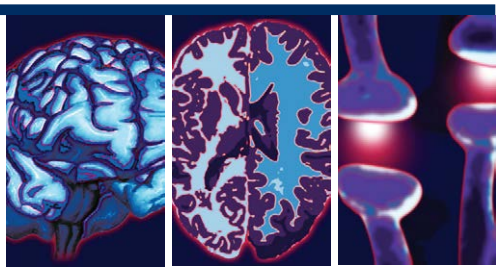
Research



Education and Cognition of Major Depressive Disorder in a Chinese Population

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Objective: Cognitive impairments have been identified as a core feature of major depressive disorder (MDD). To date, no studies on the association between education level and cognitive impairments of MDD from a Chinese population adopting the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) for cognitive measurement emerged. This study is the first to adopt the RBANS to examine whether cognitive impairments of MDD were influenced by education level in a Chinese population.

Methods: 90 patients with MDD and 90 healthy controls with matched gender and age were recruited in a case-control study. Cognitive functions were assessed using the RBANS. Moreover, the demographic and clinical data were collected from patients with MDD and healthy controls.

Results: There were significant differences in the RBANS total score ($F=19.56$, $p<0.001$), subscales of language ($F=58.21$, $p<0.001$) and delayed memory ($F=7.72$, $p=0.006$) between two groups after controlling for the variables. These differences still passed Bonferroni corrections (all, $p<0.05$). Education level of MDD was significantly correlated with the RBANS total score ($r=0.277$, $p=0.010$), language score ($r=0.255$, $p=0.018$) and delayed memory score ($r=0.220$, $p=0.042$). Stepwise multivariate regression analysis indicated that education level was an independent contributor to the RBANS total score ($t=2.666$, $p=0.009$), language score ($t=3.644$, $p<0.001$), and delayed memory score ($t=3.312$, $p=0.001$) of MDD.

Conclusions: Our findings supported that patients with MDD had poorer cognitive functions than healthy controls, especially in language and delayed memory. Moreover, education level could influence cognitive performance of MDD in a Chinese population.

Keywords

Major depressive disorder, Education; Cognition, RBANS, Association

Introduction

Depression is a prevalent and recurring psychiatric disorder affecting millions of people worldwide [1,2]. Although major depressive disorder (MDD) mainly involved the disturbance of mood, cognitive impairments have been identified as one of the most frequent residual symptoms [3,4]. Cognitive impairments

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of MDD have been reported in the following domains: executive function, episodic memory, visuospatial memory, attention, and processing speed [5-7]. A recent meta-analysis study has shown that first-episode patients with MDD had worse psychomotor speed tasks, attention, and executive functioning than healthy controls [8]. Cognitive impairments of MDD would lead to lower social activity, and poorer quality of life [9]. Cognitive impairments of MDD should be considered as a critical target for early identification and intervention. Moreover, there were significant cognitive impairments in immediate memory, attention, language, visuospatial/constructional, delayed memory, and general cognitive functions in current patients with MDD compared to healthy controls [10]. Further evidence has indicated that recurrent depressive patients with each successive episode of depression had significant decline of cognitive functions [11,12]. Cognitive functions of MDD have been reported to decrease long after the remission of depressive episodes [13]. These findings indicated that there may be the pervasive and long-lasting effect of depression on cognitive functions. However, the underlying mechanisms of cognitive impairments of MDD remain unclear.

Cognitive functions of MDD have been reported to be influenced by the demographic and clinical variables, especially education level. For example, several previous studies have shown that education attainment was involved in neuropsychological functioning of MDD [8,14]. Moreover, education level has been found to play an important role in the protection of cognitive functions of MDD [15-17]. Other studies also have indicated the effect of education level on cognitive functions in the different populations [18-20]. Further, education level was reported to be significantly positively correlated with cognitive functions [21, 22]. These findings suggested that education level could contribute to cognitive functions of MDD in a Chinese population. However, no studies reported that education level was associated with cognitive performance of MDD that was assessed using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) in a Chinese population. Therefore, we recruited patients with MDD and healthy controls with matched age and gender in a Chinese population, and cognitive functions were assessed using the RBANS. The objective of this study is to adopt the RBANS to examine cognitive functions of MDD, and to further investigate whether there is the correlation of education level with cognitive performance of MDD in a Chinese population.

Methods

Study population

Patients with MDD (n=90; male/female=30/60) were recruited from inpatient unit and outpatient clinic of the Affiliated Guangji Hospital of Soochow University. Inclusion criteria were: (a) aged 17–65 years; (b) currently confirmed the Diagnostic and Statistical Manual of Mental Disorders, Forth (DSM–IV) diagnosis for unipolar depressive patients rather than bipolar depressive patients; (c) received education for at least 4 years; and (d) provided written informed consent and were able to take part in cognitive assessment. Diagnoses were made for each patient by two independent experienced clinical psychologists and confirmed using the Structured Clinical Interview for DSM-IV.

Healthy controls (n=90; male/female=30/60) were recruited from the employees of this hospital. Current mental status and personal or family history of mental disorders were assessed using the unstructured interviews. None of healthy controls presented a personal or family history of psychiatric disorders.

All subjects were Chinese recruited at the same time from Suzhou area, and were in good physical health. Any subjects with abnormalities was excluded. Neither patients with MDD nor healthy controls were experiencing drug or alcohol abuse/dependence. This study was approved by the Institutional Review Board of the Affiliated Guangji Hospital of Soochow University and written informed consent was obtained from each subject.

Clinical measures

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

Cognitive functions were assessed using the RBANS (Form A). The RBANS aided in determining the neuropsychological status of adults, who had neurological injury or disease [23]. Several recent studies also have shown that the RBANS was used to to detect cognitive functions of MDD [10,24,25]. 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, attention, language, visuospatial/constructional, and delayed memory. Compared to assessment tools of other cognition, the benefits of the RBANS are shown as follows: (a) brief, easily manageable and fairly standardized, (b) sensitive, and (b) relatively little time (approximate 30 minutes). The RBANS was previously translated into Chinese, and its clinical validity and test-retest reliability were established in healthy controls and patients with schizophrenia [26]. The total and 5 index scores reported in this study were standard scores.

The relevant literature on the association among education, the RBANS cognitive functions, and patients with MDD was retrieved systematically via several relevant electronic databases (Pubmed, Chinese National Knowledge Infrastructure, and Wanfang Databases). However, we found that the association between education levels and the RBANS cognitive functions of MDD was not reported in the previous studies.

Statistical analysis

The clinical and demographic data between patients with MDD and healthy controls were compared using analysis of variance (ANOVA) for the continuous variables and chi-square for the categorical variables. We compared the RBANS total and index scores between two groups using ANOVA. When significant differences were found in ANOVA, the effects of gender, age, education level, body mass index (BMI), smoking, and suicide status 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. The relationships between the variables and cognitive impairments of MDD were assessed with Pearson's product moment correction coefficients. Stepwise multivariate analysis using cognitive impairments of MDD as the dependent variables was used to investigate the impact of all variables including gender, age, education level, BMI, smoking and suicide status, age of illness onset, age of first hospitalization, duration of illness, number of hospitalization, types of antidepressants, self-rating depression scale (SDS), and self-rating anxiety scale (SAS) standards score. SPSS version 17.0 was used to perform the statistical analysis. Data were presented as 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 were summarized in **Table 1**. All results were expressed as mean±SD. Patients with MDD and healthy controls significantly differed in BMI, smoking, and suicide status (all, $p<0.001$). However, there was no significant difference in gender, age, and education level between two groups (all, $p>0.05$). Mean±SD of age of illness onset, age of first hospitalization, SDS and SAS standard score in patients with MDD respectively were 31.30±10.23 years, 33.67 ± 10.54 years, 61.77 ± 12.73, and 52.00 ± 12.14. They were duration of illness for an average 50.70 ± 90.31 months, with hospitalization number for a mean of 0.96 ± 0.92 time. Types of antidepressants included serotonergic and noradrenergic reputake inhibitor (SNRI, 22.22%), selective serotonergic reuptake inhibitor (SSRI, 58.89%), and never taking antidepressants (18.89%).

Mean ± SD of the RBANS total and index scores of 90 patients with MDD and 90 healthy controls were shown in **Table 2**. There were significant differences in the RBANS total score (75.17 ± 15.15 vs. 84.73 ± 13.15, $F=20.46$, $df=1$, $p<0.001$) and subscales of language (76.70 ± 15.25 vs. 96.36 ± 13.57, $F=83.42$, $df=1$, $p<0.001$), and delayed memory (77.43 ± 19.02 vs. 95.97 ± 54.73, $F=9.21$, $df=1$, $p=0.003$) between two groups. After controlling for gender, age, education level, BMI, smoking, and suicide status, all these differences remained significant with p values for the RBANS total score ($F=19.56$, $df=1$, $p<0.001$) and subscales of language ($F=58.21$, $df=1$, $p<0.001$), and delayed memory ($F=7.72$, $df=1$, $p=0.006$) between two groups **(Table 2)**. Furthermore, significant differences in the RBANS total score and subscales of language, and delayed memory also passed Bonferroni corrections (all, $p<0.05$) **(Table 2)**.

Table 3 showed significant correlations between age, education level, age of illness onset, age of first hospitalization and the special domain scores of cognitive impairments of MDD (all, $p<0.05$). For age, education level, age of illness onset, and age of first hospitalization that had significant correlations with cognitive impairments, the relative associations between each of them and the special domain scores of cognitive impairments of MDD were examined by partial

Table 1: The clinical and demographic characteristics in patients with MDD and healthy controls.

Variables	Patients with MDD (n=90)	Healthy Controls (n=90)	F or χ^2	*P*-value
Gender (male/female)	30/60	30/60	0.00	1.00
Age (years)	34.98 ± 10.78	34.98 ± 10.70	0.00	1.00
Education (years)	10.12 ± 3.34	9.74 ± 3.55	0.57	0.45
BMI(kg/m^2)	21.62 ± 3.16	24.13 ± 3.70	23.72	**<0.001**
Smoking(smoker/nonsmoker)	8/82	26/64	11.75	**<0.001**
Suicide(attempter/no-attempter)	56/34	0/90	81.29	**<0.001**
Age of Illness Onset (years)	31.30 ± 10.23			
Age of First Hospitalization (years)	33.67 ± 10.54			
Duration of Illness (months)	50.70 ± 90.31			
Number of Hospitalizations	0.96 ± 0.92			
Types of Antidepressants				
SNRI	20 (22.22%)			
SSRI	53 (58.89%)			
Never Taking Antidepressants	17 (18.89%)			
SDS Standard Score	61.77 ± 12.73			
SAS Standard Score	52.0 ± 12.14			

The nominally significant *P*-values (p<0.05) were shown in bold.
MDD = major depressive disorder; BMI = body mass index; SNRI = serotonergic and noradrenergic reuptake inhibitor; SSRI = selective serotonergic reuptake inhibitor; SDS = self-rating depression scale; SAS = self-rating anxiety scale.

Table 2: Comparison of total and index scores of the RBANS between patients with MDD and healthy controls.

RBANS Score	Patients with MDD (n=90)	Healthy Controls (n=90)	F	*P*-value [a]	*P*-value [b] [Corrected]
Immediate Memory	75.92 ± 42.67	80.57 ± 17.21	3.81	0.053	0.318
Attention	92.82 ± 14.65	92.30 ± 18.44	0.04	0.837	1.000
Language	76.70 ± 15.25	96.36 ± 13.57	58.21	**<0.0**001	**<0.001**
Visuospatial/Constructiona	85.29 ± 15.74	80.94 ± 14.37	0.84	0.361	1.000
Delayed Memory	77.43 ± 19.02	95.97 ± 54.73	7.72	**0.006**	**0.036**
Total Score	75.17 ± 15.15	84.73 ± 13.15	19.56	**<0.001**	**<0.001**

The nominally significant *P*-values (p<0.05) were shown in bold.
MDD = major depressive disorder; BMI = body mass index.
[a] *P*-values were analyzed by controlling for gender, age, education level, BMI, smoking and suicide status.
[b] *P*-values were further adjusted by Bonferroni corrections.

Table 3: Correlate analysis model between the clinical and demographic characteristics, and cognitive impairments of MDD (n=90).

Variables	Language		Delayed memory		RBANS total score	
	r	*P*-value	r	*P*-value	r	*P*-value
Gender	0.064	0.051	-0.160	0.133	-0.125	0.240
Age	-0.266	**0.011***	-0.249	**0.018***	-0.338	**0.001****
Education	0.380	**<0.001****	0.356	**0.001****	0.432	**<0.001****
BMI	0.007	0.950	-0.035	0.742	-0.075	0.485
Smoking	0.016	0.878	-0.024	0.825	-0.099	0.352
Suicide	0.160	0.132	0.053	0.620	0.034	0.747
Age of Illness Onset	-0.304	**0.004****	-0.311	**0.003****	-0.369	**<0.001****
Age of First Hospitalization	-0.307	**0.004****	-0.271	**0.011***	-0.373	**<0.001****
Duration of Illness	0.045	0.671	-0.053	0.622	-0.036	0.735
Number of Hospitalizations	-0.006	0.954	-0.097	0.363	-0.099	0.352
Types of Antidepressants	-0.054	0.614	0.022	0.839	0.013	0.901
SDS Standard Score	0.005	0.962	-0.125	0.241	-0.042	0.696
SAS Standard Score	0.158	0.138	-0.072	0.499	0.028	0.792

The nominally significant *P*-values (p<0.05) were shown in bold.
MDD = major depressive disorder; BMI = body mass index; SDS = self-rating depression scale; SAS = self-rating anxiety scale.

correlation analysis. Finally, only education level of MDD was found significant relationship with the RBANS total score (r=0.277, p=0.010), language score (r=0.255, p=0.018) and delayed memory score (r=0.220, p=0.042).

Stepwise multivariate regression analysis showed that for patients with MDD, education level was an independent contributor to language score (ß=1.654, t=3.644, p<0.001), and delayed memory score (ß=1.872, t=3.312, p=0.001), which accounted for 36.6% of the variance in language score, and 33.6% of the variance in delayed memory score. Moreover, the RBANS total score was significantly predicted by education level (ß=1.255, t=2.666, p=0.009) and age of illness onset (ß=-0.350, t=-2.290, p=0.025), which together accounted for 46.9% of the variance in the RBANS total score.

Discussion

Results from the present study revealed that 1) patients with MDD had poorer cognitive functions, especially in language and delayed memory compared to healthy controls; 2) the level of education was positively correlated with cognitive performance of MDD in a Chinese population.

This study found that patients with MDD had significant cognitive impairments compared to healthy controls, which was line with previous studies that patients with MDD had poorer cognitive functions [10,27,28]. First-episode patients with MDD were also reported to experience greater cognitive impairments than healthy controls in a recent meta-analysis study [8]. An underlying mechanism could be that cognitive impairments are influenced by brain abnormalities of MDD. Recent studies have shown that cognitive impairments were significantly associated with structural and functional brain abnormalities in front temporal regions of MDD [29,30]. Hippocampal atrophy and amygdala enlargement, gray matter changes in the temporal lobes, and white matter abnormalities in cortico-subcortical circuits of MDD have been reported in several previous studies [31-36], suggesting that these brain abnormalities were significantly correlated with cognitive impairments of MDD [8]. Also, hippocampal formation played a critical role in the regulation of memory and other cognitive function of MDD [37]. Therefore, these findings suggest the effect of brain abnormalities on cognitive impairments of MDD. However, the inconsistent results between two studies adopting the RBANS for cognitive measurement of MDD have been reported. For example, our present study found that patients with MDD had normal immediate memory, attention, and visucospatial/constructional function; whereas another study has reported that patients with MDD had poorer immediate memory, attention and visucospatial/constructional function [10]. These discrepant results may be due to the following complex factors, including the differences of the clinical and demographic characters and ethnic background (Chinese version Australian).

This study further found that education level was significantly positively correlated with cognitive performance of MDD, suggesting that major depressive patients with less education may be more susceptible to cognitive impairments. This finding was line with the previous studies reported high education level as a protective factor against cognitive impairments of MDD [15-17]. Several studies involving different populations have shown that the level of education had a significant impact on cognitive functions [18-20]. Previous studies have indicated that fewer years of schooling were correlated with the declines of memory and verbal ability [21,22]. The level of education was reported to be significantly correlated with cognitive reserve such as vocabulary knowledge [38,39]. These results supported that after receiving many years of formal education, the brain could become more flexible and more resistant for dealing with the effect of depression on cognitive impairments, and the clinical psychologists should further give special attention to the level of education when assessing cognitive functions of MDD. However, the inconsistent findings on the education impact on cognitive functions also have been reported in the following studies. For example, the interaction between education level and depressive symptom was not found to predict cognitive performance of older adults [40]. A recent study has indicated that older adults with higher education showed more cognitive impairments than those with lower education [41]. Therefore, further studies investigating the effect of education level on cognitive functions of MDD stratified by age still need to be performed in the large samples of the different ethnicities.

This study had several limitations. First, some other clinical data including daily antidepressants dose, duration of current antidepressants treatments, psychotic status, residual symptom,

recurrent episodes and remission status were not collected, which should be considered in the statistical analysis because they could influence cognitive functions of MDD. Second, the association between education level and cognitive impairments of MDD was investigated by correlated and stepwise multivariate regression analyses. Therefore, the exploration of causal relationship was rather tentative. The longitudinal design study in the future should be performed to explain the education-cognition association of MDD. Thirdly, although patients with MDD were currently confirmed diagnosis for unipolar depressive patients rather than bipolar depressive patients using the Structured Clinical Interview for DSM-IV, few unipolar depressive patients may develop bipolar depressive patients in their future as many patients were very young. It also could lead to the bias of our results. Fourthly, although the RBANS was an overall good instrument of cognitive assessment, it also had some limitations. For example, it was unable to evaluate all domains of cognitive functions such as motor abilities and executive functioning. The RBANS was not used widely in China, and the applicability and potential use of the RBANS in Chinese individuals and patients with MDD still need to be further confirmed. Fifth, the range of age on the subjects was 17 to 65, which was a wide range. Thus, further study should enlarge the size of our sample, and adopt stratification by age, which would help the different age population adopting the different education activities to improve cognitive functions. Finally, population stratification of our samples could be a confounding factor. However, the Chinese in Suzhou area were ethnically relatively homogenous, which could not influence our results.

In summary, we found that patients with MDD experienced greater cognitive impairments than healthy controls, especially in delayed memory and language subtest of the RBANS. Moreover, the high level of education could retard the decline of cognitive impairments of MDD in a Chinese population. This study should be viewed as a preliminary investigation and future longitudinal studies adopting the RBANS with a larger sample size from the different ethnic populations should been performed to confirm our results.

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Conflict of Interest

No conflict of interest was disclosed for each author.

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