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ORIGINAL RESEARCH

Comparative Study of Cognitive Function Between Treatment-Resistant Depressive Patients and First-Episode Depressive Patients

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Objective: Despite reports of cognitive dysfunction during the acute phase of depression, there is a lack of studies in patients with treatment-resistant depression (TRD). The aim of this study was to investigate the cognitive function profile of TRD and compare cognitive dysfunction between subjects with TRD and first-episode depression.

Patients and methods: The study included 31 patients with TRD and 53 with first-episode depression. Cognitive function was assessed by a series of neuropsychological tools such as the verbal fluency test, Modified Wisconsin Card Sorting Test (M-WCST), Tower of Hanoi test, Chinese-revision of the Wechsler Adult Intelligence Scale (WAIS-RC), and Trail Making Test A and B.

Results: There were no significant demographic differences between the TRD, first-episode depression, and normal control groups (gender, age, years of education). The full-scale, verbal, and performance intelligence quotients measured with the WAIS-RC were also not significantly different ($p>0.05$). The normal group scores were all significantly better than TRD and first-episode depression, and the TRD group performed significantly worse than subjects with first-episode depression on Trail Making Test B, two WCST subscales, and the profile score of the Tower of Hanoi test (all $p<0.05$).

Conclusion: Patients with depression exhibited global impairments in cognitive function, and these were more common in TRD. Poor executive function may play an important role in TRD.

Keywords: treatment-resistant depression, first-episode depression, cognitive dysfunction

Introduction

Depression is one of the most prevalent mental disorders and one of the leading causes of disease burden worldwide. It has a greater impact on health status than chronic systemic diseases such as diabetes or heart disease.[1] Treatment effectiveness is suboptimal for a significant percentage of patients.[2] About 20% of depressive patients do not respond satisfactorily, and roughly half will experience a chronic or recurrent course of illness.[3,4] In the absence of remission, depression is associated with impairments in work, social, and family life, as well as increased mortality.[5,6]

Cognitive function impairment is a prominent characteristic in some chronic psychiatric disorders such as schizophrenia, obsessive-compulsive disorders, and bipolar disorders.[7] Poor concentration, executive function and memory dysfunction, and slowed processing speed are central features of depression.[8,9] Cognitive impairment might contribute to social and occupational impairments in different phases of depression,[10,11] and cognitive performance is likely associated with mood state. However, the relationship between depression severity and cognitive function was inconsistent in a previous meta-

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analysis.[8] Moreover, depressive individuals in remission may continue to experience cognitive dysfunction.[12] Cognitive deficits persist in euthymic patients with bipolar disorder, and these are likely related to structural and functional brain abnormalities associated with that condition.[13,14]

While depression is a more heterogeneous condition than bipolar disorder, they may share certain cognitive trait features that reflect underlying pathophysiological changes, implicating the frontal brain system. Such cognitive deficits in euthymic patients might help characterize different subtypes of depression and provide prognostic information. Cognitive impairment is correlated with both earlier onset of depressive symptoms and longer duration of episodes, which may contribute to the ineffectiveness of antidepressant therapy.[15] According to Talarowska et al,[16] subjects with first-episode depression show better results than patients with recurrent depression in terms of memory, verbal fluency, and frontal functions. Empirical studies on neurocognition in depression have provided some evidence that cognitive impairment may be associated with poorer response to treatment.[17]

Many definitions of treatment-resistant depression (TRD) have been proposed. Depression is typically considered resistant when a depressive disorder fails to show a satisfactory response to at least two appropriate antidepressant trials from two different pharmacologic classes, at appropriate doses and durations that are sufficient to produce a robust therapeutic effect.[18,19] In the past two decades, TRD has attracted growing research interest. Patients with TRD have higher rates of suicide attempts, low treatment response, relapse, and health care utilization. A large proportion of disease burden caused by depression is due to TRD.[20]

Many groups have searched for predictive factors or characteristics in an attempt to improve TRD diagnosis and treatment. However, data are sparse, and the cognitive function profile of TRD is not well understood. Most patients with TRD experience impairment in many areas of psychosocial functioning such as independent living, community participation, interpersonal relationships, and occupational achievement.[21] The purpose of the present study was to investigate the cognitive function profile of TRD and compare the degree of cognitive dysfunction in subjects with TRD and first-episode depression.

Patients and Methods

Subjects

Eighty-four patients (aged 18–65) treated as outpatients or inpatients at the department of psychiatry in Guangzhou Psychiatric Hospital of China were recruited. All participants provided written informed consent in accordance with the guideline of the Declaration of Helsinki of the World Medical Association Assembly. The investigation was approved by the Ethics Committee of Guangzhou Huai Hospital. All patients suffered from unipolar depression diagnosed based on criteria in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). Fifty-three patients (30 males and 23 females) meeting the DSM-IV criteria for a unipolar first-episode depression diagnosis were included in the study and had not been treated with any antidepressants. Thirty-one individuals (14 males and 17 females) with TRD were defined by failure to respond to at least two prior antidepressant treatments at adequate doses and durations. The 17-item Hamilton Depression Rating Scale (HAMD) was administered to assess depression severity.

Subjects were excluded if they suffered from brain damage, alcohol or substance abuse, any other severe medical illness, were psychotic, had experienced psychosis earlier in life, or had been treated with electroconvulsive therapy within the previous 6 months.

In present study, the patients with TRD had been treated with vortioxetine, paroxetine, citalopram, nortriptyline, sertraline, and amitriptyline. Twenty-eight patients with TRD were taking benzodiazepines for insomnia. Among them, 8, 11, and 9 were taking alprazolam, clonazepam, and estazolam, respectively. Benzodiazepines were prohibited for 24 hrs before cognitive function assessment.

The normal control group included 50 individuals (28 males and 22 females) aged 18–65, who were recruited from the care staff and volunteers. All normal controls gave written informed consent before entering the study. Exclusion criteria for the control group were any severe somatic disorder, any psychosis, alcohol or substance abuse, or a history of brain damage.

Prior to study initiation, the interviewers were trained by a qualified trainer to administer the study questionnaires and neuropsychological tests. A calibration session was performed to ensure a high standard of assessment.

Depressive Symptom Measurement

The HAMD is the most commonly used severity scale in clinical practice and research and was administered to assess depressive symptoms and severity. It reflects symptom characteristics based on four factors. The anxiety/somatization factor includes mental anxiety, somatic anxiety, gastrointestinal symptoms, hypochondria, and insight.

The weight factor is weight loss. The retardation factor includes depression, work and interest, retardation, and sex symptoms. The sleep disturbance factor includes difficulty falling asleep, casual sleeping, and early awakening.

Neuropsychological Assessment

We assessed cognitive domains that have proven to be sensitive to dysfunction in unipolar depression.[22] All participants completed a cognitive function assessment that included executive function, psychomotor speed, and verbal fluency. The individual intelligence of all patients was measured by the Chinese revised Wechsler adult intelligence scale (WAIS-RC).

Executive function was accessed by the modified Wisconsin card sorting test (M-WCST) (48-card version),[23] Tower of Hanoi test,[24] and Trail Making Test B.[25] Psychomotor speed was tested with Trail Making Test A,[25] and verbal fluency was measured with the verbal fluency test.[26]

The M-WCST was designed to measure concept formation, abstraction, set shifting, and ability to utilize feedback. Four measures were included in the M-WCST, but only two were used: the number of categories completed and the number of perseverative errors.

The most common planning task used to test depressive patients is the Tower of Hanoi test. This task requires participants to solve a series of problems by moving stacked disks from a given starting position to a given final position in as few moves as possible. The test comprises 12 problems with different complexity levels, and a total profile performance was computed to reflect the ability to solve the whole series of 12 problems.

The Trail Making Test was designed to measure psychomotor speed and set shifting. Part A involves drawing lines to connect numbers in ascending order, while part B requires the participants to alternate between numbers and letters in ascending order. The time to complete parts A and B was the dependent variable.

In the verbal fluency test, participants were instructed to list as many animals as possible within one minute. The dependent variable was the number of correct animals.

The WAIS-RC includes 11 subtests including similarities, arithmetic, information, vocabulary, comprehension, digit span, digit symbol, picture completion, block design, picture arrangement, and object assembly. Three scores are produced: full-scale intelligence quotient (FIQ), verbal intelligence quotient (VIQ), and performance intelligence quotient (PIQ). VIQ was assessed by the first six subtests, and PIQ was assessed by the last five subtests.

Statistical Analyses

Analyses were conducted using the Statistical Package for Social Sciences (SPSS) 17.0 for Windows (SPSS Inc., Chicago, IL, USA). A two-tailed statistical significance level was set at $p<0.05$ for all analyses. One-way analyses of variance or Chi-square tests were computed to test characteristics among groups. Independent sample t-tests were used to compare HAMD scores and factor scores, VIQ, PIQ, FIQ, age at onset, and duration of illness between the TRD and first-episode depression groups. Two independent sample nonparametric tests were used to compare the numbers of episodes between the TRD and first-episode depression groups. Multivariate analysis of variance (MANOVA) was used to compare neuropsychological performance among the three groups with number of episodes, age, years of education, and duration of illness as covariates, followed by post-hoc comparisons with Bonferroni correction provided by MANOVA.

Results

Participants' Demographic and Characteristics

The three groups did not differ significantly with regard to gender, age, or years of education (Table 1).

Comparison of Clinical Characteristics Between First-Episode Depression and TRD

The clinical characteristics for TRD and first-episode depression are presented in Table 2. The HAMD scores and four factor scores were not significantly different ($p>0.05$) between groups. Patients with TRD had longer cumulative duration and more numbers of episodes than the group with first-episode depression ($p<0.05$).

Comparison of WAIS-RC Scores Between First-Episode Depression and TRD

The WAIS-RC test results for TRD and first-episode depression are presented in Table 3. The FIQ, VIQ, and PIQ were not significantly different between groups ($p>0.05$).

Comparison of Cognitive Function

As shown in Table 4, MANOVA analysis revealed that all neuropsychological scores were significantly different between the three groups. Scores in the normal control

Table 1 Comparison of Characteristics Among the TRD, First-Episode Depression, and Normal Control Groups

Characteristics	First-Episode (n=53)	TRD (n=31)	Normal Control (n=50)	F/χ^2	P
Gender, female, n(%)	23(43.4)	17(54.8)	22(44.0)	1.1952	0.5501
Age, years	32.5±10.9	38.3±13.6	34.0±10.4	2.58	0.080
Education, years	11.4±3.5	12.6±4.1	11.8±3.8	1.00	0.371

Notes: Chi-square test was applied for qualitative data, and one-way analysis of variance with Bonferroni correction was performed for quantitative data.
Abbreviation: TRD, treatment-resistant depression.

Table 2 Comparison of Clinical Characteristics Between the First-Episode Depression and TRD Groups

	First-Episode Depression (n=53)	TRD (n=31)	t or u	P
HAMD score	25.2±5.4	27.2±5.6	1.6159	0.1099
Anxiety/somatization factor	7.0±2.1	7.2±3.2	0.3458	0.7303
Body weight factor	1.2±0.7	1.1±0.7	0.6318	0.5292
Block factor	9.6±4.0	9.7±3.2	0.1187	0.9058
Sleep disturbance factor	4.5±1.5	4.8±1.6	0.8630	0.3906
Duration of illness, months	22.4±16.6	60.3±38.6	6.2474	0.0000
Age at onset, years	32.5±10.9	36.5±12.9	1.5157	0.1334
Number of episodes[a]	1	2(1–4)	7.2035	0.0000

Note: [a]Listed as median (interquartile range).
Abbreviations: HAMD, Hamilton Depression Rating Scale; TRD, treatment-resistant depression.

Table 3 Comparison of WAIS-RC Between the First-Episode Depression and TRD Groups

	First-Episode Depression (n=53)	TRD (n=31)	t	P
Information	10.86±3.45	11.14±3.58	0.3540	0.7242
Comprehension	11.85±2.85	11.23±2.65	0.9869	0.3266
Arithmetic	9.26±2.32	9.33±2.34	0.1330	0.8945
Similarities	10.95±2.46	10.56±2.26	0.7221	0.4723
Digit span	11.18±2.35	11.25±2.48	0.1291	0.8976
Vocabulary	11.45±2.56	11.12±2.42	0.5815	0.5624
Digit symbol	11.12±3.02	11.75±3.45	0.8751	0.3840
Picture completion	8.96±2.68	8.24±2.35	1.2418	0.2178
Block design	9.82±1.63	9.78±2.14	0.0965	0.9233
Picture arrangement	9.98±2.66	9.46±2.43	0.8920	0.3750
Object assembly	9.84±2.51	9.67±2.33	0.3074	0.7593
VIQ	103.78±12.44	103.36±13.78	0.1435	0.8862
PIQ	97.54±6.22	96.87±8.26	0.4212	0.6747
FIQ	102.43±10.42	101.56±11.56	0.3546	0.7238

Abbreviations: FIQ, full intelligence quotient; PIQ, performance intelligence quotient; TRD, treatment-resistant depression; VIQ, verbal intelligence quotient; WAIS-RC, Chinese revised Wechsler adult intelligence scale.

group were all significantly better than the TRD and first-episode depression groups. Considering that number of episodes, age, years of education, and duration of illness are related to neuropsychological performance, we performed MANOVA analysis with the four variables as covariates. This revealed differences between TRD and first-episode depression, with three out of five neuropsychological test scores reaching significant differences (Pillai's F=2.415,

Table 4 Comparison of Cognitive Function Among TRD, First-Episode Depression, and Normal Control Groups

	First-Episode (n=53)	TRD (n=31)	Normal control (n=50)	F	*P*	Post hoc[a]
Verbal fluency test (n)	15.4±4.4	15.9±5.6	20.0±6.4	10.20	0.000	A,B<C
Trail Making Test A (s)	64.2±36.5	66.1±28.2	44.0±26.8	7.02	0.001	A,B>C
Trail Making Test B (s)	95.0±56.7	116.8±55.7	68.4±30.4	10.06	0.000	A,B>C; A<B
WCST (n)						
Classification number	4.0±1.8	3.2±1.4	5.0±1.6	15.34	0.000	A,B<C; A>B
Total error number	21.5±10.9	22.2±11.9	15.2±8.4	6.41	0.002	A,B>C
Continuing error number	9.7±6.7	12.8±8.6	5.0±3.4	16.10	0.000	A,B>C; A<B
Random error number	12.0±5.9	10.6±6.5	5.2±3.1	23.55	0.000	A,B>C
Tower of Hanoi test						
Completed tasks (n)	7.5±2.9	6.3±2.3	10.0±1.3	28.91	0.000	A,B<C
Mean planning time (s)	8.5±6.9	9.3±5.0	5.6±3.2	5.84	0.004	A,B>C
Mean execution time (s)	28.0±15.2	32.5±18.3	21.03±16.5	5.05	0.008	A,B>C
Profile score	44.2±17.7	36.6±17.2	58.7±16.0	18.26	0.000	A,B<C; A>B

Note: [a]The threshold for significance was p<0.05.
Abbreviations: A, first episode; B, TRD; C, normal control; TRD, treatment-resistant depression; WCST, Wisconsin card sorting test.

p<0.05). For those domains with significant main effects, we applied post hoc comparisons using Bonferroni correction and found that subjects with TRD performed significantly worse than those with first-episode depression on Trail Making Test B, the classification number and continuing error number in the M-WCST, and the profile score of Tower of Hanoi test. (p<0.05)

Discussion

Deficits have been identified in the areas of attention, memory, executive function, and psychomotor speed in patients with recurrent major depression and first-episode depression.[27,28] In the present study, subjects with TRD performed significantly worse than those with first-episode depression on Trail Making Test B, the M-WCST, and Tower of Hanoi test, all of which reflect executive function. The M-WCST mainly reflects frontal executive function by testing the abilities of color perception, abstraction, and conceptual transformation.[29] Trail Making Test B was designed to evaluate the speed of visual perception, conceptual transformation, and attention conversion. The Tower of Hanoi test reflects plan adjustment ability and suppression capacity; it can evaluate logic reasoning and problem solving.[30]

Executive functions are higher-level functions that can control and regulate lower cognitive operations; they are most likely linked to the prefrontal cortex and its associated networks.[31,32] Specifically, two circuits are considered critical for modulating or inhibiting emotional behavior. The limbic-thalamic-cortical circuit includes the amygdalae, medial thalamus, and orbital and medial prefrontal cortices. The limbic-cortical-striatal-pallidal-thalamic circuit includes components of the previous circuit with the addition of the striatum and pallidum. Impairment in the two circuits may directly or indirectly influence emotion, motivation, and the cognitive and behavioral manifestations of mood disorders.[33]

In the present study, patients with TRD had longer cumulative duration and more episodes than the group with first-episode depression (p<0.05). Whether the numbers of depressive episodes or cumulative duration affect cognitive function is unknown. Two studies did not detect evidence of an association between neuropsychological test performance and the number of previous episodes.[34,35] In contrast to this, others found a statistically significant association between the cumulative duration of depressive episodes and executive function.[12,36] Numerous reviews of studies in currently depressed individuals reported small-to-moderate impairments in several neurocognitive domains, and these were associated with a relapsing/multi-episode or chronic course of illness.[37] So, it is quite likely cognitive dysfunction that develops in the course of depression is highly variable. Considering that the number of episodes and illness duration are related to neuropsychological performance, we performed MANOVA analysis with these variables as covariates and found differences between the TRD and first-episode depression groups.

A meta-analysis reported that deficits in executive function persist beyond acute episodes of depression; between

one-third and one-half of remitted patients are affected by these deficits.[38] Executive function performance was likely associated with response to antidepressant medication,[39] while impairment in this domain was linked with a poor response to the treatment.[40,41] Therefore, executive dysfunction impairment is a core feature of TRD and may be an important trait-marker for major depression.

Limitations

This study was limited by a small sample size and its cross-sectional design. Given that this is the first investigation of cognitive function profiles in patients with TRD and first-episode depression, replication of these results in independent and large samples is needed to develop a fuller understanding of the cognitive function characteristics of TRD. In addition, when comparing cognitive function between TRD and first-episode depression, one main issue warrants comment. The diagnosis of TRD requires failed treatment with at least two classes of antidepressant treatments. In the present study, patients with TRD had been treated with vortioxetine, paroxetine, citalopram, nortriptyline, sertraline, and amitriptyline. A meta-analysis showed that antidepressants had a significant positive effect on psychomotor speed, but the effect on executive function did not reach statistical significance in head-to-head trials of tricyclic antidepressants, selective serotonin reuptake inhibitors, selective serotonin and norepinephrine reuptake inhibitors, and norepinephrine and dopamine reuptake inhibitors.[42] However, significant limitations of that meta-analysis were result heterogeneity, small sample sizes, and a limited number of studies. Since antidepressants affect neurotransmitters levels in the executive region of the brain, antidepressants may confound the predictive value of neuropsychological profiles.

Conclusions

Patients with depression exhibited global impairments in cognitive function, and these were more common in TRD. Poor executive function may play an important role in TRD. This suggested that treatments that target this cognitive domain may be effective. Clinicians should be aware of neurocognitive dysfunction in patients with depression, especially TRD.

Abbreviations

DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, fourth edition; FIQ, full intelligence quotient; HAMD, Hamilton Depression Rating Scale; MANOVA, multivariate analysis of variance; PIQ, performance intelligence quotient; TRD, treatment-resistant depression; VIQ, verbal intelligence quotient; WAIS-RC, Chinese revised Wechsler adult intelligence scale; M-WCST, modified Wisconsin card sorting test.

Ethics Statement

All participants signed a written informed consent form in accordance with the guidelines of the Declaration of Helsinki of the World Medical Association Assembly. The investigation was approved by the Ethics Committee of Guangzhou Huiai Hospital.

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Disclosure

The authors report no conflicts of interest in this work.

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