**Supplementary Information**

**Content:**

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

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

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

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

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

**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.