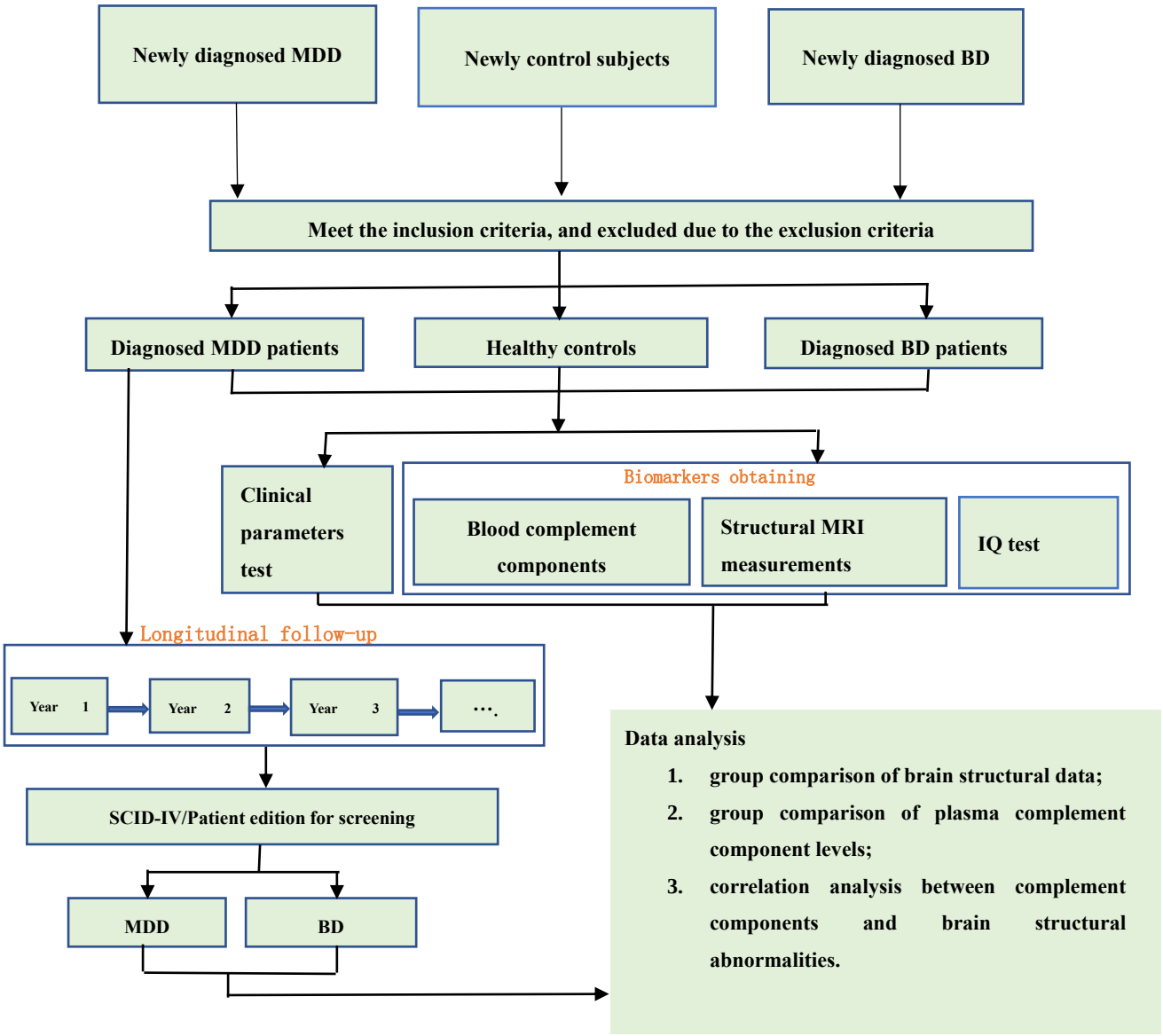
Supplementary method

Figure 1. Flow chart of the subject inclusion



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

(a) Correlation analysis of the illness duration, clinical symptoms and complement components, brain abnormal findings in bipolar patients

	Log_{10} C1q	Log_{10} C3	Log_{10} C4	Log_{10} Factor B	Log_{10} Factor H	Log_{10} 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	0.17	0.14	0.19	0.22	0.22	0.23	0.06	-0.25	-0.24	-0.02	-0.14	-0.25
	(0.056)	(0.24)	(0.34)	(0.21)	(0.11)	(0.13)	(0.12)	(0.71)	(0.10)	(0.11)	(0.91)	(0.35)	(0.09)
Manic episode	0.25	0.16	0.16	0.15	0.19	0.23	-0.23	-0.092	-0.002	-0.14	-0.004	-0.15	-0.27
	(0.11)	(0.33)	(0.32)	(0.34)	(0.23)	(0.15)	(0.17)	(0.58)	(0.99)	(0.41)	(0.98)	(0.38)	(0.11)
Depressive	0.18	-0.053	0.017	0.008	0.037	0.086	-0.11	0.16	-0.13	-0.24	0.083	-0.16	-0.31
episode	(0.27)	(0.74)	(0.91)	(0.96)	(0.81)	(0.59)	(0.53)	(0.35)	(0.43)	(0.15)	(0.63)	(0.36)	(0.067)
YMRS	-0.26	-0.005	-0.023	-0.080	-0.042	-0.19	0.023	0.023	0.024	-0.049	0.037	0.205	0.18
	(0.091)	(0.98)	(0.88)	(0.62)	(0.78)	(0.21)	(0.89)	(0.89)	(0.88)	(0.76)	(0.82)	(0.20)	(0.26)
HAMD	0.17	0.034	0.017	0.055	0.042	0.081	0.063	0.078	0.099	-0.051	-0.028	-0.055	0.026
	(0.25)	(0.81)	(0.91)	(0.72)	(0.77)	(0.58)	(0.67)	(0.60)	(0.51)	(0.74)	(0.85)	(0.71)	(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)

(b) Correlation analysis of the clinical parameters and complement components, brain abnormal findings in depressive patients

	Log_{10} C1q	Log_{10} C3	Log_{10} C4	Log_{10} Factor B	Log_{10} Factor H	Log_{10} 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	-0.18	-0.10	-0.074	-0.11	-0.12	-0.20	0.088	0.008	0.24	0.24	0.11	0.14	0.18
duration	(0.30)	(0.54)	(0.67)	(0.55)	(0.49)	(0.24)	(0.65)	(0.97)	(0.19)	(0.19)	(0.575)	(0.45)	(0.34)
Depressive	-0.31	-0.17	-0.13	-0.19	-0.25	-0.31	-0.23	-0.17	0.13	0.17	-0.089	-0.27	-0.11
episode	(0.097)	(0.36)	(0.50)	(0.32)	(0.18)	(0.10)	(0.26)	(0.41)	(0.55)	(0.41)	(0.67)	(0.20)	(0.60)
HAMD	-0.29	-0.21	-0.19	-0.31	-0.28	-0.31	0.049	-0.043	0.28	0.19	0.040	0.036	0.13
	(0.096)	(0.23)	(0.27)	(0.072)	(0.11)	(0.066)	(0.81)	(0.83)	(0.13)	(0.32)	(0.84)	(0.85)	(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	Log_{10} C1q		Log_{10} C3		Log_{10} C4		Log_{10} Factor B		Log_{10} Factor H		Log_{10} 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

Brain area	Log_{10} C1q		Log_{10} C3		Log_{10} C4		Log_{10} Factor B		Log_{10} Factor H		Log_{10} prperdin	
	r	***p***	***r***	***p***	***r***	***p***	***r***	***p***	***r***	***p***	***r***	***p***
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****

Brain area	Log_{10} C1q		Log_{10} C3		Log_{10} C4		Log_{10} Factor B		Log_{10} Factor H		Log_{10} prperdin	
	r	***p***	***r***	***p***	***r***	***p***	***r***	***p***	***r***	***p***	***r***	***p***
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 / x^2	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
Log_{10} C1q	2.74 (0.41)	2.76 (0.44)	-0.23	48	0.82
Log_{10} C3	2.17 (0.32)	2.28 (0.37)	-1.14	49	0.26
Loa_{10} C4	2.97 (0.17)	3.00 (0.19)	-0.64	49	0.53

Log_{10} factor B	2.93 (0.28)	2.99 (0.33)	-0.63	44	0.54
Log_{10} factor H	3.08 (0.30)	3.14 (0.35)	-0.63	49	0.54
Log_{10} 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 / x^2	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
Log_{10} C1q	2.80 (0.43)	2.72 (0.43)	0.65	48	0.52
Log_{10} C3	2.23 (0.33)	2.25 (0.37)	-0.11	49	0.91
Loa_{10} C4	3.00 (0.17)	2.98 (0.19)	0.30	49	0.77
Log_{10} factor B	2.96 (0.27)	2.97 (0.34)	-0.064	44	0.95
Log_{10} factor H	3.14 (0.32)	2.06 (0.31)	0.31	49	0.76

Log_{10} 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 / x^2	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
Log_{10} C1q	2.76 (0.43)	2.74 (0.43)	0.20	48	0.84
Log_{10} C3	2.24 (0.33)	2.23 (0.39)	0.055	49	0.96
Loa_{10} C4	2.99 (0.20)	2.98 (0.16)	0.12	49	0.91
Log_{10} factor B	2.98 (0.32)	2.94 (0.300	0.51	44	0.61
Log_{10} factor H	2.12 (0.33)	2.09 (0.33)	-0.028	49	0.98

Log_{10} 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 / x^2	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
Log_{10} C1q	2.61 (0.32)	2.57 (0.26)	0.35	33	0.73
Log_{10} C3	2.02 (0.25)	1.98 (0.23)	0.54	33	0.60
Loa_{10} C4	2.90(0.12)	2.89 (0.11)	0.18	33	0.86
Log_{10} factor B	2.89 (0.26)	2.84 (0.24)	0.53	33	0.60
Log_{10} factor H	2.98 (0.20)	2.94 (0.17)	0.53	33	0.60
Log_{10} 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.