**Supplementary Methods**

***Finger-Tapping Test (FTT)***

The FTT consists of tapping with the index finger on a computer mouse as many times as possible within 10 s. The test was repeated three consecutive times and performed randomly across subjects, and the order was kept constant in each subject at each session. The average number of taps was then calculated.1

***Continuous Performance Test (CPT)***

The CPT is a psychological test for humans that primarily measures attention.2, 3 The critical stimulus may be defined either as a particular single stimulus out of the available set (X task: subjects were asked to respond to number "9") or a particular sequence of two stimuli out of the available set (AX task: subjects were asked to respond whenever the number "9" was preceded by the number "1"). Only the AX task was used in the present study. Each test session began with 2 minutes of practice (repeated if the subjects required it) to ensure that they knew how to press the button correctly. During the test, numbers from 0 to 9 were randomly presented for 50 msec each, at a rate of one per second. Each subject undertook two sessions, including the non-masked task and the 25% masked task. During the masked session, a pattern of snow was used to toggle background and foreground so that the image was visually distorted. The masked CPT is more sensitive for the detection of cognitive deficits. Subject responses were recorded automatically on a diskette using the CPT machine (Sunrise Systems, version 2.20, Pembroke, MA, USA).4

**Supplementary Table 1.** Neuropsychological functional tests of the euthymic BD patients and the control subjects.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | BD  *n* = 62 | | Control  *n* = 62 | | Statistics | | |
|  | Mean | ± SD | Mean | ± SD | t | *p* value | *p*, controlling educational year |
| FTT\_dominant hand | 42.55 | ±9.17 | 48.13 | ±8.18 | -3.57 | 0.001 | 0.011 |
| FTT\_nondominant hand | 40.87 | ±8.96 | 44.51 | ±7.95 | -2.39 | 0.018 | 0.135 |
| CPT unmask d' | 4.06 | ±0.92 | 4.63 | ±0.36 | -4.59 | <0.001 | 0.001 |
| CPT mask d' | 3.43 | ±1.14 | 3.99 | ±0.98 | -2.71 | 0.008 | 0.137 |

Abbreviations: BD: bipolar disorder; FTT: finger-tapping test; CPT: continuous performance test.

**Supplementary Table 2.** Performance of the euthymic BD patients and the control subjects in the neuropsychological functional tests, subgrouped by HOMA-IR.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | BD  *N* = 62 | | Control  *N* = 62 | | *p* value | | |
|
| Non-IR  *n* = 29 | IR  *n* = 33 | Non-IR  *n* = 34 | IR  *n* = 28 | Group effect | IR effect | Group\*IR effect |
| FTT |  |  |  |  |  |  |  |
| Dominant hand | 39.26±10.87 | 45.44±6.22 | 49.48±7.66 | 46.49±8.63 | 0.006\* | 0.214 | 0.005\* |
| Nondominant hand | 37.92±10.35 | 43.47±6.66 | 45.83±7.15 | 42.91±8.68 | 0.101 | 0.280 | 0.008\* |
| CPT |  |  |  |  |  |  |  |
| Unmask d' | 3.84±1.07 | 4.25±0.72 | 4.61±0.36 | 4.66±0.36 | <0.001\* | 0.023\* | 0.201 |
| Mask d' | 3.16±1.23 | 3.70±1.00 | 4.06±0.89 | 3.89±1.11 | 0.138 | 0.263 | 0.102 |

Abbreviations: BD: bipolar disorder; HOMA-IR: homeostasis model assessment of insulin resistance; IR: insulin resistance (HOMA-IR ≥ 2.6); FTT: finger-tapping test; CPT: continuous performance test.

\**p* < 0.05

**Supplementary Table 3.** Performance of the euthymic BD patients and the control subjects in the neuropsychological functional tests, subgrouped by HOMA-IR ≥ 1.8

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | BD  *N* = 62 | | Control  *N* = 62 | | *p* value | | |
|
| Non-IR  *n* = 14 | IR  *n* = 48 | Non-IR  *n* = 14 | IR  *n* = 48 | Group effect | IR effect | Group\*IR effect |
| WCST |  |  |  |  |  |  |  |
| Preservative errors | 9.79±7.80 | 13.04±10.26 | 8.57±5.77 | 8.31±5.79 | 0.270 | 0.659 | 0.257 |
| Completed categories | 2.86±1.92 | 2.69±1.60 | 3.79±1.12 | 3.46±1.50 | 0.101 | 0.978 | 0.803 |
| FTT |  |  |  |  |  |  |  |
| Dominant hand | 41.06±9.37 | 42.99±9.17 | 51.29±7.12 | 47.21±8.31 | 0.002\* | 0.963 | 0.085 |
| Nondominant hand | 39.03±9.01 | 41.41±8.97 | 47.59±6.06 | 43.62±8.26 | 0.027\* | 0.890 | 0.071 |
| CPT |  |  |  |  |  |  |  |
| Unmask d' | 4.07±0.99 | 4.05±0.90 | 4.62±0.28 | 4.64±0.38 | 0.004\* | 0.340 | 0.957 |
| Mask d' | 3.17±1.51 | 3.52±0.99 | 3.94±0.94 | 4.00±1.01 | 0.109 | 0.095 | 0.426 |

Abbreviations: BD: bipolar disorder; HOMA-IR: homeostasis model assessment of insulin resistance; IR: insulin resistance (HOMA-IR ≥ 1.8); WCST: Wisconsin card-sorting test; FTT: finger-tapping test; CPT: continuous performance test.

\**p* < 0.05

**Supplementary Table 4.** Demographic characteristics of the euthymic BD patients among different medications.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Valproic acid | | | Valproic acid + antipsychotics | | | Lithium + antipsychotics | | | Antipsychotics | | | Statistics | | |
| N | Mean | ±SD | N | Mean | ±SD | N | Mean | ±SD | N | Mean | ±SD | F/χ2 | *p* | *p*, controlling age |
| Gender, male, n (%) |  | 9.00 | (0.43) |  | 8.00 | (0.42) |  | 4.00 | (0.33) |  | 3.00 | (0.30) | 0.71 | 0.871 |  |
| Age (years) | 21 | 36.48 | ±13.03 | 19 | 33.53 | ±11.86 | 12 | 43.58 | ±14.93 | 10 | 29.80 | ±4.94 | 2.69 | 0.055 |  |
| Educational year | 20 | 15.05 | ±2.26 | 18 | 14.72 | ±2.16 | 12 | 14.50 | ±2.11 | 9 | 15.67 | ±1.80 | 0.60 | 0.621 | 0.790 |
| HDRS | 21 | 1.43 | ±1.63 | 19 | 1.89 | ±2.26 | 12 | 1.92 | ±2.43 | 10 | 1.00 | ±2.21 | 0.54 | 0.658 | 0.746 |
| YMRS | 21 | 0.48 | ±1.08 | 19 | 0.95 | ±1.31 | 12 | 0.67 | ±1.15 | 10 | 0.40 | ±0.97 | 0.74 | 0.535 | 0.507 |
| Body mass index (kg/m2) | 21 | 29.02 | ±5.87 | 19 | 24.66 | ±3.81 | 12 | 24.66 | ±3.71 | 10 | 26.34 | ±4.32 | 3.63 | 0.018 | 0.019 |
| Insulin (uIU/ml) | 21 | 19.94 | ±16.41 | 19 | 12.55 | ±6.70 | 12 | 10.90 | ±7.09 | 10 | 21.36 | ±11.18 | 2.82 | 0.047 | 0.039 |
| Glucose (mg/dl) | 21 | 93.19 | ±16.03 | 19 | 88.21 | ±9.72 | 12 | 102.50 | ±38.28 | 10 | 93.50 | ±15.18 | 1.16 | 0.332 | 0.637 |
| HOMA-IR | 21 | 4.87 | ±4.65 | 19 | 2.72 | ±1.38 | 12 | 2.91 | ±2.41 | 10 | 5.22 | ±3.85 | 2.20 | 0.098 | 0.066 |
| HOMA-IR ≥2.6, n (%)) |  | 10.00 | (0.48) |  | 8.00 | (0.42) |  | 6.00 | (0.50) |  | 9.00 | (0.90) | 6.69 | 0.082 |  |
| WCST\_ preservative errors | 21 | 11.76 | ±7.46 | 19 | 11.95 | ±11.38 | 12 | 14.33 | ±9.46 | 10 | 11.70 | ±12.30 | 0.21 | 0.892 | 0.982 |
| WCST\_ completed categories | 21 | 2.76 | ±1.84 | 19 | 2.79 | ±1.55 | 12 | 2.08 | ±1.73 | 10 | 3.30 | ±1.34 | 1.01 | 0.395 | 0.843 |
| FTT\_dominant hand | 21 | 41.15 | ±11.89 | 19 | 41.13 | ±8.56 | 12 | 44.18 | ±6.79 | 10 | 46.24 | ±5.09 | 0.98 | 0.409 | 0.404 |
| FTT\_nondominant hand | 21 | 38.83 | ±11.31 | 19 | 39.54 | ±7.91 | 12 | 41.50 | ±7.06 | 10 | 46.96 | ±4.29 | 2.18 | 0.100 | 0.124 |
| CPT unmask d' | 21 | 3.84 | ±1.07 | 19 | 4.15 | ±0.92 | 12 | 4.05 | ±0.70 | 10 | 4.36 | ±0.79 | 0.83 | 0.484 | 0.590 |
| CPT mask d' | 17 | 3.46 | ±1.21 | 14 | 3.70 | ±0.90 | 11 | 2.62 | ±1.13 | 9 | 3.96 | ±0.95 | 3.14 | 0.034 | 0.256 |

Abbreviations: BD: bipolar disorder; HDRS: Hamilton Depression Rating Scale; YMRS: Young Mania Rating Scale; HOMA-IR: homeostasis model assessment of insulin resistance; WCST: Wisconsin card-sorting test.

**Supplementary Table 5.** Demographic characteristics of the euthymic BD patients and the control subjects, subgrouped by HOMA-IR.

(a) BD

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Non-IR  *n* = 29 | | IR  *n* = 33 | | Statistics | |
|  | Mean | ± SD | Mean | ± SD | t/χ2 | *p* value |
| Gender, male, n (%) |  | |  | |  |  |
| Age (years) | 35.07 | ±14.18 | 36.58 | ±11.36 | -0.46 | 0.644 |
| Educational year | 14.85 | ±2.18 | 15.00 | ±2.10 | -0.27 | 0.791 |
| HDRS | 1.76 | ±2.31 | 1.45 | ±1.86 | 0.57 | 0.568 |
| YMRS | 0.86 | ±1.38 | 0.45 | ±0.87 | 1.41 | 0.164 |
| Body mass index (kg/m2) | 24.28 | ±3.90 | 28.28 | ±5.11 | -3.42 | 0.001 |
| Insulin (uIU/ml) | 7.89 | ±2.79 | 23.43 | ±12.60 | -6.50 | <0.001 |
| Glucose (mg/dl) | 87.10 | ±7.36 | 99.15 | ±26.69 | -2.35 | 0.022 |
| HOMA-IR | 1.68 | ±0.57 | 5.83 | ±3.81 | -5.80 | <0.001 |
| WCST\_ preservative errors | 9.45 | ±6.36 | 14.82 | ±11.56 | -2.22 | 0.030 |
| WCST\_ completed categories | 3.07 | ±1.67 | 2.42 | ±1.62 | 1.54 | 0.128 |

(b) control

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Non-IR  *n* = 34 | | IR  *n* = 28 | | Statistics | |
|  | Mean | ± SD | Mean | ± SD | t/χ2 | *p* value |
| Gender, male, n (%) |  | |  | |  |  |
| Age (years) | 33.47 | ±11.32 | 35.00 | ±13.02 | -0.50 | 0.623 |
| Educational year | 16.44 | ±2.55 | 15.89 | ±3.05 | 0.77 | 0.443 |
| HDRS | 1.71 | ±1.49 | 1.86 | ±1.60 | -0.39 | 0.702 |
| YMRS | 0.00 | ±0.00 | 0.00 | ±0.00 | - | - |
| Body mass index (kg/m2) | 22.47 | ±3.23 | 28.50 | ±5.72 | -5.23 | <0.001 |
| Insulin (uIU/ml) | 8.06 | ±2.74 | 18.55 | ±6.30 | -8.77 | <0.001 |
| Glucose (mg/dl) | 86.29 | ±6.04 | 95.46 | ±11.68 | -3.98 | <0.001 |
| HOMA-IR | 1.72 | ±0.59 | 4.35 | ±1.52 | -9.29 | <0.001 |
| WCST\_ preservative errors | 8.71 | ±5.83 | 7.96 | ±5.71 | 0.50 | 0.617 |
| WCST\_ completed categories | 3.65 | ±1.35 | 3.39 | ±1.52 | 0.70 | 0.488 |

Abbreviations: BD: bipolar disorder; HDRS: Hamilton Depression Rating Scale; YMRS: Young Mania Rating Scale; HOMA-IR: homeostasis model assessment of insulin resistance; WCST: Wisconsin card-sorting test.

**Supplementary Table 6.** Fasting plasma high-sensitivity C-reactive protein (hs-CRP) of the euthymic BD patients and the control subjects.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | hs-CRP, mg/L | | Statistics | | Pearson correlation with HOMA-IR | | Pearson correlation with insulin | |
|  | Mean | ±SD | t | *p* | r | p | r | p |
| BD | 329,591 | ±377,106 | 0.38 | 0.70 | 0.54 | <0.001 | 0.61 | <0.001 |
| Control | 301,215 | ±399,979 |  |  | 0.50 | <0.001 | 0.44 | 0.001 |

Abbreviations: BD: bipolar disorder; HOMA-IR: homeostasis model assessment of insulin resistance