**Table S1**. Demographic and Clinical Characteristics of Participants.

|  |  |  |
| --- | --- | --- |
|  | HC (N = 130) | Depression (N = 195) |
| Male, No. (%) | 59 (45.38) | 95 (48.7) |
| Age, mean (SD) [range], y | 21.25 (5.33) [12-36] | 18.14 (4.47) [11-37] |
| Educational level, mean (SD), y | 13.56 (4.50) | 10.11 (2.13） |
| Duration of illness, mean (SD), m | - | 15.74 (16.96) |
| HAMD score, mean (SD), [range] | - | 22.38 (5.72) [12-48]a39.29 (11.68) [20-61]b |
| Handedness, right/left | 130/0 | 195/0 |
| Age of first onset, y | - | 16.81 (4.40) |

Abbreviations: HAMD, Hamilton rating scale for depression; a,17-items HAMD for 167 patients; b, 24-items HAMD for 28 patients.

**Table S2**. The clinical demographics of patients at different stages and matched HCs.

|  |  |  |  |
| --- | --- | --- | --- |
|  | Stage 1 | Stage 2 | Stage 3 |
|  | depression | HC | *p* | depression | HC | *p* | depression | HC | *p* |
| Age (years), mean ± SD | 17.170 ± 3.58 | 17.020 ± 2.762 | 0.999a | 18.146 ± 4.759 | 17.173 ± 2.821 | 0.148a | 18.617 ± 3.645 | 17.739 ± 2.975 | 0.164a |
| Gender, male : female | 44 : 44 | 36 : 40 | 0.958b | 25 : 30 | 36 : 39 | 0.995b | 23 : 24 | 32 : 33 | 0.971b |
| Duration of illness (months), mean ± SD | 4.046 ± 2.458 |  |  | 12.891 ± 2.015 |  |  | 39.064 ± 17.732 |  |  |
| Years of education, mean ± SD | 10.048 ± 2.200 | 10.553 ± 2.905 | 0.214a | 9.816 ± 2.058 | 10.413 ± 2.727 | 0.193a | 9.816 ± 2.058 | 10.413 ± 2.727 | 0.427a |
| Handedness, right/left | 88/0 | 76/0 |  | 55/0 | 75/0 |  | 47/0 | 65/0 |  |
| Age of first onset (years) | 16.796 ± 3.589 |  |  | 16.964 ± 4.710 |  |  | 15.468 ± 3.816 |  |  |

Note: a two-tailed two sample *t* test; b Chi-square *t*-test; HC, healthy control

**Table S3**. Overall GMV alterations in depression.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Clusters | Voxles | Including regions | Peak MNI (x,y,z) | T |
| 1 | 20260 | Thalamus | -9, -35, -3 | -7.004 |
|  |  | Parahippocampa gyrus |  |  |
|  |  | Lingual Gyrus |  |  |
|  |  | Hippocampus |  |  |
|  |  | Fusiform |  |  |
|  |  | Cerebrum |  |  |
| 2 | 1361 | Ventral medial prefrontal cortex | -15, 3, -18 | 4.327 |
|  |  | Amygdala |  |  |
| 3 | 824 | Precuneus | 23, -54, 72 | 3.877 |
|  |  | Postcentral gyrus |  |  |
|  |  | Superior parietal gyrus |  |  |
|  |  | Superior parietal lobule |  |  |

**Table S4**. Different GMV alterations at different stages in depression.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Stages | Clusters | Voxles | Including regions | Peak MNI (x,y,z) | T |
| Stage 1 | 1 | 1509 | Ventral medial prefrontal cortex | -2, 18, -12 | 3.824 |
|  |  | Bilateral olfactory |  |  |
|  |  | Bilateral Amygdala |  |  |
|  |  | Temporal pole |  |  |
| 2 | 3066 | Cerebellum posterior lobe | 26, -59, -39 | -4.743 |
| 3 | 1130 | Cerebellum | -21, -48, -42 | -4.313 |
| 4 | 4525 | Bilateral hippocampus | 21, -35, 9 | 4.680 |
|  |  | Bilateral thalamus |  |  |
|  |  | Parahippocampa gyrus |  |  |
|  |  | Right lingual |  |  |
| Stage 2 | 1 | 2061 | Right insula | 27, 6 , -12 | 4.329 |
|  |  | Right rolandic operculum |  |  |
|  |  | Right amygdala |  |  |
|  |  | Right putamen |  |  |
|  |  | Superior temporal gyrus |  |  |
| 2 | 1055 | Inferior frontal gyrus | -42, 44, -18 | 4.515 |
| 3 | 1032 | Bilateral Thalamus | 6, -3, 12 | -4.075 |
| 4 | 1367 | Right dorsolateral frontal gyrus | 24, 48, 29 | 3.719 |
|  |  | Right anterior cingulate |  |  |
|  |  | Superior frontal gyrus |  |  |
| 5 | 1126 | Right dorsolateral frontal gyrus | 32, 32, 33 | 3.908 |
| Stage 3 | 1 | 32437 | Cerebellum posterior lobe | -5, -63, -27 | -6.289 |
|  |  | Bilateral thalamus |  |  |
|  |  | Bilateral lingual |  |  |
|  |  | Right fusiform |  |  |
|  |  | Parahippocampa gyrus |  |  |
|  |  | Bilateral hippocampus |  |  |
| 2 | 954 | Right precuneus | 11,-72,34.5 | -3.835 |
|  |  | Right cuneus |  |  |
| 3 | 1522 | Precentral gyrus | -6,-27,74 | -4.445 |
|  |  | Medial frontal gyrus |  |  |

**Table S5**. Altered GMVs in patients with shorter illness duration (< 3/6 months).

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Illness duration | Clusters | Voxles | Including regions | Peak MNI (x,y,z) | T |
| < 3 months | 1 | 1292 | Ventral medial prefrontal cortex | -2, 18, -12 | 3.814 |
| 2 | 1572 | Bilateral hippocampus | 30, -35, 9 | -3.550 |
|  |  | Bilateral thalamus |  |  |
| < 6 months | 1 | 1247 | Ventral medial prefrontal cortex | -6, 11, 17 | 3.602 |
|  |  | Parahippocampa gyrus |  |  |
|  |  | Bilateral amygdala |  |  |
| 2 | 1195 | Cerebellum | -26, -50, -38 | -2.620 |
| 3 | 8244 | Cerebellum | 29, -72, -20 | -2.620 |
|  |  | Bilateral thalamus |  |  |
|  |  | Bilateral hippocampus |  |  |
|  |  | Parahippocampa gyrus |  |  |

**Table S6**. The causal effects of GMV alterations pattern in depression.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Seeds | Clusters | Voxles | Including regions | Peak MNI (x,y,z) | Z |
| vmPFC | 1 | 821 | Cerebellum posterior lobe | 41, -72, -29 | 7.568 |
| 2 | 1069 | Anterior Cingulate | -2, 18, -12 | -52.521 |
|  |  | Bilateral nucleus accumbens |  |  |
|  |  | Medial frontal gyrus |  |  |
| 3 |  | Left calcarine | -24, -63, 8 | -10.189 |
|  |  | Left precuneus |  |  |
|  |  | Posterior cingulate |  |  |
| 4 | 477 | Left rolandic operculum | -45, -20, 12 | -7.862 |
|  |  | Left insula |  |  |
| 5 | 623 | Left precuneus | -17, -68, 23 | 10.296 |
|  |  | Left cuneus |  |  |
|  |  | Left superior occipital gyrus |  |  |
| Left hippocampus | 1 | 878 | Right nucleus accumbens | 14, 14, 6 | 10.081 |
| 2 | 586 | Left Bilateral nucleus accumbens | -14, 11, 12 | 9.992 |
| 3 | 641 | Right calcarine | 14, -69, 11 | 8.651 |
|  |  | Bilateral precuneus |  |  |
| 4 | 226 | Right inferior frontal gyrus | 41, 24, 23 | -9.848 |
| 5 | 379 | Left inferior parietal lobule | -32, -57, 39 | -9.043 |
| 6 | 200 | Right precuneus | 5, -56, 56 | 7.636 |
| 7 | 427 | Left middle occipital gyrus | -41, -74, 20 | 8.437 |
|  |  | Middle temporal gyrus |  |  |
| Right hippocampus | 1 | 1848 | Cerebellum posterior lobe | 12, -57, -50 | 8.268 |
| 2 | 232 | Right nucleus accumbens | 12, 15, 3 | 7.699 |
| 3 | 231 | Superior medial frontal gyrus | 8, 51, 17 | 7.585 |
| 4 | 575 | Right precuneus | 12, -54, 14 | 9.995 |
|  |  | Right calcarine |  |  |
| 5 | 392 | Left cuneus | -15, -59, 18 | 10.913 |
|  |  | Left precuneus |  |  |
| 6 | 287 | Right dorsolateral frontal gyrus | 42, 35, 33 | 7.650 |
| 7 | 653 | Left dorsolateral frontal gyrus | -35, 20, 41 | 9.216 |
| 8 | 1170 | Right dorsolateral frontal gyrus | 41, 5, 41 | 10.552 |

**Table S7**. Coefficient-based GC values from bilateral hippocampus and the vmPFC to other brain regions drawn in Figure 5.

|  |  |
| --- | --- |
| Region | Seed |
| vmPFC | Hipp |
| MTG | -10.51 | - |
| IPL | - | -7.76 |
| IFG | - | -9.62 |
| MO | - | 10.20 |
| NAc | 9.32 | 10.08 |
| DLPFC | 7.99 | 7.70 |
| CB | 6.21 | 8.06 |
| Pre | -10.34 | 9.99 |
| ACC | 10.39 | 7.58 |
| RO | -6.42 | - |
| Cal | -6.64 | - |

Note: vmPFC, ventral medial prefrontal cortex; Cal, calcarine; RO, rolandic operculum; ACC, anterior cingulate cortex; Pre, precuneus; CB, Cerebelum; Hip, hippocampus; DLPFC, dorsolateral frontal gyrus; NAc, nucleus accumbens; MO, middle occipital gyrus; IFG, inferior frontal gyrus; IPL, inferior parietal lobule; MTG, middle temporal gyrus.

**Figure S1**. Correlation between GMV and clinical characteristics.



**Figure S2**. The comparative results of GMV alteration in patients with depression at stage 3. The results were not corrected multiple comparisons (voxel *p* < 0.05). As we saw, the GMV of medial fontal gyrus (temporally increased at stage 2) presented decreasing trend in patients with longer illness duration although the difference was not significant.

