Impaired visual, working, and verbal memory in first-episode, drug-naive patients with major depressive disorder in a Chinese population

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Abstract

Cognitive impairment has been observed in patients with major depressive disorder (MDD). However, it remains unclear whether the deficits in specific cognitive domains are present in first-episode, drug-naïve patients or medicated patients. In the present study, using the CogState battery (CSB) Chinese language version, we evaluated the visual, working, and verbal memory in first-episode drug-naïve patients and medicated patients with MDD in a Chinese population. We measured the cognitive function in first-episode drug-naïve patients (n = 36), medicated MDD patients (n = 71), and age- and sex-matched healthy control subjects (n = 59) in a Chinese population. The CSB composite scores in both first-episode drug-naïve patients and medicated patients were significantly poorer than those in the healthy control subjects. The CSB sub-scores, including visual, working, and verbal memory were also significantly poorer in both patient groups than those in the healthy control subjects. The CSB sub-scores, including visual, working, and verbal memory were also significantly poorer in both patient groups than those in the healthy control subjects. In contrast, processing speed, attention/vigilance, executive function, spatial working memory, and social cognition were no different from healthy controls, whereas the executive function was significantly better in the medicated patients than in the healthy control subjects and first-episode drug-naïve patients. These findings suggest an impairment in the visual, working, and verbal memory in first-episode, drug-naïve MDD patients in a Chinese population.

Introduction

Major depressive disorder (MDD) is a leading cause of functional disability worldwide [1]. MDD patients usually have cognitive impairments, and these cognitive impairments may contribute to functional impairment [2–5]. There is also some evidence of impairment across most domains of cognitive function, including processing speed [6,7], attention [2,8,9],...
learning and memory \[2,10\], and executive function \[11,12\]. Interestingly, research has suggested that the cognitive impairment persists even after the remission of depressive symptoms \[13–15\]. A large meta-analysis showed that treatment most commonly affects the domains of verbal memory, working memory, processing speed, and executive function \[16\]. In contrast, a recent randomized longitudinal study demonstrated no relative improvement with acute treatment (controlled for time or repeated testing), irrespective of the antidepressant treatment group, even in patients whose depression acutely improved according to clinical measures \[17\]; this finding reinforced the fact that cognitive impairment is an unmet need in MDD patients \[18\]. Thus, it remains unclear whether deficits in specific cognitive domains are present in first-episode, drug-naïve patients or in medicated patients.

The CogState battery (CSB) is a sensitive, computer-based cognitive assessment instrument and is suitable for assessing cognitive impairment in patients with schizophrenia \[19–23\], MDD \[24\], and substance abuse \[25\]. In addition, the CSB has been widely used in clinical trials for a number of new drugs \[26–30\]. A recent study suggested that the CSB may be more suitable than the Food Drug Administration (FDA)-accepted MATRICS consensus cognitive battery (MCCB) to measure changes in the absence of repeated baselines \[31\].

In the present study, using the Chinese language version of the CSB \[21,22,25\], we measured cognitive function in first-episode, drug-naïve patients; medicated patients with MDD; and age- and sex-matched healthy control subjects in a Chinese population. Furthermore, we examined the correlations between cognitive domains and clinical variables in these patients.

**Materials and methods**

**Subjects**

Hundred-seven hospitalized patients with major depression including 36 first-episode drug-naïve and 71 medicated patients were recruited from the First Hospital of Xi’an Jiaotong University, Xi’an, Shaanxi, China (Table 1). All patients satisfied the diagnostic and statistical

| Table 1. Demographic and clinical characteristic of subjects. |
|-------------------|-------------------|-------------------|
|                   | First-episode drug naïve group (n = 36) | Medicated group (n = 71) | Control group (n = 59) |
| Age               | 30.72 (8.591)     | 30.86 (7.904)     | 31.32 (9.228)     |
| Male (Female)     | 16 (20)           | 25 (46)           | 27(32)            |
| Years of education| 13.22 (3.217)     | 14.04 (2.515)     | 13.88 (3.057)     |
| QOL               | 66.00 (11.720)*** | 64.28 (10.751)*** | 86.72 (9.735)     |
| SASS              | 26.24 (5.255)***  | 27.25 (6.443)***  | 34.79 (5.199)     |
| CWRT              | 92.34 (8.247)     | 93.74 (7.586)     | 95.45 (4.306)     |
| HAMD              | 21.90 (4.647)**   | 16.11 (8.256)     | —                 |
| HAMA              | 19.41 (5.295)**   | 15.08 (7.646)     | —                 |
| MADRS             | 29.34 (8.217)*    | 21.35 (11.341)    | —                 |

Data are shown as mean (S.D).

* compared between the First episode/ Medicine treatment with Controls:

** *** p < 0.001.

* compared between the First episode with Medicine treatment:

p < 0.05.

** **p < 0.01.

CWRT: Chinese Word Reading Test; SASS: Social Adaptation Self-evaluation Scale; QOL: Quality of Life; HAMD: The Hamilton depression rating scale; HAMA: The Hamilton anxiety scale; MADRS: Montgomery–Åsberg depression rating scale.

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Cognitive impairment in drug-naive patients with depression

manual of mental disorders criteria (DSM-IV) for depression according to the structured clinical interview for DSM-IV [32]. The inclusion criteria for the study were (1) written, informed consent; (2) >9 years of education; (3) aged 18–50 years; and (4) normal or corrected-to-normal vision and hearing. The exclusion criteria for the study were (1) current or previous episodes of a psychiatric disorder, including alcohol or drug dependence; (2) traumatic brain injury, cerebrovascular disease, epilepsy, spasms, or intellectual disability; (3) inability to follow the study protocol due to severe aggressive behavior or suicidal tendencies and/or behavior; (4) treatment with cognitive-enhancing drugs (such as donepezil) within 6 months prior to study entry; and (5) the presence of cataract or other ophthalmic diseases or hearing impairment, which would compromise completion of the CSB. All medicated patients were treated by using oral administration of antidepressant drugs, selective serotonin reuptake inhibitors (SSRIs: paroxetine, fluoxetine, escitalopram, fluvoxamine) or serotonin norepinephrine reuptake inhibitors (SNRIs: venlafaxine, duloxetine), and no performed psychotherapy or behavior therapy. Healthy normal controls were matched by sex, age and years of education of both MDD patient groups were recruited from the community of Xi’an city, China (Table 1). Healthy controls without pre-existing any DSM-IV Axis I disorders and affective disorder or schizophrenia in their first degree family histories were included. The inclusion and exclusion criteria for the healthy controls were the same as those for the patients. This study was approved by the Institutional Review Board of the First Hospital of Xi’an Jiaotong University. All subjects were given a full explanation of the study, which included potential risks and benefits of study participation. Then we received the written, informed consent from them. Our study was performed in keeping with the Declaration of Helsinki II.

Clinical variables

The Hamilton depression rating scale [33] is the most common application scale for assessing clinical depression. This scale has 17 items and was tested by two trained clinicians through conversation and observation. The Hamilton anxiety scale [34] was used to assess anxiety; this scale includes 14 items and the patient is evaluated by a physician. Montgomery–Åsberg depression rating scale (MADRS) [35] is a 14-item scale for the assessment of clinical depression. The social adaptation self-evaluation scale (SASS) is a 21-item, self-reporting scale to evaluate broad areas of social functioning (such as spare time, work, family, life-coping skills). The response scores (0 to 3), with higher scores represent better social adjustment [36]. The Chinese version of the SASS [37] was used.

The World Health Organization (WHO)–Quality of Life (QOL) instrument (WHOQOL-BREF) is a 26-item, self-administered questionnaire. This is also a shortened version of the WHOQOL-100 scale, which measures the four domains of physical health and wellbeing, psychological health and wellbeing, social relationships, and the environment. A previous study showed that higher scores represent a better QOL [38]. Therefore, the Chinese version of the WHOQOL-BREF [39] was used in this study.

Instruments

The Chinese language version of the CSB contains the following eight tasks: the detection task (DET, speed of processing), identification task (IDN, attention/vigilance), one card learning task (OCL, visual learning and memory), two back task (TWOB, working memory), international shopping list task (ISL, verbal learning and memory), the Groton maze learning task (GML, problem solving/error monitoring), social emotional cognition task (SEC, social cognition), and continuous paired association learning task (CPAL, spatial working memory) [21,25]. The CSB includes all seven cognitive domains of the MCCB [19–21, 40]. These tasks
were presented on a green screen along with standardized instructions that were provided by trained researchers before the commencement of each task to ensure that the subjects completely understood and followed the rules. The results were uploaded to a secure account on the CogState server site (http://www.Cogstate.com), where the data were calculated and normalized (logarithmic transformation for reaction time, arcsine transformation for accuracy). The results of each domain on the CSB were calculated as Z-scores, where the healthy control mean was set to 0 and the standard deviation was set to 1; this followed the methodology used by Keefe et al [41]. A composite score was calculated by averaging all Z-scores of the eight primary measures from the CSB.

**Procedures**

The subjects were enrolled from January 2014 to December 2017. We collected demographic data and performed semi-structured interviews to obtain clinical histories. Each subject performed the CSB in a quiet room. The subjects were allowed to have a short break of approximately 5 min to prevent fatigue and withdrawal symptoms. All subjects performed the tests in their entirety, but some subjects could not complete the tests. The clinicians examined the HAMD, HAMA, and MADRS tests and the Chinese word reading test (CWRT).

**Data analysis**

SPSS 13.0 was used to describe and analyze the data (S1 Table). Differences between the groups were examined using multivariate analysis of variance (MANOVA), followed by the post-hoc Fisher’s least significant difference testing. One-way ANOVA (ANOVA) was used to evaluate the effects of the following independent variables on cognitive performance: age, years of education, the CWRT, SASS, and QOL. In addition, using only patient data, student’s t-test was used to examine the following variables: HAMD, HAMA, and MADRS. Factor analysis was determined by adopting the Principal Component extraction methods, with Quartimax rotation. The correlation matrix of the inter-subsets for the patients (first-episode, drug-naive patients and medicated patients) was tested using the Pearson rank correlation test. Statistical significance was determined as a P-value of <0.05.

**Results**

**Demographic and clinical characteristics of the sample**

The demographic and clinical variables of all subjects are presented in Table 1. Demographic variables, such as age, sex, and education, as well as CWRT scores did not differ between the groups. The SASS and QOL scores were significantly different between the two groups (controls vs. first-episode, drug-naive group, controls vs. medicated group). The HAMD, HAMA, and MADRS scores in the first-episode, drug-naive group were significantly higher than those of medicated group (Table 1).

**Cognitive impairment in first-episode, drug-naive patients and medicated patients**

Fig 1 shows the cognitive performance of the first-episode, drug-naive patients and medicated patients compared with that of the healthy controls. The analysis revealed significant effects (F = 8.369, P < 0.001). Compared with the healthy controls, significant differences in the OCL, TWOB, GML, ISL, and composite were observed for first-episode, drug-naive patients (Fig 1). The scores for the OCL, TWOB, ISL, and composite of the medicated patients were significantly poorer than those of the healthy controls (Fig 1). Interestingly, the MANOVA analysis
revealed a significant effect of antidepressant treatment in the improvement of the GML scores in medicated patients (medicated group vs. controls: \(P < 0.001\); medicated group vs. first-episode, drug-naive group: \(P = 0.008\)) (Fig 1). However, there was no difference of GML scores between SSRIs and SNRIs in the medicated patients.

**Correlation between cognition and clinical variables**

The correlation matrix of the inter-subsets between the CSB composite score and clinical variables for patients is shown in Tables 2-4 and Fig 2. First, we examined the inter-correlations for all patients (n = 107). We found that the OCL were negatively correlated with the HAMD (\(r = -0.339, P = 0.006\)), HAMA (\(r = -0.385, P = 0.002\)), and MADRS scores (\(r = -0.267, P = 0.032\)); the TWOB scores were negatively correlated with the HAMD (\(r = -0.391, P = 0.001\)), HAMA (\(r = -0.392, P = 0.001\)), and MADRS scores (\(r = -0.362, P = 0.003\)); and the composite scores were negatively correlated with the HAMD (\(r = -0.391, P = 0.001\)), HAMA (\(r = -0.434, P = 0.000\)), and MADRS scores (\(r = -0.394, P = 0.001\)) in all patients (Fig 2A). We also found that the DET scores negatively correlated with QOL (\(r = -2.297, P = 0.020\)). The ISL scores positively correlated (\(r = 0.306, P = 0.012\)) with the CWRT scores.

Next, we examined the inter-correlations between different scores in the first-episode, drug-naive patients (n = 36)(Table 3). We found that the DET scores negatively correlated with the QOL scores (\(r = -0.388, P = 0.050\)) in first-episode, drug-naive patients (n = 33), the OCL scores negatively correlated with the HAMD (\(r = -0.415, P = 0.028\)), and HAMA scores (\(r = -0.376, P = 0.049\)) in first-episode, drug-naive patients (n = 35). In addition, the CPAL scores positively correlated with the MADRS scores (\(r = 0.397, P = 0.041\)) and negatively
correlated with the CWRT scores \( r = -0.425, P = 0.027 \) in first-episode, drug-naive patients \( n = 34 \).

We examined the inter-correlations between different scores for medicated patients \( n = 71 \) (Table 4). The TWOB scores negatively correlated with the HAMD \( r = -0.570, P = 0.000 \), HAMA \( r = -0.545, P = 0.000 \), and MADRS scores \( r = -0.494, P = 0.002 \) in medicated patients \( n = 71 \) (Fig 2B). There were no other significant correlations between the subtests of the CSB and clinical variables.

### Table 2. The correlation matrix of inter-subset for the all MDD patients.

| Patient group | DET (n = 103) | IDN (n = 106) | OCL (n = 106) | TWOB (n = 107) | GML (n = 103) | ISL (n = 107) | SEC (n = 106) | CPAL (n = 105) | Composite (n = 107) |
|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|----------------|---------------------|
| HAMD (n = 66) | Pearson Correlation | 0.000 | 0.109 | **-0.339** | **-0.391** | -0.012 | -0.195 | -0.167 | 0.037 | **-0.391** |
| Sig. (2-tailed) | 1.000 | 0.387 | **0.006** | 0.001 | 0.925 | 0.117 | 0.179 | 0.769 | **0.001** |
| HAMA (n = 66) | Pearson Correlation | 0.008 | 0.071 | **-0.385** | **-0.392** | -0.015 | -0.165 | -0.163 | -0.042 | **-0.439** |
| Sig. (2-tailed) | 0.954 | 0.574 | **0.002** | 0.001 | 0.906 | 0.186 | 0.191 | 0.744 | 0.000 |
| MADRS (n = 66) | Pearson Correlation | 0.028 | 0.061 | **-0.267** | **-0.362** | -0.097 | -0.184 | -0.157 | 0.128 | **-0.369** |
| Sig. (2-tailed) | 0.826 | 0.630 | **0.032** | 0.003 | 0.455 | 0.139 | 0.209 | 0.314 | **0.002** |
| QOL (n = 65) | Pearson Correlation | **-0.297** | -0.128 | 0.089 | 0.025 | 0.082 | 0.090 | 0.030 | -0.049 | -0.028 |
| Sig. (2-tailed) | 0.020 | 0.314 | 0.485 | 0.842 | 0.529 | 0.477 | 0.813 | 0.704 | 0.828 |
| SASS (n = 65) | Pearson Correlation | -0.112 | 0.093 | -0.129 | -0.174 | 0.126 | -0.114 | -0.134 | 0.083 | -0.153 |
| Sig. (2-tailed) | 0.389 | 0.465 | 0.309 | 0.165 | 0.331 | 0.367 | 0.288 | 0.520 | 0.224 |
| CWRT (n = 67) | Pearson Correlation | -0.069 | -0.223 | 0.092 | 0.046 | 0.044 | **0.306** | 0.080 | -0.218 | 0.065 |
| Sig. (2-tailed) | 0.589 | 0.072 | 0.465 | 0.712 | 0.734 | **0.012** | 0.522 | 0.081 | 0.601 |

\( p < 0.05, \quad **p < 0.01 \)

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### Table 3. The correlation matrix of inter-subset for the first-episode drug naive MDD patients.

| First-episode drug naive group | DET (n = 33) | IDN (n = 36) | OCL (n = 35) | TWOB (n = 36) | GML (n = 34) | ISL (n = 36) | SEC (n = 35) | CPAL (n = 34) | Composite (n = 36) |
|-------------------------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|---------------|---------------------|
| HAMD (n = 29) | Pearson Correlation | 0.085 | 0.294 | **-0.415** | -0.218 | 0.230 | -0.265 | -0.352 | 0.302 | -0.227 |
| Sig. (2-tailed) | 0.680 | 0.122 | **0.028** | 0.256 | 0.249 | 0.164 | 0.061 | 0.126 | 0.237 |
| HAMA (n = 29) | Pearson Correlation | 0.173 | 0.238 | **-0.376** | -0.236 | 0.109 | -0.129 | **-0.381** | 0.112 | -0.268 |
| Sig. (2-tailed) | 0.398 | 0.214 | **0.049** | 0.217 | 0.588 | 0.504 | **0.041** | 0.578 | 0.160 |
| MADRS (n = 29) | Pearson Correlation | 0.166 | 0.136 | -0.202 | -0.268 | -0.061 | -0.177 | -0.293 | **0.397** | -0.215 |
| Sig. (2-tailed) | 0.418 | 0.483 | 0.303 | 0.160 | 0.762 | 0.358 | 0.123 | **0.041** | 0.263 |
| QOL (n = 29) | Pearson Correlation | **-0.388** | -0.055 | 0.085 | -0.212 | 0.160 | 0.154 | -0.079 | -0.057 | -0.080 |
| Sig. (2-tailed) | 0.050 | 0.776 | 0.667 | 0.269 | 0.424 | 0.426 | 0.685 | 0.776 | 0.680 |
| SASS (n = 29) | Pearson Correlation | -0.223 | 0.041 | -0.023 | -0.164 | 0.001 | 0.027 | -0.254 | 0.089 | -0.140 |
| Sig. (2-tailed) | 0.272 | 0.832 | 0.907 | 0.394 | 0.995 | 0.889 | 0.183 | 0.660 | 0.470 |
| CWRT (n = 29) | Pearson Correlation | -0.077 | -0.261 | -0.028 | 0.073 | -0.083 | 0.323 | 0.199 | **-0.425** | -0.010 |
| Sig. (2-tailed) | 0.708 | 0.171 | 0.888 | 0.708 | 0.681 | 0.088 | 0.302 | **0.027** | 0.958 |

\( p < 0.05 \)

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Factor analysis of the CSB

In the factor analysis of the CSB for all patients, the eigenvalue-greater-than-one rule and scree plot converged on a three-factor solution that accounted for 63.48% of the total variance. The factor loadings were presented in Table 5. The OCL and TWOB were loaded on Factor 2, and the GML, ISL, SEC, and CPAL were loaded on Factor 1. Subtests that needed speed loaded on Factor 3, including the DET and IDN.

We further examined the factor analysis of the CSB for the first-episode patients and medicated patients. For the first group, the eigenvalue-greater-than-one rule and scree plot converged on a three-factor solution that accounted for 70.15% of the total variance. The GML, ISL, SEC, and CPAL were loaded on Factor 1. The OCL and TWOB were loaded on Factor 2. Subtests that needed speed loaded on factor 3, including DET and IDN. For the second group, the eigenvalue-greater-than-one rule and scree plot converged on a three-factor solution that accounted for 62.14% of the total variance. The GML, ISL, SEC, and CPAL were also loaded on Factor 1. The OCL and TWOB were loaded on Factor 2. Subtests that needed speed loaded on Factor 3, including DET and IDN was not loaded on which one of three-factor. The DET and IDN were also loaded on Factor 3.

Discussion

The major findings of this study were that cognitive function in first-episode, drug-naive patients with MDD was significantly poorer than that in healthy control subjects. Across all cognitive domains on the CSB, the visual, working, and verbal memory were significantly poorer in first-episode, drug-naive patients than those in healthy control subjects. Furthermore, working and verbal memory were also significantly poorer in medicated patients than in healthy control subjects. In contrast, cognitive domains, including processing of speed, attention/vigilance, executive function (reasoning and problem solving), spatial working memory, and social cognition, were intact in MDD patients in a Chinese population.

Cognitive performances, reflected in some scores of the CSB subset, were significantly poorer in the first-episode, drug-naive patients and medicated patients compared with their respective age-, sex-, and education-matched healthy controls; this indicated that both

Table 4. The correlation matrix of inter-subset for the medicated MDD patients.

| Medicated group | DET (n = 70) | IDN (n = 70) | OCL (n = 71) | TWOB (n = 71) | GML (n = 69) | ISL (n = 71) | SEC (n = 71) | CPAL (n = 71) | Composite (n = 71) |
|----------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|------------------|
| HAMD (n = 37)  | Pearson Correlation | 0.036       | 0.036       | 0.311       | -0.570**    | 0.151       | -0.151      | -0.154       | -0.016           | -0.447**         |
|                | Sig. (2-tailed) | 0.837       | 0.835       | 0.061       | 0.000       | 0.387       | 0.373       | 0.363        | 0.927            | 0.006            |
| HAMA (n = 37)  | Pearson Correlation | -0.009      | -0.028      | -0.388*     | -0.545**    | 0.126       | -0.171      | -0.096       | -0.082           | -0.529**         |
|                | Sig. (2-tailed) | 0.957       | 0.869       | 0.018       | 0.000       | 0.471       | 0.311       | 0.573        | 0.630            | 0.001            |
| MADRS (n = 37) | Pearson Correlation | 0.038       | 0.020       | -0.287      | -0.494**    | 0.099       | -0.170      | -0.140       | 0.055            | -0.413*          |
|                | Sig. (2-tailed) | 0.824       | 0.910       | 0.085       | 0.002       | 0.573       | 0.313       | 0.408        | 0.748            | 0.011            |
| QOL (n = 36)   | Pearson Correlation | -0.242      | -0.206      | 0.109       | 0.242       | 0.114       | 0.025       | 0.114        | -0.034           | 0.077            |
|                | Sig. (2-tailed) | 0.161       | 0.235       | 0.527       | 0.155       | 0.523       | 0.886       | 0.509        | 0.845            | 0.655            |
| SASS (n = 36)  | Pearson Correlation | -0.089      | 0.136       | -0.219      | -0.178      | -0.183      | -0.259      | -0.056       | 0.069            | -0.228           |
|                | Sig. (2-tailed) | 0.611       | 0.434       | 0.200       | 0.300       | 0.301       | 0.127       | 0.746        | 0.688            | 0.180            |
| CWRT (n = 38)  | Pearson Correlation | -0.076      | -0.184      | 0.179       | 0.028       | 0.071       | 0.282       | -0.006       | -0.082           | 0.110            |
|                | Sig. (2-tailed) | 0.654       | 0.275       | 0.283       | 0.866       | 0.679       | 0.087       | 0.970        | 0.623            | 0.510            |

*p<0.05, **p<0.01

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Fig 2. Correlations between the scores of CogState battery (composite and TWOB score) and clinical variables (HAMD, HAMA and MADRS score) in all MDD patients (A), and in the medicated MDD patients (B). TWOB: Two back task (working memory). HAMD: The Hamilton depression rating scale. HAMA: The Hamilton anxiety scale. MADRS: Montgomery–Åsberg depression rating scale.

Table 5. Factor load of the CogState subsets.

| Subsets (cognitive domains)       | Total patients | First-episode drug naive group | Medicated group |
|----------------------------------|----------------|--------------------------------|----------------|
|                                  | Factor 1  | Factor 2  | Factor 3  | Factor 1  | Factor 2  | Factor 3  | Factor 1  | Factor 2  | Factor 3  | Factor 1  | Factor 2  | Factor 3  |
| DET (processing speed)           | -0.042   | 0.019    | 0.863    | -0.045   | 0.058    | 0.883    | -0.041   | 0.008    | 0.860    |
| IDN (attention)                  | -0.058   | 0.022    | 0.859    | 0.025    | 0.151    | 0.842    | -0.068   | -0.041   | 0.852    |
| OCL (visual memory)              | 0.059    | 0.849    | 0.029    | -0.057   | 0.905    | 0.107    | 0.068    | 0.790    | -0.037   |
| TWOB (working memory)            | 0.223    | 0.850    | 0.031    | 0.172    | 0.813    | 0.153    | 0.158    | 0.882    | 0.014    |
| GML (error monitoring)           | -0.579   | -0.293   | 0.083    | -0.613   | 0.022    | -0.073   | -0.532   | -0.453   | 0.011    |
| ISL (verbal memory)              | 0.753    | -0.996   | -0.073   | 0.861    | -0.219   | -0.033   | 0.675    | 0.079    | -0.144   |
| SEC (social emotional cognition) | 0.651    | 0.0274   | -0.136   | 0.658    | 0.370    | -0.119   | 0.597    | 0.322    | -0.150   |
| CPAL (visual spatial working memory) | -0.738  | -0.087   | -0.103   | -0.790   | -0.409   | 0.025    | -0.773   | 0.032    | -0.110   |

Extraction Method: Principal Component Analysis.
Rotation Method: Quartimax with Kaiser Normalization.

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groups of patients exhibited cognitive impairment on neuropsychological tasks. Interestingly, we found that the GML (executive function) subtest in medicated patients was significantly better than that in first-episode, drug-naive patients. These findings suggested that an antidepressant medication may improve executive function in MDD patients as antidepressants have neurotrophic actions. The reasons underlying the better scores in medicated patients compared with control subjects are currently unknown. In contrast, a recent meta-analysis showed that antidepressants had a positive effect on psychomotor speed and delayed recall, but not executive function [42]. Furthermore, a recent randomized longitudinal study showed that cognitive impairments (attention, response inhibition, verbal memory, decision speed, information processing) in depressed patients showed no relative improvement with acute treatment [17]. A recent follow-up study showed that depressive symptoms at baseline were predicted by verbal memory, while 12-month changes were predicted by executive function and language [43], suggesting that cognitive performance might predict depressive symptoms at baseline and at follow-up. To further examine the effects of medication on GML, follow-up longitudinal studies on cognitive performance in first-episode, drug-naive patients will be necessary.

For the cognitive domains, impairment has been reported for executive function in MDD patients [12,44]. A recent meta-analysis showed significant executive dysfunction in MDD patients compared with healthy controls and an improvement in the Stroop performance during the course of treatment [12]. However, in this study, we did not find any difference in the GML (executive function) in first-episode, drug-naive MDD patients. Furthermore, we also found that several domains, including processing of speed, attention/vigilance, spatial working memory, and social cognition were not impaired in any MDD patient including the first-episode, drug-naive patients. In contrast, drug-free MDD patients (n = 44) were significantly impaired in a range of cognitive domains, including attention, executive function, and visual-spatial learning and memory, compared with healthy controls (n = 44) [2]. The reasons underlying this discrepancy are currently unknown. Interestingly, there are some papers showing racial and ethnic differences in cognitive function in adults [45,46]. One possibility is an ethnic difference (Chinese vs. Caucasian). Another possibility is a difference in the specific battery used (CSB vs. CANTAB). Nonetheless, further study using a large sample size with different ethnic populations will be needed.

The composite scores of the CSB subdomains [OCL (visual memory) and TWOB (working memory)] showed significant negative correlations with the HAMD, HAMA, and MADRS scores in all patients, suggesting a negative correlation between visual and working memory and the severity of depression and anxiety symptoms in MDD patients. Therefore, cognitive impairment is a substantial unmet need in patients with MDD [18] because most MDD patients complain about cognitive problems even after other symptoms of depression have improved [15]. In addition, the localization of cognitive impairments in MDD patients remains poorly understood [47]. Further detailed studies using neuroimaging will be needed to ascertain anatomical localization of cognitive impairments in MDD.

This study has some limitations such as small sample size, age, education, work information. Further study on the role of blood biomarkers (e.g., brain-derived neurotrophic factor, inflammatory cytokines, metabolites) [48–52] in the cognitive function in MDD is needed.

Conclusions
This study suggests significant impairment in the visual, working, and verbal memory in first-episode, drug-naive MDD patients in a Chinese population. Furthermore, there are negative correlations between visual memory (or working memory) and the severity of depression and
anxiety scores in MDD patients. A follow-up longitudinal study of the effects of antidepressants on cognitive performance in first-episode, drug-naive patients will be necessary.

Supporting information
S1 Table. Raw data.
(XLSX)

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