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ORIGINAL PAPER

Cognitive Impairments in First-Episode Drug-Naïve Versus Medicated Depressive Patients: RBANS in a Chinese Population

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Abstract

Cognitive deficits are a core feature of major depressive disorder (MDD). However, there are no previous studies that directly compare cognitive performance between first-episode drug-naive depressive patients (FDDP) and medicated depressive patients (MDP). Therefore, the aim of this study was to investigate whether there were the differences in cognitive functions between FDDP and MDP. Sixty-two FDDP, 111 MDP and 90 healthy controls were enrolled in a Chinese population. Cognitive functions were assessed using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). There were the differences in the RBANS total score ($F = 26.55$, $p < 0.001$), subscales of immediate memory ($F = 3.95$, $p = 0.02$), language ($F = 54.11$, $p < 0.001$) and delayed memory ($F = 11.19$, $p = 0.001$) among the three groups after controlling for gender, education, smoking and body mass index (BMI). These differences in the RBANS total score, subscales of language and delayed memory passed the Bonferroni corrections (all, $p < 0.05$). Compared to healthy controls, FDDP and MDP had poorer cognitive performance including the RBANS total score, and subscales of language and delayed memory (all, $p < 0.05$) after controlling for the variables. FDDP experienced greater language deficits than MDP ($p < 0.05$) after controlling for the variables. Education was correlated with the language score in FDDP ($r = 0.61$, $p < 0.001$). Multivariate regression analysis indicated that education was an independent contributor to the language score in FDDP ($ß = 3.11$, $t = 5.48$, $p < 0.001$). Our findings indicated that FDDP had poorer language performance than MDP. Moreover, education could influence the language performance in FDDP.

Keywords Depressive patients · Cognitive impairments · Education · Correlation

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Approximately two-thirds of patients with major depressive disorder (MDD) experience cognitive deficits [1, 2], and cognitive deficits are regarded as a core feature of MDD [3, 4]. Cognitive deficits in patients with MDD mainly occurred in the multiple domains, such as executive function, memory, and processing speed [2, 5]. Cognitive functions in patients with first-episode MDD are impaired in memory, executive functioning, psychomotor speed tasks and selective cognitive control [6–8]. Moreover, cognitive deficits in patients with MDD will further cause a decline in social activity, poor life quality, and even unemployment [9]. Therefore, cognitive deficits should be considered a critical therapeutic target in patients with MDD. However, the underlying mechanisms of cognitive deficits in patients MDD are still unclear.

Cognitive deficits have been reported to appear in different stages of MDD. Previous studies have indicated that patients with first-onset and previously untreated minor depressive disorder had poorer working memory and selective cognitive control than healthy controls [7, 8]. There were significant cognitive differences between patients with current MDD and healthy controls [10]. Two recent studies have shown that the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) total score was significantly lower in patients with MDD than healthy controls [11, 12]. Cognitive functions in patients with recurrent MDD were found to significantly decline with each successive episode of depression [13, 14]. Cognitive performance in patients with MDD still decreased long after the remission of depressive episodes [15]. There were significant differences in immediate memory and attention between patients with previous MDD and healthy controls [10]. These results suggested that the effect of depression on cognitive performance could be pervasive and long-lasting. Furthermore, the RBANS has become a widely used screening instrument in neuropsychological assessment and has been applied to detect cognitive performance in patients with MDD [10, 16, 17]. In China, the RBANS was previously translated into Chinese, and its clinical validity and test-retest reliability were established in healthy controls and patients with schizophrenia [18]. Recently, a few studies on MDD, schizophrenia, substance abuse, type 2 diabetes and Parkinson's disease in a Chinese population adopting the RBANS for cognitive performance have been published [11, 12, 19–22].

However, previous studies did not investigate whether there were significant differences in cognitive functions between first-episode drug-naïve depressive patients (FDDP) and medicated depressive patients (MDP) in a Chinese population using the RBNAS. Therefore, the objective of this study was to examine whether there were significant cognitive differences between FDDP and MDP in a Chinese population.

Methods

Ethics Statement

This study was conducted in the Suzhou area between September 2014 and March 2017. A clinical psychologist explained the research protocol and procedures to the potential subjects. The description of this study was tailored to maximize the understanding of the subjects using the local language appropriate to the subject's level of comprehension and emotional readiness. If the subject was willing to consent to participate in this study, this psychologist provided an in-depth description to the subject and their relatives. Informed consent was obtained before all subjects were enrolled. This research protocol employed was approved by the Institutional Review Board of the Affiliated Guangji Hospital of Soochow University, and all experiments were carried out in accordance with the approved guidelines and regulations.

Participants

FDDP ($n = 62$; male/female = 30/32) were recruited from outpatient clinic of the Affiliated Guangji of Soochow University. The catchment area of this hospital, with approximately 1200 beds, covered a population of approximately 13,651,000. The following inclusion criteria were applied: (a) Han Chinese, (b) 15–66 years of age, (c) a diagnosis of unipolar depression according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth (DSM-IV), (d) Unipolar depression is diagnosed firstly, (e) at least 2 years of education (f) no previous exposure to antidepressants, and (g) provision written informed consent and the ability to participate in the cognitive assessment.

MDP ($n = 111$; male/female = 38/73) were recruited from the inpatient unit of this hospital. The following inclusion criteria were applied: (a) Han Chinese, (b) 15–66 years of age, (c) a diagnosis of unipolar depression according to the DSM-IV, (c) at least 2 years of education (d) receipt of a stable dose of oral antidepressants before entry into the study, and (e) provision of written informed consent and the ability to participate in the cognitive assessment. Diagnoses for FDDP and MDP were performed by two independent experienced clinical psychologists and confirmed using the Structured Clinical Interview for the DSM-IV.

Healthy controls ($n = 90$; male/female = 30/60) were recruited from the employees of this hospital. The following inclusion criteria were applied: (a) Han Chinese, (b) 15–66 years of age, (c) at least 2 years of education, and (d) provision written informed consent and the ability to participate in the cognitive assessment. They were in good physical health, and any subjects with healthy conditions such as schizophrenia, dementia, drug or alcohol abuse/dependence, cancer, diabetes, and pregnancy were excluded.

Clinical Measurements

A detailed questionnaire, including a complete medical history, physical examination, and medical and psychological conditions, was obtained from FDDP, MDP and healthy controls. Additional information was collected from available medical records.

Cognitive functions were assessed using the RBANS (Form A) [23]. The RBANS comprised 12 subtests that were used to calculate 5 age-adjusted index scores and a total score. The test indices were immediate memory (composed of list learning and story memory tasks), visuospatial/constructional (composed of figure copy and line orientation tasks), attention (composed of digit span and coding tests), language (composed of picture naming and semantic fluency tests), and delayed memory (composed of list recall, story recall, figure recall, and list recognition tests). The total score and 5 index scores reported in this study were standard scores. The attending psychologists were trained in the use of the RBANS prior to the start of this study. After training, repeated assessments showed a correlation coefficient of greater than 0.84 for the RBANS.

Statistical Analysis

The clinical and demographic data among FDDP, MDP and healthy controls were compared using Analysis of variance (ANOVA) for continuous variables and the chi-squared test for categorical variables. We compared the RBANS total and index scores among three groups using ANOVA. Fisher's least significant difference (LSD) test was used to perform post hoc pairwise comparisons (FDDP versus healthy controls, MDP versus healthy controls, and

FDDP versus MDP). When the significant differences were found, the effects of gender, age, education, body mass index (BMI), and smoking were tested by adding these variables to the analysis model as the covariates. Bonferroni corrections were applied to each test to adjust for multiple testing. Relationships between the variables and cognitive deficits in FDDP compared to MDP, were assessed with Pearson's product moment correction coefficients. Further stepwise multivariate analysis using cognitive deficits in FDDP compared to MDP as a dependent variable was used to investigate the impact of all variables, including gender, education, BMI, smoking, and types of antidepressants. SPSS version 17.0 was used to perform the statistical analysis. Data were presented as the mean and standard (mean ± SD), and all p values were two-tailed with the significance level set at 0.05.

Results

The clinical and demographic characteristics among FDDP, MDP and healthy controls are summarized in Table 1. FDDP, MDP and healthy controls were similar in gender and education (both $p > 0.05$), but significantly differed in age, BMI and smoking (all $p < 0.001$). Post hoc analysis showed that MDP were older than FDDP and healthy controls (both $p < 0.001$), and there were significant differences in BMI and smoking between healthy controls and FDDP or MDP (both $p < 0.001$). The mean ± SD of illness duration (months) in MDP is 64.53 ± 36.44. The types of antidepressants in MDP mainly included serotonergic and noradrenergic reputake inhibitor (SNRI, 22.25%), selective serotonergic reuptake inhibitor (SSRI, 58.60%), and other antidepressants (18.90%).

The mean ± SD of the RBANS total and index scores among 62 FDDP, 111 MDP and 90 healthy controls are shown in Table 2. ANOVA revealed that there were the differences in the RBANS total score ($F = 22.94$, $p < 0.001$) and subscales of immediate memory ($F = 4.80$, $p = 0.009$), language ($F = 63.77$, $p < 0.001$), attention ($F = 5.105$, $p = 0.007$) and delayed memory ($F = 10.81$, $p < 0.001$) except for the visuospatial/constructional index ($F = 0.25$, $p > 0.05$) among the three groups. After controlling for gender, age, education, BMI, and smoking, the RBANS total score ($F = 26.55$, $p < 0.001$) and subscales of immediate memory ($F = 3.95$, $p = 0.02$), language ($F = 54.11$, $p < 0.001$) and delayed memory ($F = 11.19$, $p = 0.001$)

Table 1 Clinical and demographic characteristics among the FDDP, MDP and healthy controls

Variable	Healthy controls ($n = 90$)	FDDP ($n = 62$)	MDP ($N = 111$)	F or χ^2	P value
Gender (male/female)	30/60	30/32	38/73	4.31	0.12
Age (years)	34.98 ± 10.70	35.35 ± 12.74	41.57 ± 12.07	9.58	**<0.001**
Education (years)	9.74 ± 3.55	10.03 ± 3.43	9.14 ± 3.43	1.53	0.22
BMI(kg/m^2)	24.13 ± 3.70	21.71 ± 2.85	22.11 ± 3.77	11.23	**<0.001**
Smoking(smoker/nonsmoker)	26/64	7/55	8/103	18.90	**<0.001**
Illness Duration (months)			64.53 ± 36.44		
Types of Antidepressants					
SNRI			25 (22.50%)		
SSRI			65 (58.60%)		
Other Antidepressants			21 (18.90%)		

The nominally significant P-values ($p < 0.05$) are shown in bold

FDDP first-episode drug-naive depressive patients, *MDP* medicated depressive patients, *BMI* body mass index, *SNRI* serotonergic and noradrenergic reuptake inhibitor, *SSRI* selective serotonergic reuptake inhibitor

Table 2 Comparisons of the RBANS total and index scores among the FDDP, MDP and healthy controls

RBANS Score	Healthy controls ($n = 90$)	FDDP ($n = 62$)	MDP ($n = 111$)	F	*P*-value [a]	*P* value [b] [Corrected]
Immediate Memory	80.57 ± 17.21	75.34 ± 50.18	67.98 ± 18.33 [e]	3.95	**0.02**	**0.06**
Attention	92.30 ± 18.44	92.81 ± 18.49	85.24 ± 17.95	3.25	0.04	0.12
Language	96.36 ± 13.57	73.35 ± 16.14 [c, d]	75.98 ± 14.49 [e]	54.11	**<0.001**	**<0.001**
Visuospatial/Constructiona	80.94 ± 14.37	82.52 ± 15.48	82.26 ± 16.57	0.06	0.94	1.000
Delayed Memory	95.97 ± 54.73	74.00 ± 19.20 [d']	74.69 ± 19.29 [e']	11.19	**<0.001**	**<0.001**
Total Score	84.73 ± 13.15	72.19 ± 15.96 [d]	71.31 ± 15.63 [e]	26.55	**<0.001**	**<0.001**

The nominally significant *P*-values ($p < 0.05$) are shown in bold. *FDDP* first-episode drug-naive depressive patients, *MDP* medicated depressive patients

[a] *P* values were analyzed by controlling for gender, age, education, BMI, and smoking

[b] *P* values were further adjusted by the Bonferroni correction

[c] FDDP differed from MDP after controlling for gender, education, BMI, and smoking, $p < 0.05$

[d] FDDP differed from healthy controls after controlling for gender, age, education, BMI, and smoking, $p < 0.001$; d': $p < 0.01$

[e] MDP differed from healthy controls after controlling for gender, age, education, BMI, and smoking, $p < 0.001$; e': $p < 0.01$

remained significantly different among the three groups (Table 2). These differences in the RBANS total score and subscales of language and delayed memory passed Bonferroni corrections (all $p < 0.05$) (Table 2).

Compared to MDP, FDDP exhibited relative weakness in the language score ($F = 4.28$, $p = 0.04$) after controlling for gender, age, education, BMI, and smoking (Table 2). There were significant differences in the RBANS total score ($F = 38.95$, $p < 0.001$) and subscales of language ($F = 81.10$, $p < 0.001$) and delayed memory ($F = 9.57$, $p = 0.003$) between FDDP and healthy controls after controlling for gender, age, education, BMI, and smoking (Table 2). Moreover, the RBANS total score ($F = 31.98$, $p < 0.001$) and subscales of immediate memory ($F = 15.05$, $p < 0.001$), language ($F = 65.63$, $p < 0.001$) and delayed memory ($F = 11.47$, $p = 0.001$) were significantly lower in MDP than healthy controls after controlling for gender, age, education, BMI, and smoking (Table 2).

The Pearson correlation analysis showed that the language score was associated with education ($r = 0.61$, $p < 0.001$) in FDDP. Multivariate regression analysis also indicated that education ($ß = 3.11$, $t = 5.48$, $p < 0.001$) was an independent contributor to the language score in FDDP, which together accounted for 64.7% of the variance in the language score.

Discussion

Results from the present study revealed that 1) compared to healthy controls, FDDP had significant cognitive deficits, especially in language and delayed memory; 2) FDDP had poorer language performance than MDP; and 3) education was positively correlated with the language score in FDDP.

This study found that FDDP experienced greater cognitive deficits, especially in language and delayed memory than healthy controls, which aligns with several previous studies reporting that cognitive deficits have been viewed as one of the core features in patients with

MDD [3, 4]. A meta-analysis study has shown that there were significant differences in cognitive functions between patients with first-episode MDD and healthy controls [6]. Previous studies have also indicated that first-episode and untreated patients with minor depressive disorder had poorer cognitive performance than healthy controls [7, 8]. Recent studies have found that patients with MDD had significantly lower RBANS total score than healthy controls [11, 12]. Moreover, several previous studies have reported that cognitive performance in patients with MDD was significantly impaired compared to healthy controls [3, 10, 15, 24, 25]. An underlying mechanism could be that brain abnormalities are involved in cognitive deficits in patients with MDD. For example, reduced hippocampal volume was reported to be significantly associated with cognitive deficits in patients MDD [26]. The variables of hippocampal formation were found to be closely related to the regulation of memory and other cognitive performance [27, 28]. Therefore, these results suggested that brain abnormalities in FDDP might play a vital role in cognitive deficits. However, the underlying mechanisms of cognitive deficits in FDDP still are not fully understood, and they should be further investigated in the future.

Interestingly, we found that FDDP had lower language score than MDP. The possible underlying mechanism is that although the reduction in neurotransmitters, serotonin (5-HT) and norepinephrine (NE) in FDDP can lead to a decline in language function, the use of antidepressants can regulate the balance of these molecules in the brain and may further improve language recovery. A recent study has shown that venlafaxine, which is the latest SNRI antidepressant, could more effectively ameliorate language function by influencing the language cortex in a healthy population [29]. A previous study using functional magnetic resonance imaging (fMRI) also indicated that the SSRI antidepressants could improve language recovery by modulating the brain cortex [30]. Moreover, amphetamine and dexamphetamine were reported to be able to improve language deficits in the acute stage of stoke [31, 32]. Therefore, the use of antidepressants can elevate the levels of neurotransmitters, 5-HT and NE, which will further regulate the synapses, increase the expression of neurotrophic factors, and improve brain organization [33–35]. These findings further supported our result that FDDP had poorer language function than MDP.

This study was to find that education was positively correlated with the language score in FDDP, suggesting that education could influence the language performance in patients with MDD. This result is consistent with several previous studies reporting that education has been regarded as a protective factor against cognitive deficits in patients with MDD [36–38]. Several studies have shown the effect of education on cognitive performance in patients with central nervous system degenerative disease [39, 40]. Fewer years of schooling was reported to be closely correlated with the decline in cognitive performance [41, 42]. Vocabulary knowledge was found to be influenced by education [43, 44]. These results suggest that clinical psychologists should pay special attention to education when assessing the language performance in patients with MDD. However, the discrepant results have emerged in the following studies. For example, older adults with higher education levels were found to experience greater cognitive deficits than those with less education [45]. Therefore, these results indicated that further studies on patients with MDD by age stratification should investigate the effect of education on cognitive performance in the large samples of different ethnicities.

Some limitations of this study should be noted. First, correlated and stepwise multivariate regression analyses showed significant relationship between education and language score in FDDP. However, the exploration of causal relationship was rather tentative. Second, although this study did not investigate the effect of education

on cognitive performance in FDDP by age stratification, the sample size is very small. Therefore, further study should be performed on a large sample of different ethnicities. Third, the population stratification of our samples could be a confounder. However, all subjects in this study were from a Han Chinese population in the Suzhou area, so this did not influence our results. Fourth, although the patients were confirmed with a diagnosis for unipolar depression rather than bipolar depression at the entry level of the study, a few unipolar depressive patients may develop to bipolar depressive patients in the follow-ups. Finally, other clinical data, including sleep status and suicide status, were not collected in this study, and these omission should be considered when interpreting the results of the statistical analysis because they could influence cognitive performance in patients.

In summary, we found that FDDP had poorer language performance than MDP and that FDDP experienced greater cognitive deficits than healthy controls, especially in delayed memory and language. Moreover, education could influence the language performance in FDDP. However, this study still should be viewed as a preliminary investigation, and future studies with a larger sample size from different ethnic populations should be performed to exclude the possibility of false-positive results.

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Compliance with Ethical Standards

Conflict of Interest No conflict of interest was disclosed for each author.

Human and Animal Rights All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in this study.

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