**Supplementary Information**

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**Supplementary Table 1** Demographic and clinical characteristics of schizophrenia patients between principal dataset and replication dataset.

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| --- | --- | --- | --- |
| **Characteristic** | **Principal dataset**  **Patients (n = 60)** | **Replication dataset**  **Patients (n = 40)** | ***P*-values** |
| Age (y) | 24.7 ± 5.2 | 25.4 ± 6.3 | 0.772a |
| Gender (M/F) | 33/27 | 24/16 | 0.621b |
| Education level (y) | 12.0 ± 3.1 | 12.7 ± 3.4 | 0.264a |
| Illness duration (mon) | 17.0 ± 25.4 | 10.5 ± 13.7 | 0.392a |
| PANSS scores |  |  |  |
| Positive score | 21.7 ± 5.2 | 23.6 ± 8.5 | 0.329a |
| Negative score | 20.2 ± 7.6 | 22.9 ± 7.6 | 0.074a |
| General psychopa-  thology score | 43.5 ± 7.4 | 48.7 ± 8.9 | 0.002c |
| Total score | 85.4 ± 12.4 | 95.2 ± 18.5 | 0.005c |
| Brain age estimation | 29.3 ± 4.9 | 27.9 ± 6.4 | 0.001a |
| Brain-PAD | 4.6 ± 3.2 | 2.6 ± 3.5 | 0.004c |

Note: y, year; M/F, Male/Female; mon, month;

a Wilcoxon signed-rank test was performed due to the non-normal distribution of samples.

b Chi-square test.

c Independent-sample *t* test.

**Supplementary Table 2** Correlation between brain-PAD and socio-demography among datasets.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Brain PAD (principal dataset)** | | **Model I (adjusted)** | |
| **Characteristic** | **Patients**  **(n = 60)** | **Healthy controls**  **(n = 60)** | **Patients**  **(n = 60)** | **Healthy controls**  **(n = 60)** |
| Age | *r* = −0.406, *P* = 0.001a | *r* = −0.695, *P* < 0.001a | *r* = −0.392, *P* = 0.003 c | *r* = −0.542, *P* < 0.001 c |
| Gender | *r* = 0.212, *P* = 0.104a | *r* = −0.032, *P* = 0.806a | *r* = 0.263, *P* = 0.048 c | *r* = −0.032, *P* = 0.813 c |
| Education level | *r* = 0.238, *P* = 0.067a | *r* = −0.147, *P* = 0.261a | *r* = 0.197, *P* = 0.141 c | *r* = −0.176, *P* = 0.187 c |
| Illness duration | *r* = −0.047, *P* =0.720a | NA | *r* = 0.004, *P* =0.979 c | NA |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Brain PAD (replication dataset)** | | **Model I (adjusted)** | |
| **Characteristic** | **Patients**  **(n = 40)** | **Healthy controls**  **(n = 40)** | **Patients**  **(n = 40)** | **Healthy controls**  **(n = 40)** |
| Age | *r* = −0.245, *P* = 0.127b | *r* = −0.190, *P* =0.241a | *r* = −0.286, *P* = 0.086 c | *r* = −0.267, *P* =0.105 c |
| Gender | *r* = 0.345, *P* = 0.029a | *r* = −0.026, *P* = 0.873a | *r* = 0.254, *P* = 0.129 c | *r* = −0.100, *P* = 0.548 c |
| Education level | *r* = −0.340, *P* = 0.032a | *r* = −0.255, *P* = 0.112a | *r* = −0.364, *P* = 0.027 c | *r* = −0.295, *P* = 0.072 c |
| Illness duration | *r* = −0.367, *P* =0.020a | NA | *r* = −0.368, *P* =0.025 c | NA |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Brain PAD (pooled dataset)** | | **Model I (adjusted)** | |
| **Characteristic** | **Patients**  **(n = 100)** | **Healthy controls**  **(n = 100)** | **Patients**  **(n = 100)** | **Healthy controls**  **(n = 100)** |
| Age | *r* = −0.369, *P* < 0.001a | *r* = −0.478, *P* < 0.001a | *r* = −0.367, *P* < 0.001 c | *r* = −0.289, *P* =0.004 c |
| Gender | *r* = 0.263, *P* = 0.008a | *r* = −0.018, *P* = 0.861a | *r* = 0.298, *P* = 0.003 c | *r* = −0.076, *P* = 0.459 c |
| Education level | *r* = −0.036, *P* = 0.724a | *r* = −0.016, *P* = 0.876a | *r* = −0.074, *P* = 0.472 c | *r* = −0.186, *P* = 0.067 c |
| Illness duration | *r* = −0.131, *P* =0.194a | NA | *r* = −0.038, *P* =0.710 c | NA |

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Brain PAD** | | **The changes of Brain PAD** |
| **Characteristic** | **Patients after medication**  **(n = 21)** | **Healthy controls**  **(n = 21)** | **Patients**  **(n = 21)** |
| Age | *r* = −0.641, *P* = 0.004 c | *r* = −0.502, *P* = 0.028 c | *r* = 0.106, *P* = 0.676 c |
| Gender | *r* = 0.464, *P* = 0.052 c | *r* = 0.176, *P* = 0.470 c | *r* = −0.023, *P* = 0.929 c |
| Education level | *r* = 0.347, *P* = 0.158 c | *r* = −0.247, *P* = 0.308 a | *r* = 0.096, *P* = 0.705 c |
| Illness duration | *r* = 0.530, *P* =0.024 c | NA | *r* = −0.222, *P* =0.376 c |

Note: NA, not applicable.

a Spearman correlation was performed due to the non-normal distribution.

b Pearson correlation coefficient.

c Partial correlation.

Model I: adjusted the age, gender, education level, illness duration (patient group).

**Supplementary Table 3** Clinical characteristics of 21 patients with first-episode schizophrenia after medication compared with HCs.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **HCs**  **(n = 21)** |  | **Patients (after medication)**  **(n = 21)** | ***P* -values** |
| Age (y) | 26.14 ± 4.23 |  | 24.33 ± 6.62 | 0.300a |
| Gender (M/F) | 10/11 |  | 9/12 | 0.757b |
| Education level (y) | 17.43 ± 2.77 |  | 12.05 ± 3.14 | < 0.001a |
| Brain age estimation | 27.03 ± 3.74 |  | 27.05 ± 5.27 | 0.590c (0.893d) |
| Brain-PAD | 0.89 ± 1.87 |  | 2.72 ± 3.82 | 0.058a (0.047d) |

Note: y, year; M/F, Male/Female; HCs, healthy controls;

a Paired sample *t* test.

b Chi-square test.

c Wilcoxon signed-rank test was performed due to the non-normal distribution of samples.

d Analysis of Covariance (ANCOVA), adjusting for education level, age.

**Supplementary Table 4** Comparison of FA values (Features, i.e. 33 white matter tracts) in 21 subjects before and after treatment.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Age-sensitive tracts** | **Before**  **mean (SD)** | **After**  **mean (SD)** | **t Value** | ***P* Value** |
| 1 Middle cerebellar peduncle | 0.492 (0.015) | 0.470 (0.022) | 5.407 | <0.001a |
| 3 Genu of corpus callosum | 0.594 (0.017) | 0.585 (0.023) | 2.374 | 0.028 a |
| 4 Body of corpus callosum | 0.603 (0.027) | 0.562 (0.034) | 7.476 | <0.001 a |
| 5 Splenium of corpus callosum | 0.693 (0.019) | 0.643 (0.026) | 9.377 | <0.001 a |
| 6 Fornix (column and body of fornix) | 0.413 (0.016) | 0.474 (0.069) | -4.680 | <0.001 a |
| 11 Inferior cerebellar peduncle R | 0.520 (0.017) | 0.464 (0.031) | 8.184 | <0.001 a |
| 12 Inferior cerebellar peduncle L | 0.426 (0.013) | 0.459 (0.031) | -4.951 | <0.001 a |
| 13 Superior cerebellar peduncle R | 0.460 (0.017) | 0.529 (0.034) | -11.321 | <0.001 a |
| 14 Superior cerebellar peduncle L | 0.432 (0.017) | 0.515 (0.030) | -14.846 | <0.001 a |
| 15 Cerebral peduncle R | 0.571 (0.023) | 0.665 (0.038) | -11.354 | <0.001 a |
| 16 Cerebral peduncle L | 0.617 (0.023) | 0.660 (0.041) | -5.144 | <0.001 a |
| 19 Posterior limb of internal capsule R | 0.546 (0.027) | 0.676 (0.043) | -15.538 | <0.001 a |
| 20 Posterior limb of internal capsule L | 0.605 (0.028) | 0.665 (0.039) | -7.377 | <0.001 a |
| 23 Anterior corona radiata R | 0.399 (0.018) | 0.395 (0.020) | 1.471 | 0.157 |
| 24 Anterior corona radiata L | 0.405 (0.018) | 0.392 (0.019) | 4.743 | <0.001 a |
| 26 Superior corona radiata L | 0.482 (0.022) | 0.460 (0.027) | 3.779 | 0.001 a |
| 29 Posterior thalamic radiation (include optic radiation) R | 0.539 (0.027) | 0.525 (0.025) | 2.839 | 0.010 a |
| 30 Posterior thalamic radiation (include optic radiation) L | 0.537 (0.031) | 0.516 (0.029) | 4.412 | <0.001 a |
| 31 Sagittal stratum (include inferior longitidinal fasciculus and inferior fronto-occipital fasciculus) R | 0.534 (0.031) | 0.506 (0.033) | 4.806 | <0.001 a |
| 32 Sagittal stratum (include inferior longitidinal fasciculus and inferior fronto-occipital fasciculus) L | 0.523 (0.035) | 0.502 (0.034) | 3.302 | 0.004 a |
| 33 External capsule R | 0.379 (0.025) | 0.363 (0.022) | 3.231 | 0.004 a |
| 34 External capsule L | 0.399 (0.025) | 0.378 (0.026) | 3.938 | 0.001 a |
| 35 Cingulum (cingulate gyrus) R | 0.433 (0.033) | 0.406 (0.035) | 4.829 | <0.001 a |
| 38 Cingulum (hippocampus) L | 0.421 (0.033) | 0.363 (0.039) | 9.455 | <0.001 a |
| 39 Fornix (cres) / Stria terminalis (can not be resolved with current resolution) R | 0.529 (0.032) | 0.495 (0.044) | 4.085 | 0.001 a |
| 40 Fornix (cres) / Stria terminalis (can not be resolved with current resolution) L | 0.521 (0.033) | 0.511 (0.037) | 1.171 | 0.255 |
| 41 Superior longitudinal fasciculus R | 0.461 (0.028) | 0.429 (0.030) | 5.128 | <0.001 a |
| 42 Superior longitudinal fasciculus L | 0.451 (0.028) | 0.424 (0.025) | 4.844 | <0.001 a |
| 43 Superior fronto-occipital fasciculus (could be a part of anterior internal capsule) R | 0.455 (0.040) | 0.437 (0.040) | 2.190 | 0.041 a |
| 44 Superior fronto-occipital fasciculus (could be a part of anterior internal capsule) L | 0.483 (0.043) | 0.447 (0.042) | 5.689 | <0.001 a |
| 45 Inferior fronto-occipital fasciculus R | 0.499 (0.036) | 0.470 (0.031) | 6.685 | <0.001 a |
| 46 Inferior fronto-occipital fasciculus L | 0.447 (0.037) | 0.418 (0.033) | 6.326 | <0.001 a |
| 50 Tapetum L | 0.418 (0.028) | 0.401 (0.031) | 3.196 | 0.005 a |

Note: a Statistical significance after false discovery rate (FDR) correction for multiple comparisons (*P* < 0.05).

**Supplementary Table 5** Correlation between brain-PAD and PANSS scores and cognitive assessment in the patient groups at baseline and after treatment.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Brain PAD**  **(before treatment)** | |  | **Brain PAD**  **(after treatment)** | **The changes of**  **brain-PAD** |
| **Characteristic** | **Principal dataset**  **(n = 60)** | **Replication dataset**  **(n = 40)** |  | **Patients after treatment**  **(n = 21)** | **Patients after treatment**  **(n = 21)** |
| PANSS scores |  |  |  |  |  |
| Positive score | *r* = −0.326, *P* = 0.014 | *r* = −0.003, *P* = 0.986 |  | *r* = −0.375, *P* = 0.187 | *r* = 0.058, *P* = 0.845 |
| Negative score | *r* = 0.081, *P* = 0.552 | *r* = −0.220, *P* = 0.197 |  | *r* = −0.001, *P* = 0.997 | *r* = 0.246, *P* = 0.397 |
| General psychopa-  thology score | *r* = 0.201, *P* = 0.138 | *r* = −0.200, *P* = 0.241 |  | *r* = −0.307, *P* = 0.285 | *r* = 0.292, *P* = 0.311 |
| Total score | *r* = 0.121, *P* = 0.784 | *r* = −0.188, *P* = 0.272 |  | *r* = −0.202, *P* = 0.488 | *r* = 0.195, *P* = 0.504 |
| Cognitive measures |  |  |  |  |  |
| Digit symbol | *r* = −0.208, *P* = 0.125 | NA |  | *r* = 0.085, *P* = 0.773 | *r* = −0.335, *P* = 0.242 |
| Digit Span |  |  |  |  |  |
| Forward | *r* = 0.149, *P* = 0.274 | NA |  | *r* = −0.019, *P* = 0.948 | *r* = −0.154, *P* = 0.600 |
| Backward | *r* = 0.139, *P* = 0.306 | NA |  | *r* = −0.400, *P* = 0.157 | *r* = 0.003, *P* = 0.992 |
| Semantic verbal fluency | *r* = −0.195, *P* = 0.149 | NA |  | *r* = −0.632, *P* = 0.015 | *r* = 0.150, *P* = 0.610 |
| Scan interval, mon | NA | NA |  | *r* = −0.016, *P* = 0.957 | *r* = −0.105, *P* = 0.721 |
| Antipsychotic dose, mg/db | NA | NA |  | *r* = −0.339, *P* = 0.236 | *r* = 0.440, *P* = 0.115 |

Note: Correlation coefficients were analyzed by partial correlation, regarding age, gender, education level, and illness duration as control factors.