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

Ce Chen[1☯], Wen-hui Jiang[1☯], Wei Wang[1], Xian-cang Ma[1], Ye Li[1], Jin Wu[2], Kenji Hashimoto[2‡]*, Cheng-ge Gao[1‡]*

1 Department of Psychiatry, First Affiliated Hospital of Medical College of Xi'an Jiaotong University, Xi'an, Shaanxi, China, **2** Division of Clinical Neuroscience, Chiba University Center for Forensic Mental Health, Chiba, Japan

☯ These authors contributed equally to this work.
‡ These authors also contributed equally to this work.
* hashimoto@faculty.chiba-u.jp (KH); yaogaow@163.com (CG)

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-naive 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-naive 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. 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-naive 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-naive 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-naive 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-naive 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 naive 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.

https://doi.org/10.1371/journal.pone.0196023.t001

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-naïve 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-naïve 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-naïve 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
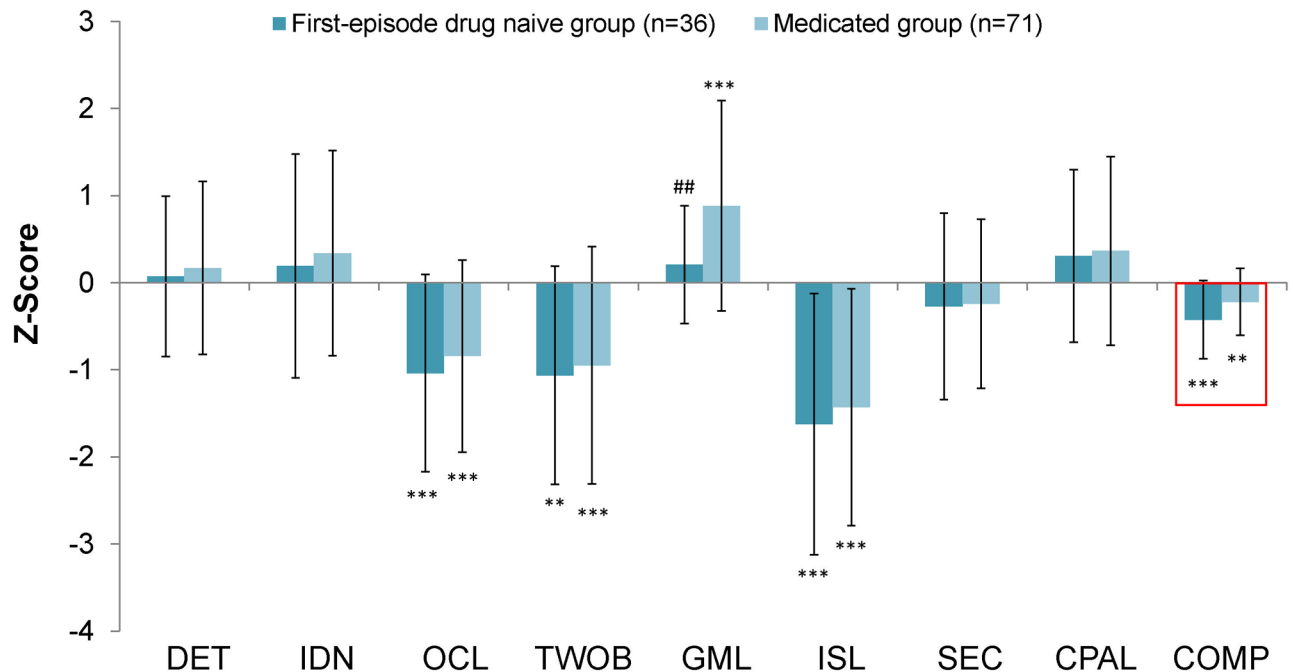
Fig 1. Magnitude of cognitive impairment in first-episode drug naive MDD patients and medicated MDD patients relative to healthy controls.
DET: Detection task (processing speed), IDN: Identification task (attention/vigilance), OCL: One card learning task (visual memory), TWOB: Two back task (working memory), GML: Groton maze learning task (executive function), ISL: International shopping list task (verbal memory), SEC: Social emotional cognition task (social emotional cognition) and CPAL: Continuous paired association learning task (visual spatial working memory). The data are the mean +/- SD. $^*p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ compared with respective healthy controls. $^\#p < 0.05$ compared with the medicated patient group.

https://doi.org/10.1371/journal.pone.0196023.g001

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

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

Patient group (n = 107)		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

*$p<0.05$,

**$p<0.01$

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). The composite scores negatively correlated with the HAMD (r = −0.447, P = 0.006), HAMA (r = −0.529, P = 0.001), and MADRS scores (r = −0.413, P = 0.011) in medicated patients (n = 71)(Fig 2B). There were no other significant correlations between the subtests of the CSB and clinical variables.

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

First-episode drug naive group (n = 36)		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

*$p<0.05$

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

| Medicated group (n = 71)		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

*$p<0.05$,

**$p<0.01$

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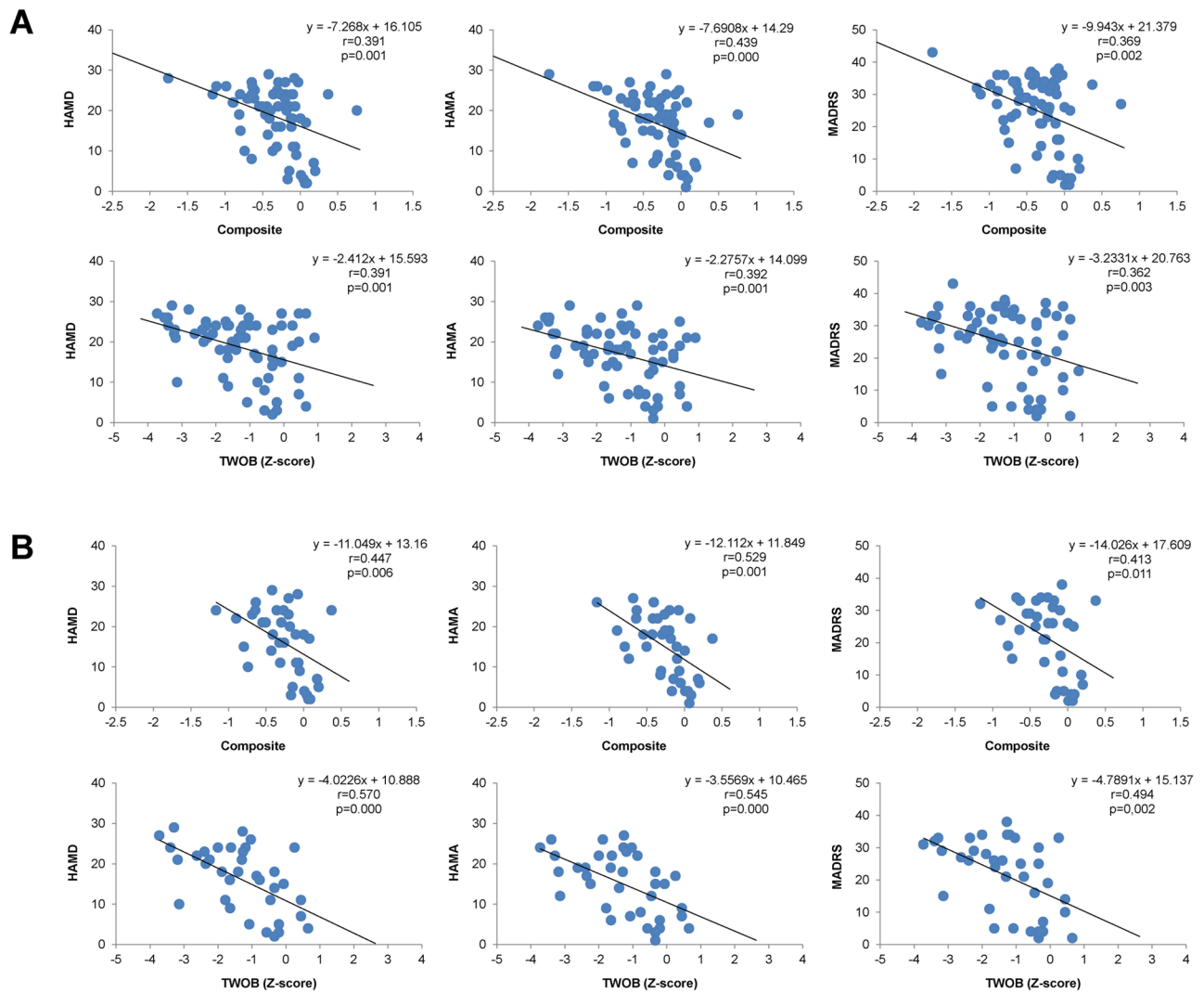
Fig 2. Correlations between the scores of CogState battery (composite and TWOB score) and clinical variables (HAMD, HAMA and MADRS score) in all MDD patients (A), and in the medicated MDD patients (B). TWOB: Two back task (working memory). HAMD: The Hamilton depression rating scale. HAMA: The Hamilton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

https://doi.org/10.1371/journal.pone.0196023.g002

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
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**	-0.096	-0.073	**0.861**	-0.219	-0.033	**0.675**	0.079	-0.144
SEC (social emotional cognition)	**0.651**	00.274	-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.

https://doi.org/10.1371/journal.pone.0196023.t005

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-naïve 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-naïve 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 visuo-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)

Acknowledgments

We would like to thank to all subjects who participated in this study.

Author Contributions

Conceptualization: Ce Chen, Wen-hui Jiang, Wei Wang, Xian-cang Ma, Ye Li, Cheng-ge Gao.

Data curation: Ce Chen, Wen-hui Jiang, Wei Wang, Xian-cang Ma, Ye Li, Cheng-ge Gao.

Formal analysis: Ce Chen, Wen-hui Jiang, Xian-cang Ma, Jin Wu.

Funding acquisition: Cheng-ge Gao.

Investigation: Ce Chen, Wen-hui Jiang, Wei Wang, Xian-cang Ma, Ye Li.

Methodology: Ce Chen, Wen-hui Jiang, Xian-cang Ma, Ye Li.

Project administration: Xian-cang Ma, Jin Wu, Cheng-ge Gao.

Supervision: Kenji Hashimoto, Cheng-ge Gao.

Writing – original draft: Ce Chen, Wen-hui Jiang, Jin Wu, Kenji Hashimoto, Cheng-ge Gao.

Writing – review & editing: Kenji Hashimoto.

References

1. Whiteford HA, Degenhardt L, Rehm J, Baxter AJ, Ferrari AJ, Erskine HE, et al. Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. Lancet 2013; 382: 1575–1586. https://doi.org/10.1016/S0140-6736(13)61611-6 PMID: 23993280

2. Porter RJ, Gallagher P, Thompson JM, Young AH. Neurocognitive impairment in drug-free patients with major depressive disorder. Br J Psychiatry 2003; 182: 214–220. PMID: 12611784

3. Hindmarch I, Hashimoto K. Cognition and depression: the effects of fluvoxamine, a sigma-1 receptor agonist, reconsidered. Hum Psychopharmacol 2010; 25:193–200. https://doi.org/10.1002/hup.1106 PMID: 20373470

4. Marazziti D, Consoli G, Picchetti M, Carlini M, Faravelli L. Cognitive impairment in major depression. Eur J Pharmacol 2010; 626: 83–86. https://doi.org/10.1016/j.ejphar.2009.08.046 PMID: 19835870

5. Evans VC, Iverson GL, Yatham LN, Lam RW. The relationship between neurocognitive and psychosocial functioning in major depressive disorder: a systematic review. J Clin Psychiatry 2014; 75: 1359–1370. https://doi.org/10.4088/JCP.13r08939 PMID: 25551235

6. Tsourtos G, Thompson JC, Stough C. Evidence of an early information processing speed deficit in unipolar major depression. Psychol Med 2002; 32: 259–265. PMID: 11866321

7. Den Hartog HM, Derix MM, Van Bemmel AL, Kremer B, Jolles J. Cognitive functioning in young and middle-aged unmedicated out-patients with major depression: testing the effort and cognitive speed hypotheses. Psychol Med 2003; 33: 1443–1451. PMID: 14672253

8. Landrø NI, Stiles TC, Sletvold H. Neuropsychological function in nonpsychotic unipolar major depression. Neuropsychiatry Neuropsychol Behav Neurol 2001; 14: 233–240. PMID: 11725217

9. Preiss M, Kramska L, Dockalova E, Holubova M, Kucerova H. Attentional networks in euthymic patients with unipolar depression. Eur. Psychiatry 2010; 25: 69–74. https://doi.org/10.1016/j.eurpsy.2009.08.007 PMID: 19926265

10. Preiss M, Kucerova H, Lukavsky J, Stepankova H, Sos P, Kawaciukova R. Cognitive deficits in the euthymic phase of unipolar depression. Psychiatry Res 2009; 169: 235–239. https://doi.org/10.1016/j.psychres.2008.06.042 PMID: 19765829

11. Snyder HR. Major depressive disorder is associated with broad impairments on neuropsychological measures of executive function: a meta-analysis and review. Psychol Bull 2013; 139: 81–132. https://doi.org/10.1037/a0028727 PMID: 22642228

12. Wagner S, Doering B, Helmreich I, Lieb K, Tadić A. A meta-analysis of executive dysfunctions in unipolar major depressive disorder without psychotic symptoms and their changes during antidepressant treatment. Acta Psychiatr Scand 2012; 125: 281–292. https://doi.org/10.1111/j.1600-0447.2011.01762.x PMID: 22007857

13. Austin MP, Mitchell P, Goodwin GM. Cognitive deficits in depression. Possible implications for functional neuropathology. Bri J Psychiatry 2001; 178: 200–206.

14. Paelecke-Habermann Y, Pohl J, Leplow B. Attention and executive functions in remitted major depression patients. See comment in PubMed Commons belowJ Affect Disord 2005; 89: 125–135.

15. Fava M, Graves LM, Benazzi F, Scalla MJ, Iosifescu DV, Alpert JE, et al. A cross-sectional study of the prevalence of cognitive and physical symptoms during long-term antidepressant treatment. J Clin Psychiatry 2006; 67: 1754–1759. PMID: 17196056

16. Keefe RS, McClintock SM, Roth RM, Doraiswamy PM, Tiger S, Madhoo M. Cognitive effects of pharmacotherapy for major depressive disorder: a systematic review. J Clin Psychiatry 2014; 75: 864–876. https://doi.org/10.4088/JCP.13r08609 PMID: 25099527

17. Shilyansky C, Williams LM, Gyurak A, Harris A, Usherwood T, Etkin A. Effect of antidepressant treatment on cognitive impairments associated with depression: a randomised longitudinal study. Lancet Psychiatry 2016; 3: 425–435. https://doi.org/10.1016/S2215-0366(16)00012-2 PMID: 26995298

18. Keefe RS. Treating cognitive impairment in depression: an unmet need. Lancet Psychiatry 2016; 3: 392–393. https://doi.org/10.1016/S2215-0366(16)00095-X PMID: 26995299

19. Maruff P, Thomas E, Cysique L, Brew B, Collie A, Snyder P, et al. Validity of the CogState brief battery: relationship to standardized tests and sensitivity to cognitive impairment in mild traumatic brain injury, schizophrenia, and AIDS dementia complex. Arch Clin Neuropsychol 2009; 24: 165–178. https://doi.org/10.1093/arclin/acp010 PMID: 19395350

20. Yoshida T, Suga M, Arima K, Muranaka Y, Tanaka T, Eguchi S, et al. Criterion and constract validity of the CogState Schizophrenia Battery in Japanese patients with schizophrenia. PLoS ONE 2011; 6: e20469. https://doi.org/10.1371/journal.pone.0020469 PMID: 21637776

21. Zhong N, Jiang H, Wu J, Chen H, Lin S, Zhao Y, et al. Reliability and validity of the CogState battery Chinese language version in schizophrenia. PLoS One 2013; 8: e74258. https://doi.org/10.1371/journal.pone.0074258 PMID: 24023931

22. Chen C, Jiang W, Zhong N, Wu J, Jiang H, Du J, et al. Impaired processing speed and attention in first-episode drug naive schizophrenia with deficit syndrome. Schizophr Res 2014; 159: 478–484. https://doi.org/10.1016/j.schres.2014.09.005 PMID: 25261044

23. Nishinaka H, Nakane J, Nagata T, Imai A, Kuroki N, Sakikawa N, et al. Neuropsychological impairment and its association with violence risk in Japanese forensic psychiatric patients: a case-control study. PLoS One 2016; 11: e0148354. https://doi.org/10.1371/journal.pone.0148354 PMID: 26824701

24. Yoshida T, Ishikawa M, Niitsu T, Nakazato M, Watanabe H, Shiraishi T, et al. Decreased serum levels of mature brain-derived neurotrophic factor (BDNF), but not its precursor proBDNF, in patients with major depressive disorder. PLoS One 2012; 7: e42676. https://doi.org/10.1371/journal.pone.0042676 PMID: 22880079

25. Zhong N, Jiang H, Du J, Zhao Y, Sun H, Xu D, et al. The cognitive impairments and psychological well-being of methamphetamine dependent patients compared with health controls. Prog Neuropsychopharmacol Biol Psychiatry 2016; 69: 31–37. https://doi.org/10.1016/j.pnpbp.2016.04.005 PMID: 27085943

26. Jarskog LF, Lowy MT, Grove RA, Keefe RS, Horrigan JP, Ball MP, et al. A Phase II study of a histamine H_3 receptor antagonist GSK239512 for cognitive impairment in stable schizophrenia subjects on antipsychotic therapy. Schizophr Res 2015; 164: 136–142. https://doi.org/10.1016/j.schres.2015.01.041 PMID: 25728831

27. Keefe RS, Meltzer HA, Dgetluck N, Gawryl M, Koenig G, Moebius HJ, et al. Randomized, double-blind, placebo-controlled study of encenicline, an α7 nicotinic acetylcholine receptor agonist, as a treatment for cognitive impairment in schizophrenia. Neuropsychopharmacology 2015; 40: 3053–3060. https://doi.org/10.1038/npp.2015.176 PMID: 26089183

28. Shiina A, Kanahara N, Sasaki T, Oda Y, Hashimoto T, Hasegawa T, et al. An open study of sulforaphane-rich broccoli sprout extract in patients with schizophrenia. Clin. Psychopharmacol. Neurosci. 2015; 13: 62–67. https://doi.org/10.9758/cpn.2015.13.1.62 PMID: 25912539

29. Walling D, Marder SR, Kane J, Fleischhacker WW, Keefe RS, Hosford DA, et al. Phase 2 trial of an alpha-7 nicotinic receptor agonist (TC-5619) in negative and cognitive symptoms of schizophrenia. Schizophr Bull 2016; 42: 335–343. https://doi.org/10.1093/schbul/sbv072 PMID: 26071208

30. Girgis RR, Van Snellenberg JX, Glass A, Kegeles LS, Thompson JL, Wall M, et al. A proof-of-concept, randomized controlled trial of DAR-0100A, a dopamine-1 receptor agonist, for cognitive enhancement in schizophrenia. J Psychopharmacol 2016; 30: 428–435. https://doi.org/10.1177/0269881116636120 PMID: 26966119

31. Lees J, Applegate E, Emsley R, Lewis S, Michalopoulou P, Collier T, et al. Calibration and cross-validation of MCCB and CogState in schizophrenia. Psychopharmacology (Berl) 2015; 232: 3873–3882

32. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Washington, D.C. American Psychiatric Press. 1994.

33. Hamilton M. A rating scale for depression. J Neurol Neurosrg Psychiatry 1960; 23: 56–62.

34. Hamilton MC, Schutte NS, Malouff JM. Hamilton anxiety scale (HAMA): Source book of adult assessment. New York, Plenum Press, 1959; pp154–157.

35. Montogomery SA, Asberg M. A new depression scale designed to be sensitive to cahnge. Bri J Psychiatry 1979; 134: 382–389.

36. Bosc M, Dubini A, Polin V. Development and validation of a social functioning scale, the Social Adaptation Self-evaluation Scale. Eur Neuropsychopharmacol 1997; 7 Suppl 1: S57–70; discussion S71-53.

37. Tse WS, Bond AJ. Psychometric analysis of the Chinese version of Social Adaptation Self-evaluation Scale (C-SASS). Psychiatry Res 2007; 153: 277–281. https://doi.org/10.1016/j.psychres.2006.09.009 PMID: 17688952

38. Saxena S, Carlson D, Billington R. The WHO quality of life assessment instrument (WHOQOL-Bref): the importance of its items for cross-cultural research. Qual Life Res 2001; 10: 711–721. PMID: 11871592

39. Xia P, Li N, Hau KT, Liu C, Lu Y. Quality of life of Chinese urban community residents: a psychometric study of the mainland Chinese version of the WHOQOL-BREF. BMC Med Res Methodol 2012; 12: 37. https://doi.org/10.1186/1471-2288-12-37 PMID: 22452994

40. Pietrzak RH, Olver J, Norman T, Piskulic D, Maruff P, Snyder PJ. A comparison of the CogState Schizophrenia Battery and the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Battery in assessing cognitive impairment in chronic schizophrenia. J Clin Exp Neuropsychol 2009; 31: 848–859. https://doi.org/10.1080/13803390802592458 PMID: 19142774

41. Keefe RS, Goldberg TE, Harvey PD, Gold JM, Poe MP, et al. The Brief Assessment of Cognition in Schizophrenia: reliability, sensitivity, and comparison with a standard neurocognitive battery. Schizophr Res 2004; 68: 283–297. https://doi.org/10.1016/j.schres.2003.09.011 PMID: 15099610

42. Rosenblat JD, Kakar R, McIntyre RS. The cognitive effects of antidepressants in major depressive disorder: a systematic review and meta-analysis of randomized clinical trials. Int J Neuropsychopharmacol 2015; 19: pyu082.

43. Vicent-Gil M, Keymer-Gausset A, Serra-Blasco M, Carceller-Sindreu M, de Diego-Adeliño J, et al. Cognitive predictors of illness course at 12 months after first-episode of depression. Eur Neuropsychopharmacol 2018; Feb 23. https://doi.org/10.1016/j.euroneuro.2018.02.001 PMID: 29482974

44. Fossati P, Coyette F, Ergis AM, Allilaire JF. Influence of age and executive functioning on verbal memory of inpatients with depression. J Affect Disord 2002; 68: 261–271. PMID: 12063154

45. Díaz-Venegas C, Downer B, Langa KM, Wong R. Racial and ethnic differences in cognitive function among older adults in the USA. Int J Geriatr Psychiatry 2016; 31: 1004–1012. https://doi.org/10.1002/gps.4410 PMID: 26766788

46. Rivera Mindt M, Byrd D, Saez P, Manly J. Increasing culturally competent neuropsychological services for ethnic minority populations: a call to action. Clin Neuropsychol 2010; 24: 429–453. https://doi.org/10.1080/13854040903058960 PMID: 20373222

47. Murray EA, Wise SP, Drevets WC. Localization of dysfunction in major depressive disorder: prefrontal cortex and amygdala. Biol Psychiatry 2011; 69: e43–e54. https://doi.org/10.1016/j.biopsych.2010.09.041 PMID: 21111403

48. Hashimoto K. Brain-derived neurotrophic factor as a biomarker for mood disorders: an historical overview and future directions. Psychiatry Clin. Neurosci. 2010; 64: 341–357. https://doi.org/10.1111/j.1440-1819.2010.02113.x PMID: 20653908

49. Strawbridge R, Arnone D, Danese A, Papadopoulos A, Herane Vives A, Cleare AJ. Inflammation and clinical response to treatment in depression: A meta-analysis. Eur Neuropsychopharmacol 2015; 25: 1532–1543. https://doi.org/10.1016/j.euroneuro.2015.06.007 PMID: 26169573

50. Yang JJ, Wang N, Yang C, Shi JY, Yu HY, Hashimoto K. Serum interleukin-6 is a predictive biomarker for ketamine's antidepressant effect in treatment-resistant patients with major depression. Biol Psychiatry 2015; 77: e19–e20. https://doi.org/10.1016/j.biopsych.2014.06.021 PMID: 25104172

51. Hashimoto K. Inflammatory biomarkers as differential predictors of antidepressant response. Int J Mol Sci 2015; 16: 7796–7801. https://doi.org/10.3390/ijms16047796 PMID: 25856677

52. Hashimoto K. Metabolomics of major depressive disorder and bipolar disorder: overview and future perspective. Adv Clin Chem 2018; 84: 81–99. https://doi.org/10.1016/bs.acc.2017.12.005 PMID: 29478517