**Supplementary method**

Figure 1. Flow chart of the subject inclusion

**Newly diagnosed BD**

**Newly control subjects**

**Newly diagnosed MDD**

**IQ test**

**Structural MRI measurements**

**Blood complement components measurements**

**Clinical parameters test**

**Biomarkers obtaining**

**Diagnosed BD patients**

**Healthy controls**

**Diagnosed MDD patients**

**Meet the inclusion criteria, and excluded due to the exclusion criteria**

….

**Data analysis**

1. **group comparison of brain structural data;**
2. **group comparison of plasma complement component levels;**
3. **correlation analysis between complement components and brain structural abnormalities.**

**BD**

**MDD**

**Year 2 222year year year**

**Year 3 33yearyearyear**

**Year 1 yearyearyearyearyear year**

**Longitudinal follow-up**

**SCID-IV/Patient edition for screening**

Abbreviations: BD: bipolar disorder; MDD: major depressive disorder; IQ: intelligence quotient.

**Details of the inclusion and exclusion criteria for BD, MDD, and HC**

**Bipolar disorder group**

**Inclusion criteria:**

1) Meet the diagnostic criteria of bipolar disorder in DSM-IV/5;

2) Demographic information standard: age: 18-55 years old, nationality: Han nationality, handedness: right handedness;

3) Treatment: subjects can take any mood stabilizer, antidepressant, anti-psychotic or sedative sleeping pills;

4) Voluntarily participate in this study and sign informed consent;

5) Intelligence level: Wechsler Intelligence ≥ 70 points, education level: primary school graduate, or educated years ≥ 6 years.

**Exclusion criteria:**

1) Have serious physical diseases and neurological system diseases;

2) Any other mental disorder diagnosed according to DSM-IV/5;

3) There are metal objects in the body (such as metal dentures, cardiac pacemakers, etc.) that affect the magnetic resonance examination;

4) Those who cannot complete the examination effectively, such as color blindness.

**Major depressive disorder group**

**Inclusion criteria:**

1) Meet the diagnostic criteria of DSM-IV/5 moderate and severe depression;

2) Demographic information standard: age: 18-55 years old, nationality: Han nationality, handedness: right handedness;

3) No treatment: did not take any mood stabilizer, antidepressant, antipsychotic or sedative sleeping pills or did not take any mood stabilizer, antidepressant, antipsychotic or sedative sleeping pills 3 months before enrollment;

4) Voluntarily participate in this study and sign informed consent;

5) Intelligence level: Wechsler Intelligence ≥ 70 points, education level: primary school graduate, or educated years ≥ 6 years.

**Exclusion criteria:**

1) Young mania rating scale score > 6;

2) Have serious physical diseases and nervous system diseases;

3) Comply with DSM-IV/5 and any other mental disorder diagnosis;

4) There are metal objects in the body (such as metal dentures, cardiac pacemakers, etc.) that affect the magnetic resonance examination;

5) Those who cannot complete the examination effectively, such as color blindness.

**Normal control group**

**Inclusion criteria:**

1) Demographic information standard: age: 18-55 years old, nationality: Han nationality, handedness: right handedness;

2) Intelligence level: Wechsler Intelligence ≥ 70 points, education level: primary school graduate or above or education age ≥ 6 years;

3) Good social function (normal work, school, non-sick leave), with complete behavior and responsibility ability;

4) Voluntarily participate in this study and sign informed consent.

**Exclusion criteria:**

1) Disease history: those diagnosed with DSM-IV/5 axis I and Axis II, and those with serious physical and brain organic diseases;

2) History of drug treatment: taking psychotropic drugs;

3) Family history: those who have a family history of mental illness within two lines and three generations;

4) There are metal objects in the body (such as metal dentures, cardiac pacemakers, etc.) that affect the magnetic resonance examination;

5) Those who cannot complete the assessment effectively, such as color blindness.

**Supplementary Method**

***Statistical analysis***

In order to further analyze the relationship between medication use and the complement levels detected in the sample, we split our BD group into antipsychotic-drug treated group VS not antipsychotic-drug treated group, mood stabilizer treated group VS not mood stabilizer treated group, and anti-depressant treated group VS not anti-depressant treated group. We also split our MDD group into anti-depressant treated group VS not anti-depressant treated group. We compared the difference of the complement components in the four pairs of groups.

**Supplementary Table 1**

1. **Correlation analysis of the illness duration, clinical symptoms and complement components, brain abnormal findings in bipolar patients**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Log10 C1q | Log10 C3 | Log10 C4 | Log10 Factor B | Log10 Factor H | Log10 Properdin | CT of L SFG | CT of L PreCG | V. of L MPFC | V. of R MPFC | V. of L MCC | V. of R MCC | V. of R. PreCG |
| Illness duration | 0.27 (0.056) | 0.17  (0.24) | 0.14  (0.34) | 0.19  (0.21) | 0.22  (0.11) | 0.22  (0.13) | 0.23 (0.12) | 0.06  (0.71) | -0.25 (0.10) | -0.24  (0.11) | -0.02 (0.91) | -0.14 (0.35) | -0.25  (0.09) |
| Manic episode | 0.25  (0.11) | 0.16  (0.33) | 0.16  (0.32) | 0.15  (0.34) | 0.19  (0.23) | 0.23  (0.15) | -0.23 (0.17) | -0.092 (0.58) | -0.002 (0.99) | -0.14  (0.41) | -0.004 (0.98) | -0.15 (0.38) | -0.27  (0.11) |
| Depressive episode | 0.18  (0.27) | -0.053 (0.74) | 0.017 (0.91) | 0.008  (0.96) | 0.037  (0.81) | 0.086  (0.59) | -0.11 (0.53) | 0.16  (0.35) | -0.13 (0.43) | -0.24  (0.15) | 0.083 (0.63) | -0.16 (0.36) | -0.31  (0.067) |
| YMRS | -0.26 (0.091) | -0.005 (0.98) | -0.023 (0.88) | -0.080 (0.62) | -0.042 (0.78) | -0.19  (0.21) | 0.023 (0.89) | 0.023  (0.89) | 0.024 (0.88) | -0.049 (0.76) | 0.037 (0.82) | 0.205 (0.20) | 0.18  (0.26) |
| HAMD | 0.17  (0.25) | 0.034 (0.81) | 0.017 (0.91) | 0.055  (0.72) | 0.042  (0.77) | 0.081  (0.58) | 0.063 (0.67) | 0.078  (0.60) | 0.099 (0.51) | -0.051 (0.74) | -0.028 (0.85) | -0.055 (0.71) | 0.026  (0.86) |

1. YMRS: Young mania rating scale, HAMD: Hamilton depression rating scale, CT: cortical thickness, SFG: superior frontal gyrus, V.: volume, PreCg: precentral gyrus, MPFC: medial prefrontal cortex, MCC: middle cingulate cortex. For correlation with brain structures, age, sex, body mass index and educational years were controlled. Total intracranial volume was additionally controlled for gray matter analysis.
2. \*p<0.05, \*\*p<0.01, \*\*\*p<0.001. Bold represents statistically significant results (p<0.05)
3. **Correlation analysis of the clinical parameters and complement components, brain abnormal findings in depressive patients**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Log10 C1q | Log10 C3 | Log10 C4 | Log10 Factor B | Log10 Factor H | Log10 properdin | CT of L SFG | CT of L PreCG | V. of L. MPFC | V. of R. MPFC | V. of L. MCC | V. of R. MCC | V. of R. PreCG |
| Illness duration | -0.18  (0.30) | -0.10  (0.54) | -0.074 (0.67) | -0.11  (0.55) | -0.12  (0.49) | -0.20  (0.24) | 0.088  (0.65) | 0.008  (0.97) | 0.24  (0.19) | 0.24  (0.19) | 0.11  (0.575) | 0.14  (0.45) | 0.18  (0.34) |
| Depressive episode | -0.31 (0.097) | -0.17  (0.36) | -0.13  (0.50) | -0.19  (0.32) | -0.25  (0.18) | -0.31  (0.10) | -0.23  (0.26) | -0.17  (0.41) | 0.13  (0.55) | 0.17  (0.41) | -0.089 (0.67) | -0.27  (0.20) | -0.11  (0.60) |
| HAMD | -0.29 (0.096) | -0.21  (0.23) | -0.19  (0.27) | -0.31 (0.072) | -0.28  (0.11) | -0.31 (0.066) | 0.049  (0.81) | -0.043 (0.83) | 0.28  (0.13) | 0.19  (0.32) | 0.040  (0.84) | 0.036 (0.85) | 0.13  (0.49) |

1. HAMD: Hamilton depression rating scale, CT: cortical thickness, SFG: superior frontal gyrus, V.: volume, PreCg: precentral gyrus, MPFC: medial prefrontal cortex, MCC: middle cingulate cortex. For partial correlation with brain structures, age, sex, body mass index and educational years were controlled. TIV was additionally controlled for gray matter analysis.
2. \*p<0.05, \*\*p<0.01, \*\*\*p<0.001. Bold represents statistically significant results (p<0.05).

**Supplementary Table 2. Partial correlation analysis between the extracted GMV and CT values and complement components.**

| **Brain area** | **Log10 C1q** | | **Log10 C3** | | **Log10 C4** | | **Log10 Factor B** | | **Log10 Factor H** | | **Log10 prperdin** | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| ***r*** | ***p*** | ***r*** | ***p*** | ***r*** | ***p*** | ***r*** | ***p*** | ***r*** | ***p*** | ***r*** | ***p*** |
| **Healthy controls** | | | | | | | | | | | | |
| **CT of L SFG** | 0.289 | **0.046\*** | 0.392 | **0.006\*\*** | 0.245 | 0.094 | 0.200 | 0.173 | 0.242 | 0.097 | 0.264 | 0.069 |
| **CT of L PreCG** | 0.23 | 0.115 | 0.317 | **0.028\*** | 0.113 | 0.446 | 0.198 | 0.176 | 0.153 | 0.298 | 0.207 | 0.158 |
| **V. L mPFC** | -0.12 | 0.44 | -0.03 | 0.823 | -0.03 | 0.839 | -0.02 | 0.917 | -0.08 | 0.61 | -0.16 | 0.292 |
| **V. R mPFC** | -0.05 | 0.758 | 0.025 | 0.865 | -0.04 | 0.780 | 0.037 | 0.805 | -0.04 | 0.791 | -0.047 | 0.752 |
| **V. L MCC** | 0.091 | 0.543 | 0.174 | 0.243 | 0.111 | 0.459 | 0.148 | 0.321 | 0.211 | 0.154 | 0.133 | 0.374 |
| **V. R MCC** | -0.05 | 0.737 | 0.212 | 0.153 | 0.003 | 0.982 | 0.063 | 0.673 | 0.067 | 0.655 | --0.009 | 0.950 |
| **V. R PreCG** | -0.29 | **0.048\*** | -0.03 | 0.843 | -0.19 | 0.197 | -0.26 | 0.082 | -0.21 | 0.157 | -0.252 | 0.088 |
| **Patients with BD** | | | | | | | | | | | | |
| **CT of LSFG** | -0.04 | 0.843 | -0.01 | 0.965 | 0.037 | 0.804 | 0.04 | 0.79 | 0.03 | 0.85 | -0.01 | 0.97 |
| **CT of L PreCG** | -0.36 | **0.015\*** | -0.34 | **0.030\*** | -0.33 | **0.026\*** | -0.31 | **0.048\*** | -0.33 | **0.024\*** | -0.29 | 0.05 |
| **V. L mPFC** | -0.238 | 0.115 | -0.267 | 0.073 | -0.264 | 0.076 | -0.192 | 0.229 | -0.264 | 0.076 | -0.264 | 0.083 |
| **V. R mPFC** | -0.268 | 0.075 | -0.265 | 0.075 | -0.235 | 0.115 | -0.182 | 0.254 | -0.266 | 0.074 | -0.213 | 0.166 |
| **V. L MCC** | 0.073 | 0.64 | -0.007 | 0.96 | 0.046 | 0.76 | 0.004 | 0.98 | 0.030 | 0.85 | 0.092 | 0.55 |
| **V. R MCC** | -0.10 | 0.51 | -0.057 | 0.71 | -0.077 | 0.61 | -0.083 | 0.60 | -0.084 | 0.58 | -0.11 | 0.48 |
| **R PreCG** | -0.086 | 0.58 | -0.008 | 0.96 | 0.013 | 0.93 | 0.092 | 0.57 | 0.016 | 0.92 | -0.11 | 0.49 |
| **Patients with MDD** | | | | | | | | | | | | |
| **CT of L SFG** | -0.082 | 0.66 | -0.096 | 0.61 | -0.037 | 0.84 | -0.096 | 0.61 | -0.100 | 0.59 | -0.11 | 0.57 |
| **CT of L PreCG** | -0.254 | 0.17 | -0.45 | **0.010\*** | -0.36 | **0.049\*** | -0.33 | 0.071 | -0.31 | 0.094 | -0.26 | 0.158 |
| **V. L mPFC** | -0.11 | 0.55 | 0.11 | 0.58 | 0.18 | 0.34 | 0.036 | 0.85 | 0.040 | 0.83 | -0.077 | 0.69 |
| **V. R mPFC** | -0.12 | 0.53 | 0.13 | 0.49 | 0.13 | 0.50 | 0.003 | 0.99 | -0.062 | 0.75 | -0.090 | 0.64 |
| **V. L MCC** | 0.14 | 0.47 | 0.12 | 0.54 | 0.015 | 0.94 | -0.003 | 0.99 | -0.005 | 0.98 | 0.16 | 0.39 |
| **V. R MCC** | 0.15 | 0.44 | 0.24 | 0.21 | 0.27 | 0.15 | 0.16 | 0.39 | 0.17 | 0.36 | 0.17 | 0.38 |
| **V. R PreCG** | 0.17 | 0.37 | 0.24 | 0.21 | 0.29 | 0.13 | 0.28 | 0.14 | 0.21 | 0.26 | 0.15 | 0.43 |
| **All subjects** | | | | | | | | | | | | |
| **CT of L SFG** | -0.002 | 0.99 | 0.025 | 0.78 | -0.065 | 0.45 | -0.057 | 0.52 | -0.073 | 0.40 | -0.095 | 0.28 |
| **CT of L PreCG** | -0.26 | **0.003\*\*** | -0.16 | 0.063 | -0.27 | **0.002\*\*** | -0.23 | **0.009\*\*** | -0.26 | **0.003\*\*** | -0.24 | **0.006\*\*** |
| **V. L mPFC** | -0.331 | **0.000\*\*\*** | -0.22 | **0.010\*** | -0.29 | **0.001\*\*** | -0.27 | **0.002\*\*** | -0.31 | **0.000\*\*\*** | -0.35 | **0.000\*\*\*** |
| **V. R mPFC** | -0.30 | **0.001\*\*** | -0.18 | **0.035\*** | -0.25 | **0.004\*\*** | -0.22 | **0.014\*** | -0.29 | **0.001\*\*** | -0.27 | **0.002\*\*** |
| **V. L MCC** | -0.074 | 0.40 | -0.015 | 0.86 | -0.097 | 0.27 | -0.11 | 0.21 | -0.085 | 0.33 | -0.058 | 0.51 |
| **V. R MCC** | -0.022 | 0.80 | 0.086 | 0.33 | 0.004 | 0.97 | 0.005 | 0.96 | -0.006 | 0.95 | -0.026 | 0.77 |
| **V. R PreCG** | -0.19 | **0.031\*** | -0.025 | 0.78 | -0.13 | 0.13 | -0.056 | 0.53 | -0.12 | 0.17 | -0.20 | **0.020\*** |

1. BD: bipolar disorder; MDD: major depressive disorder; TMT-A: Trail Making Test Parts A; TMT-B: Trail Making Test Parts B; DSST: digit symbol substitution test; C1q: Complement component 1q; C3: Complement component 3 ; C4: Complement component 4; Factor B: Complement factor B; Factor H: Complement factor B; CT: cortical thickness, L:left, R: right, SFG: superior frontal gyrus, V.: volume, PreCg: precentral gyrus, MPFC: medial prefrontal cortex, MCC: middle cingulate cortex.SFG: superior frontal gyrus; MFG: middle frontal gyrus; PreCG: precentral gyrus.
2. \*p < 0.05, \*\*p < 0.01, \*\*\*p < 0.001. Age, sex, body mass index and educational years were controlled. Total intracranial volume was additionally controlled for gray matter analysis.

**Supplementary Table 3. Group differences of plasma complement components compared between different drug treatment groups.**

**(a) Group comparison of complement factors between mood stabilizer treated group and none mood stabilizer treated group in BD patients**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **None mood stabilizers treated group**  **Mean (SD)** | **Mood stabilizer treated group**  **Mean (SD)** | **T / x²** | **df** | **p** |
| Age (age) | 28.27 (11.36) | 29.40 (11.69) | -0.35 | 50 | 0.73 |
| Gender | 7 males / 15 females | 14 males / 16 females | 1.16 | 1 | 0.28 |
| Education (year) | 12.66 (3.55) | 13.48 (2.99) | -0.89 | 50 | 0.38 |
| BMI | 23.48 (3.87) | 22.82 (3.77) | 0.61 | 50 | 0.54 |
| Illness duration (month) | 59.86 (53.29) | 68.07 (63.71) | -0.49 | 50 | 0.63 |
| Manic/hypomanic episode | 1.73(0.96) | 2.11 (1.89) | -0.72 | 40 | 0.47 |
| Depressive episode | 2.53 (1.85) | 2.07 (1.21) | 0.98 | 40 | 0.34 |
| Log10 C1q | 2.74 (0.41) | 2.76 (0.44) | -0.23 | 48 | 0.82 |
| Log10 C3 | 2.17 (0.32) | 2.28 (0.37) | -1.14 | 49 | 0.26 |
| Loa10 C4 | 2.97 (0.17) | 3.00 (0.19) | -0.64 | 49 | 0.53 |
| Log10 factor B | 2.93 (0.28) | 2.99 (0.33) | -0.63 | 44 | 0.54 |
| Log10 factor H | 3.08 (0.30) | 3.14 (0.35) | -0.63 | 49 | 0.54 |
| Log10 properdin | 2.09 (0.33) | 2.11 (0.33) | -0.24 | 47 | 0.81 |

**(b) Group comparison of complement factors between antipsychotics treated group and none antipsychotics treated group in BD patients**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **None antipsychotic treated group**  **Mean (SD)** | **Antipsychotics treated group**  **Mean (SD)** | **T / x²** | **df** | **p** |
| Age (year) | 27.10 (12.26) | 30.16 (10.90) | -0.95 | 50 | 0.35 |
| Gender | 7 males /14 females | 14 males / 17 females | 0.73 | 1 | 0.39 |
| Education (year) | 12.07 (3.42) | 13.84 (2.95) | -2.00 | 50 | 0.052 |
| BMI | 23.41 (4.24) | 22.89 (3.50) | 0.49 | 50 | 0.63 |
| Illness duration (month) | 78.19 (66.10) | 55.39 (53.01) | 1.38 | 50 | 0.18 |
| Manic/hypomanic episode | 1.64 (0.75) | 2.14 (1.90) | -0.94 | 40 | 0.35 |
| Depressive episode | 2.67 (1.84) | 2.00 (1.84) | 1.43 | 40 | 0.16 |
| Log10 C1q | 2.80 (0.43) | 2.72 (0.43) | 0.65 | 48 | 0.52 |
| Log10 C3 | 2.23 (0.33) | 2.25 (0.37) | -0.11 | 49 | 0.91 |
| Loa10 C4 | 3.00 (0.17) | 2.98 (0.19) | 0.30 | 49 | 0.77 |
| Log10 factor B | 2.96 (0.27) | 2.97 (0.34) | -0.064 | 44 | 0.95 |
| Log10 factor H | 3.14 (0.32) | 2.06 (0.31) | 0.31 | 49 | 0.76 |
| Log10 properdin | 2.16 (0.34) | 2.06 (0.31) | 1.14 | 47 | 0.26 |

**(c) Group comparison of complement factors between antidepressants treated group and none antidepressants treated group in BD patients**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **None antidepressant treated group**  **Mean (SD)** | **Antidepressant treated group**  **Mean (SD)** | **T / x²** | **df** | **p** |
| Age (yeay) | 25.57 (9.52) | 32.83 (12.44) | -2.38 | 50 | **0.021\*** |
| Gender | 9 males / 19 females | 12 males /12 females | 1.71 | 1 | 0.19 |
| Education (year) | 12.98 (3.13) | 13.29 (3.41) | -1.11 | 40 | 0.27 |
| BMI | 23.07 (4.22) | 23.14 (3.30) | -0.065 | 50 | 0.95 |
| Illness duration (month) | 47.21 (35.06) | 84.88 (74.21) | -2.39 | 50 | **0.020\*** |
| Manic/hypomanic episode | 2.23 (2.14) | 1.70 (0.66) | 1.06 | 40 | 0.30 |
| Depressive episode | 2.00 (1.35) | 2.50 (1.57) | -1.11 | 40 | 0.27 |
| Log10 C1q | 2.76 (0.43) | 2.74 (0.43) | 0.20 | 48 | 0.84 |
| Log10 C3 | 2.24 (0.33) | 2.23 (0.39) | 0.055 | 49 | 0.96 |
| Loa10 C4 | 2.99 (0.20) | 2.98 (0.16) | 0.12 | 49 | 0.91 |
| Log10 factor B | 2.98 (0.32) | 2.94 (0.300 | 0.51 | 44 | 0.61 |
| Log10 factor H | 2.12 (0.33) | 2.09 (0.33) | -0.028 | 49 | 0.98 |
| Log10 properdin | 2.11 (0.33) | 2.09 (0.33) | 0.31 | 47 | 0.76 |

**(d) Group comparison of complement factors between antidepressants treated group and none antidepressants treated group in MDD patients**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **None antidepressant treated group**  **Mean (SD)** | **Antidepressant treated group**  **Mean (SD)** | **T / x²** | **df** | **p** |
| Age (year) | 27.65 (9.22) | 32.72 (10.82) | -1.49 | 33 | 0.15 |
| Gender | 8 males / 9 females | 7 males / 11 females | 0.24 | 1 | 0.63 |
| Education (year) | 12.53 (3.89) | 12.44 (4.89) | 0.060 | 33 | 0.95 |
| BMI | 21.42 (3.15) | 20.80 (2.80) | 0.61 | 33 | 0.55 |
| Illness duration (month) | 47.06 (66.99) | 31.78 (41.23) | 0.82 | 33 | 0.42 |
| Depressive episode | 1.93 (1.33) | 1.63 (0.81) | 0.77 | 28 | 0.45 |
| Log10 C1q | 2.61 (0.32) | 2.57 (0.26) | 0.35 | 33 | 0.73 |
| Log10 C3 | 2.02 (0.25) | 1.98 (0.23) | 0.54 | 33 | 0.60 |
| Loa10 C4 | 2.90(0.12) | 2.89 (0.11) | 0.18 | 33 | 0.86 |
| Log10 factor B | 2.89 (0.26) | 2.84 (0.24) | 0.53 | 33 | 0.60 |
| Log10 factor H | 2.98 (0.20) | 2.94 (0.17) | 0.53 | 33 | 0.60 |
| Log10 properdin | 2.05 (0.24) | 1.99 (0.20) | 0.78 | 33 | 0.44 |

1. BD: bipolar disorder; MDD: major depressive disorder; C1q: Complement component 1q; C3: Complement component 3 ; C4: Complement component 4; Factor B: Complement factor B; Factor H: Complement factor B.
2. \*p < 0.05, \*\*p < 0.01, \*\*\*p < 0.001.