
| Sagittal stratum R | 39.1 | -20.4 | -8.4 | 121 | 0.043 |
| Sagittal stratum L | -40.0 | -31.4 | -9.3 | 232 | 0.031 |
| External capsule R | 31.5 | 0.3 | -1.4 | 601 | 0.027 |
| External capsule L | -30.3 | 0.4 | 0.1 | 691 | 0.024 |
| Fornix / Stria terminalis R | 30.3 | -22.3 | -6.9 | 84 | 0.043 |
| Superior fronto-occipital fasciculus R | 22.2 | 5.7 | 20.9 | 68 | 0.009 |
| Superior fronto-occipital fasciculus L | -21.1 | 4.2 | 20.8 | 84 | 0.014 |
|  |  |  |  |  |  |
| **JHU WM tractography atlas** |   |   |   |  |  |
|  |  |  |  |  |  |
| Anterior thalamic radiation L | -19.8 | 16.0 | 10.0 | 518 | 0.017 |
| Anterior thalamic radiation R | 20.2 | 17.6 | 8.6 | 338 | 0.015 |
| Corticospinal tract L | -22.5 | -23.5 | 40.9 | 218 | 0.022 |
| Corticospinal tract R | 24.0 | -21.6 | 26.9 | 211 | 0.042 |
| Inferior fronto-occipital fasciculus L | -31.2 | 6.1 | -0.6 | 625 | 0.022 |
| Inferior fronto-occipital fasciculus R | 31.5 | 8.7 | 0.1 | 877 | 0.024 |
| Inferior longitudinal fasciculus L | -41.6 | -31.2 | -7.0 | 311 | 0.031 |
| Superior longitudinal fasciculus L | -37.0 | -37.9 | 26.8 | 520 | 0.030 |
| Superior longitudinal fasciculus R | 35.5 | -23.0 | 32.1 | 458 | 0.037 |
| Uncinate fasciculus L | -28.4 | 10.4 | -8.1 | 87 | 0.018 |
| Uncinate fasciculus R | 30.6 | 8.5 | -9.6 | 59 | 0.017 |
| Anterior thalamic radiation L | -19.8 | 16.0 | 10.0 | 518 | 0.017 |

#### 5.2.4 Association between radial diffusivity (RD) and NES subscale sensory integration

**Table S12.** Location of significant linear relationship between **sensory integration** and white matter microstructure (**RD**) in patients with schizophrenia.

|  |  |  |  |
| --- | --- | --- | --- |
|  | Center of Gravity (mm coordinates) | Cluster size | *P(FWE-corr)* |
|  | X | Y | Z |  |  |
| **JHU WM labels atlas** |  |  |  |  |  |
| Genu of corpus callosum | 0.5 | 27.9 | 8.7 | 1405 | 0.016 |
| Body of corpus callosum | -0.9 | 0.5 | 28.6 | 1413 | 0.022 |
| Splenium of corpus callosum | 6.1 | -43.1 | 19.9 | 590 | 0.040 |
| Anterior limb of internal capsule R | 20.6 | 10.5 | 9.7 | 298 | 0.024 |
| Anterior limb of internal capsule L | -18.4 | 9.3 | 9.0 | 416 | 0.022 |
| Retrolenticular part of internal capsule R | 31.4 | -23.9 | 2.3 | 123 | 0.037 |
| Retrolenticular part of internal capsule L | -33.1 | -30.2 | 4.3 | 153 | 0.039 |
| Anterior corona radiata R | 21.5 | 28.2 | 10.2 | 1153 | 0.019 |
| Anterior corona radiata L | -20.1 | 29.1 | 10.0 | 1134 | 0.018 |
| Superior corona radiata R | 22.1 | 5.1 | 31.5 | 311 | 0.021 |
| Superior corona radiata L | -21.0 | -4.1 | 33.1 | 443 | 0.023 |
| Posterior corona radiata R | 23.0 | -44.0 | 30.0 | 135 | 0.040 |
| Posterior corona radiata L | -23.5 | -42.2 | 29.6 | 103 | 0.039 |
| Posterior thalamic radiation R | 29.9 | -62.1 | 14.4 | 179 | 0.038 |
| Posterior thalamic radiation L | -32.6 | -56.3 | 7.5 | 609 | 0.038 |
| Sagittal stratum R | 39.3 | -21.9 | -7.5 | 97 | 0.037 |
| Sagittal stratum L | -39.6 | -32.3 | -8.7 | 245 | 0.040 |
| External capsule R | 31.2 | 1.6 | -2.7 | 555 | 0.025 |
| External capsule L | -29.9 | 2.2 | -0.6 | 809 | 0.028 |
| Fornix / Stria terminalis R | 28.7 | -25.6 | -3.9 | 144 | 0.037 |
| Fornix / Stria terminalis L | -29.2 | -24.5 | -6.6 | 52 | 0.048 |
| Superior fronto-occipital fasciculus R | 22.2 | 5.5 | 21.1 | 64 | 0.027 |
| Superior fronto-occipital fasciculus L | -21.1 | 4.5 | 20.8 | 91 | 0.021 |
|  |  |  |  |  |  |
| **JHU WM tractography atlas** |   |   |   |  |  |
|  |  |  |  |  |  |
| Anterior thalamic radiation L | -19.5 | 16.1 | 9.4 | 496 | 0.022 |
| Anterior thalamic radiation R | 21.4 | 21.4 | 8.5 | 292 | 0.022 |
| Corticospinal tract L | -20.9 | -23.2 | 45.4 | 99 | 0.030 |
| Inferior fronto-occipital fasciculus L | -31.6 | -13.0 | -0.9 | 829 | 0.031 |
| Inferior fronto-occipital fasciculus R | 30.7 | 8.9 | 1.1 | 740 | 0.024 |
| Inferior longitudinal fasciculus L | -39.9 | -35.7 | -6.0 | 438 | 0.039 |
| Superior longitudinal fasciculus L | -37.0 | -28.3 | 27.6 | 844 | 0.035 |
| Uncinate fasciculus L | -28.9 | 9.7 | -8.2 | 129 | 0.018 |
| Uncinate fasciculus R | 30.5 | 9.1 | -9.3 | 75 | 0.019 |

### 5.3 Results for the association of NES subscale sequence of complex motor tasks with DTI parameters in patients with schizophrenia

#### 5.3.1 Association between axial diffusivity (AD) and NES subscale sequence of complex motor tasks

**Table S13**. Location of significant linear relationship between **sequence of complex motor tasks** and white matter microstructure (**AD**) in patients with schizophrenia.

|  |  |  |  |
| --- | --- | --- | --- |
|  | Center of Gravity (mm coordinates) | Cluster size | *P(FWE-corr)* |
|  | X | Y | Z |  |  |
| **JHU WM labels atlas** |  |  |  |  |  |
| Genu of corpus callosum | 0.9 | 28.3 | 7.2 | 1035 | 0.028 |
| Body of corpus callosum | -1.6 | 7.9 | 23.2 | 552 | 0.038 |
| Posterior limb of internal capsule R | 24.6 | -16.5 | 10.1 | 208 | 0.045 |
| Anterior corona radiata R | 21.6 | 26.3 | 17.5 | 140 | 0.037 |
| Superior corona radiata R | 25.2 | -8.1 | 31.0 | 647 | 0.034 |
| Posterior corona radiata R | 23.1 | -30.6 | 33.2 | 103 | 0.041 |
| External capsule R | 31.3 | -6.9 | 12.2 | 86 | 0.047 |
| Fornix / Stria terminalis R | 29.7 | -23.3 | -6.1 | 50 | 0.049 |
|  |  |  |  |  |  |
| **JHU WM tractography atlas** |   |   |   |  |  |
|  |  |  |  |  |  |
| Corticospinal tract R | 24.0 | -21.2 | 28.1 | 388 | 0.041 |
| Superior longitudinal fasciculus R | 36.4 | -21.6 | 30.8 | 396 | 0.042 |

#### 5.3.2 Association between mean diffusivity (MD) and NES subscale sequence of complex motor tasks

**Table S14**. Location of significant linear relationship between **sequence of complex motor tasks** and white matter microstructure (**MD**) in patients with schizophrenia.

|  |  |  |  |
| --- | --- | --- | --- |
|  | Center of Gravity (mm coordinates) | Cluster size | *P(FWE-corr)* |
|  | X | Y | Z |  |  |
| **JHU WM labels atlas** |  |  |  |  |  |
|  |  |  |  |  |  |
| Genu of corpus callosum | 1.7 | 28.3 | 6.9 | 884 | 0.038 |
| Body of corpus callosum | 3.2 | 15.6 | 20.1 | 143 | 0.043 |
| Anterior corona radiata R | 17.4 | 34.2 | 8.4 | 54 | 0.042 |

##

## 6. Results for the partial correlations between the NES scores and three motor fiber tracts

**Table S15**. Partial correlations between the NES scores and fractional anisotropy (FA) of the bilateral superior longitudinal fiber (SLF) tract, the corticospinal fiber tract and the aslant fiber tract in patients with schizophrenia (corrected for age and medication dose).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Fiber tract | NES total | Sensory Integration | Motor Coordination | Sequence |
|  | r | p | r | p | r | p | r | p |
| Corticospinal Tract R FA | .10 | .54 | .10 | .54 | .23 | .15 | .18 | .27 |
| Corticospinal Tract L FA | .13 | .41 | .24 | .13 | .23 | .15 | .12 | .47 |
| SLF R FA | .22 | .17 | .11 | .50 | .28 | .08 | .26 | .11 |
| SLF L FA | -.10 | .53 | -.28 | .08 | -.03 | .84 | .13 | .40 |
| Aslant R FA | .17 | .29 | .04 | .82 | .39 | **.01** | .37 | **.02** |
| Aslant L FA | .07 | .68 | -.04 | .83 | .16 | .32 | .22 | .17 |

## References

**1.** Leemans A, Jeurissen B, Sijbers J, Jones DK. ExploreDTI: A graphical toolbox for processing, analyzing, and visualizing diffusion MR data. *Proceedings of the 17th Scientific Meeting, International Society for Magnetic Resonance in Medicine, Honolulu, USA, p 3537* 2009.

**2.** Leemans A, Jones DK. The B-matrix must be rotated when correcting for subject motion in DTI data. *Magn Reson Med* Jun 2009;61(6):1336-1349.

**3.** Wu M, Chang LC, Walker L, Lemaitre H, Barnett AS, Marenco S, Pierpaoli C. Comparison of EPI distortion correction methods in diffusion tensor MRI using a novel framework. *Med Image Comput Comput Assist Interv* 2008;11(Pt 2):321-329.

**4.** Basser PJ, Mattiello J, LeBihan D. Estimation of the effective self-diffusion tensor from the NMR spin echo. *J Magn Reson B* Mar 1994;103(3):247-254.

**5.** Bracht T, Steinau S, Federspiel A, Schneider C, Wiest R, Walther S. Physical activity is associated with left corticospinal tract microstructure in bipolar depression. *Neuroimage Clin* 2018;20:939-945.

**6.** Bracht T, Viher PV, Stegmayer K, Strik W, Federspiel A, Wiest R, Walther S. Increased structural connectivity of the medial forebrain bundle in schizophrenia spectrum disorders is associated with delusions of paranoid threat and grandiosity. *Neuroimage Clin* 2019;24:102044.

**7.** Szeszko PR, Tan ET, Ulug AM, et al. Investigation of superior longitudinal fasciculus fiber complexity in recent onset psychosis. *Prog Neuropsychopharmacol Biol Psychiatry* Feb 2 2018;81:114-121.

**8.** Catani M, Dell'acqua F, Vergani F, Malik F, Hodge H, Roy P, Valabregue R, Thiebaut de Schotten M. Short frontal lobe connections of the human brain. *Cortex* Feb 2012;48(2):273-291.

**9.** Catani M, Mesulam MM, Jakobsen E, et al. A novel frontal pathway underlies verbal fluency in primary progressive aphasia. *Brain* Aug 2013;136(Pt 8):2619-2628.

**10.** Broce I, Bernal B, Altman N, Tremblay P, Dick AS. Fiber tracking of the frontal aslant tract and subcomponents of the arcuate fasciculus in 5-8-year-olds: Relation to speech and language function. *Brain Lang* Oct 2015;149:66-76.

**11.** Guy W. *ECDEU Assessment Manual for Psychopharmacology*. Rockville, MD: US Department of Health, Education and Welfare; 1976.

**12.** Fahn S, Elton RL, Members UP. Unified Parkinson’s disease rating scale. In: Fahn S, Marsden CD, Goldstein M, Calne DB, eds. *Recent Developments in Parkinson’s Disease.* Vol 2. Florham Park: NJ: Macmillan Healthcare Information; 1987.

**13.** Bush G, Fink M, Petrides G, Dowling F, Francis A. Catatonia. I. Rating scale and standardized examination. *Acta Psychiatr Scand* Feb 1996;93(2):129-136.