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Standardized Treatment and Shortened Depression Course can Reduce Cognitive Impairment in Adolescents With Depression

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Objectives: This study aimed to explore the influence of depression severity, disease course, treatment status, and other factors on cognitive function in adolescents with depressive disorders.
Methods: Participants who met the inclusion criteria were enrolled in the study. Sociodemographic data of each participant were recorded, including age, sex, and family history of mental disorders. Zung's Self-Rating Depression Scale was used to assess depression status in adolescents. Moreover, P300 and mismatch negativity (MMN) were used to objectively evaluate the participants' cognitive function.
Results: Only 26.8% of the adolescents with depression received standard antidepressant treatment. The latencies of N2 (267.80±23.34 ms), P3 (357.71±32.09 ms), and MMN (212.10±15.61 ms) in the adolescent depression group were longer than those in the healthy control group ($p<0.01$). Further analysis revealed that the latency of MMN was extended with increased levels of depression in adolescents. The MMN latency was short in participants with depression receiving standardized treatment. Furthermore, the latency of MMN was positively correlated with the severity and duration of depression (correlation coefficients were 0.465 and 0.479, respectively) ($p<0.01$).
Conclusion: Receiving standardized treatment and shortening the course of depression can reduce cognitive impairment in adolescents with depression.

Keywords: Adolescent; Depression; Standardized treatment; Depression course; Cognitive function.

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INTRODUCTION

With the increase in social and academic pressure, depressive disorders have become rampant in adolescents [1]. In China, the prevalence of adolescent depressive disorders is increasing annually. Currently, the prevalence of adolescent depressive disorder in China exceeds 15% [2]. Depression is a significant disorder that jeopardizes the physical and mental well-being of adolescents.

Cognition refers to the process through which the brain receives external information, undergoes certain processes, and transforms it into internal mental activity, thereby facilitating the acquisition and application of knowledge. Previous studies have indicated that cognitive functions and emotions are closely related [3]. In recent years, numerous studies have identified that in addition to depression, decreased motivation, intellectual disability, and other symptoms [4], some patients with depression also have varying degrees of cognitive dysfunction [5]. For major depressive disorder in particular, a growing consensus is present that objective cognitive impairment can occur not only in the acute phase but also in the remission phase [6]. Cognitive deficits may affect social and occupational functions in patients with depressive disorder [7]. Therefore, the severity of cognitive deficits in patients with depressive disorders is of great significance in their clinical management [8]. Moreover, the degree of cognitive impairment in patients with depressive disorder not only affects the treatment strategy but also the subsequent treatment course [9,10]. Previous studies have demonstrated that

a significant proportion of adolescents with depression have varying degrees of cognitive impairment [11]. Therefore, reducing the severity of cognitive impairment may be a key factor in shortening the course of the disease and promoting full recovery in adolescents with depressive disorder.

Although the clinical importance of cognitive function is being increasingly recognized, the risk factors and intervention targets for cognitive impairment in patients with depressive disorders remain unclear. Previous studies have demonstrated that antidepressant treatment [12,13], neuromodulation [14,15], and psychotherapy [16] can reduce the severity of depressive symptoms and the degree of cognitive impairment in patients with depressive disorders to a certain extent. However, whether other factors, such as the severity and duration of depression, presence of psychotic symptoms, and treatment status, are associated with cognitive impairment in adolescents with depressive disorder remains unclear. The identification of related risk factors may provide new entry points for the treatment of depression and reduction of cognitive impairment in adolescents with depressive disorders.

This study aimed to explore the influence of depression severity, disease course, treatment status, and other factors on cognitive function in adolescents with depressive disorder providing valuable insights for mitigating cognitive impairments in this population and fostering comprehensive rehabilitation.

METHODS

This study was conducted between April 2022 and June 2023 at the Affiliated Brain Hospital of Guangzhou Medical University. The study was approved by the Ethics Committee of the Affiliated Brain Hospital of Guangzhou Medical University (reference code: AF/SC-08/02.3., file number: 2022-031) and conformed to the provisions of the Declaration of Helsinki.

Samples and data collection

All enrolled adolescents with depression met the following criteria: 1) under 18 years of age; 2) were diagnosed by two psychiatrists and their main indications and symptoms met the diagnostic criteria of International Diseases and Classification 10th Revision (ICD-10) [17] for depressive disorder; 3) Zung's Self-Rating Depression Scale (SDS) [18] score ≥53; 4) no comorbidity of any other psychiatric disorder; and 5) can cooperate with the staff to complete the relevant data collection and evaluation. Exclusion criteria were as follows: 1) suffering from psychological disorders other than depressive disorder; 2) suffering from serious physical diseases; and 3) failing to cooperate with the staff to complete the relevant information collection and evaluation.

At the same time, some healthy adolescents were included as healthy controls. Patients were recruited from the community who met the following criteria: 1) less than 18 years old, 2) no mental illness, 3) no physical diseases, and 4) willingness to cooperate with staff to complete the relevant data collection and evaluation.

Written informed consent was obtained from all participants before their partaking in the study.

Sociodemographic

Sociodemographic data of each participant were recorded, including age, sex, and family history of mental disorders.

The duration of depression and treatment

The duration of depression was recorded for all participants diagnosed with adolescent depression. Information regarding previous treatment was collected from each participant with adolescent depression. The treatments of the participants were classified according to the data collected. Participants who had no prior history of treatment were identified as having "no previous treatment." Participants who had received antidepressant treatment in the past, but had a history of receiving treatment that was not prescribed regularly, were identified as having "received nonstandard treatment." Participants who received regular antidepressant treatment in strict compliance with their doctor's instructions without interruption were considered to have "received standard treatment."

Assessment of depression status

SDS was used to assess the status of depression in adolescent participants: 1) a total score of 53–62 indicated mild depression, 2) a total score of 63–72 was considered moderate depression, and 3) a total score ≥73 was considered severe depression. The reliability and validity of the scale were satisfactory.

Assessment of cognitive function

The measurement results of the P300 [19] and mismatch negativity (MMN) [20] were not affected by the subjective judgment of the test executive or the subjective factors of the participants, so they were used to objectively evaluate the cognitive function of the respondents.

P300 acquisition

The reference electrode was placed behind the ear on the mastoid, the recording electrode was placed at the midline central (Cz), and the ground electrode was placed in the middle of the forehead. The electrical impedance of each elec-

trode was below 5 KΩ, and the sensitivity was 5 μV. The auditory Oddball mode was employed using the stimuli consisting of two sounds with different frequencies. One of these sounds was the target stimulus with an occurrence rate was 20%. The other was a non-target stimulus with an occurrence rate of 80%, and the two stimuli appeared irregularly alternately, with an interval of 1.5 s between acoustic stimuli. The test was repeated twice, and the average value was calculated. The latencies of the P300 (N2 and P3) were recorded and analyzed.

MMN detection

The reference electrode was placed behind the ear on the mastoid, the recording electrode was placed at Cz, and the ground electrode was placed in the middle of the forehead. The electrical impedance of each electrode was below 5 kΩ, and the sensitivity was 5 μV. The auditory Oddball mode was used and the stimuli comprised two sounds with different frequencies. The first was the target stimulus, also known as a high-pitched stimulus, which had an occurrence rate of 20%. The second was a non-target stimulus, also known as the Bass stimulus, with an occurrence rate of 80%. The two stimuli appeared irregularly and alternately, and the sound stimulus interval was 1.5 s. The subjects sat on a soft chair in a quiet electrophysiology room, closed their eyes, and relaxed. The measurements were repeated twice, and the data of the two measurements were superimposed. The waveforms evoked by the standard and deviation stimuli were collected and subtracted. After processing, the maximum negative wave between 150 ms and 250 ms was defined as the MMN and its latency was recorded.

Statistical analysis

IBM SPSS version 27 (IBM Corp., Armonk, NY, USA) was used to analyze the data. Student's t-test was used to detect differences between continuous variables in the two groups. The chi-square test was used to analyze the differences between categorical variables in the groups. One-way analysis of variance was used to detect differences in continuous variables among the three groups. Pairwise comparisons were adjusted for multiple testing using the least significant difference correction. Additionally, Pearson's and Spearman's correlations were used to describe the association between different factors and the P300 or MMN. Statistical (two-tails) significance was set at $p<0.05$.

RESULTS

A total of 41 adolescent participants with depression and 33 healthy controls were included in this study. Forty-one adolescent participants with depression were assigned to the depression group, and 33 healthy participants to the control group.

Characteristics of adolescent depressed participants

The characteristics of the participants with adolescent depression are displayed in Table 1. The mean age of 41 participants with adolescent depression included in this study was 16.05 years. Among them, 48.8% were male, while 20 patients (48.8%) had a family history of mental disorders. In terms of depression, 12 (29.3%), 13 (31.7%), and 16 (39.0%) patients had mild, moderate, and severe depression, respectively. Twenty-two patients had psychotic symptoms, and their average duration of depression was 17.84±10.37 mo. Only 11 patients (26.8%) received standard antidepressant treatment.

Table 1. Characteristics of participants with depression

Characteristics	Depression group (n=41)
Age (yr)	16.05±1.55
Sex, male	20 (48.8)
Family history of mental disorders, yes	20 (48.8)
Depression levels	
Mild	12 (29.3)
Moderate	13 (31.7)
Severe	16 (39.0)
With psychotic symptoms or not, yes	22 (53.7)
The course of depression (mo)	17.84±10.37
Treatment status	
No previous treatment	14 (34.1)
Received nonstandard treatment	16 (39.0)
Received standard treatment	11 (26.8)

Values are presented as mean±standard deviation or number (%).

Table 2. The comparison between depression group and normal control group

Variable	Depression group (n=41)	Healthy control group (n=33)	p
Age (yr)	16.05±1.55	16.18±1.10	0.668
Sex, male	20 (48.8)	15 (45.5)	0.777
P300			
N2 (ms)	267.80±23.34	240.61±29.76	<0.01**
P3 (ms)	357.71±32.09	314.64±24.12	<0.01**
MMN (ms)	212.10±15.61	177.21±15.61	<0.01**

Values are presented as mean±standard deviation or number (%). T-test was used to detect the differences between continuous variables in the two groups. Chi-square test was used to detect the differences between categorical variables in the two groups. **p<0.01. MMN, mismatch negativity

Table 3. The comparison between different groups

Variable	Mild depression group (a) (n=12)	Moderate depression group (b) (n=13)	Severe depression group (c) (n=16)	Healthy control group (d) (n=33)	p	Post-test†
Age (yr)	16.00±1.54	15.62±1.61	16.44±1.50	16.18±1.10	0.428	
Sex, male	7 (58.30)	6 (46.10)	7 (43.70)	15 (45.50)	0.869	
Family history of mental disorders, yes	5 (41.70)	8 (61.50)	7 (43.80)	-	0.860	
With psychotic symptoms or not, yes	6 (50.00)	8 (61.50)	8 (50.00)	-	0.359	
The course of depression (mo)	15.04±10.41	11.38±6.83	25.19±8.38		<0.01**	a-b (0.29) a-c (0.004**) b-c (<0.01**)
Treatment status					0.873	
No previous treatment	4 (33.30)	5 (38.40)	5 (31.25)	-		
Received nonstandard treatment	5 (41.70)	5 (38.40)	6 (37.50)	-		
Received standard treatment	3 (25.00)	3 (23.20)	5 (31.25)	-		
P300						
N2 (ms)	263.67±19.15	272.69±26.35	266.94±24.34	240.61±29.76	0.001**	a-b (0.40) a-c (0.75) a-d (0.01*) b-c (0.56) b-d (<0.01**) c-d (0.002**)
P3 (ms)	348.58±31.05	351.23±31.12	369.81±31.69	314.64±24.12	<0.01**	a-b (0.82) a-c (0.05) a-d (0.001**) b-c (0.08) b-d (<0.01**) c-d (<0.01**)
MMN (ms)	204.83±14.74	207.38±18.66	221.38±7.68	177.21±15.98	<0.01**	a-b (0.67) a-c (0.005**) a-d (<0.01**) b-c (0.01*) b-d (<0.01**) c-d (<0.01**)

Values are presented as mean±standard deviation or number (%). Chi-square test was used to detect the differences of categorical variables between different groups. One-way ANOVA was used to detect the differences of continuous variables between different groups. *p<0.05; **p<0.01; †pairwise comparisons were adjusted for multiple testing using LSD correction. ANOVA, analysis of variance; LSD, least significant difference; MMN, mismatch negativity

Adolescents with depression had longer latency of P300 and MMN compared to healthy adolescent participants

The results of the comparison of each characteristic between the depression group and the healthy control group are presented in Table 2. No significant differences were observed between the two groups in terms of age or sex (all p> 0.05).

The latencies of N2 (267.80±23.34 ms) and P3 (357.71±32.09 ms) of the participants in the adolescent depression group were longer than those in the healthy control group (p<0.01). Furthermore, the latency of MMN (212.10±15.61 ms) of the participants in the adolescent depression group was longer than that in the healthy control group (177.21±15.61 ms) (p< 0.01).

Participants with higher levels of depression had longer MMN latency

In this study, adolescent participants with depression were further categorized into mild, moderate, and severe depression groups based on the severity of their symptoms. A comparison of the characteristics of the different groups is displayed in Table 3.

No significant differences were observed in age, sex, family history of mental disorders, comorbid psychotic symptoms, or treatment among the three groups (p>0.05). Participants in the severe depression group had a longer disease duration (25.19±8.38 mo) compared to those in both the mild depression group (15.04±10.41 mo) and the moderate depression group (11.38±6.83 mo) (p<0.05). However, no significant difference between the mild and moderate depression groups was identified (p=0.29).

In terms of cognitive function assessment, the latencies of the N2, P3, and MMN in each depression group were longer than those in the healthy control group, with statistically significant differences (all p<0.05). The MMN latency of severe depression group (221.38±7.68 ms) was longer than that of mild depression group (204.83±14.74 ms) and moderate depression group (207.38±18.66 ms) (p<0.05). However, no significant difference was identified in the N2 and P3 latencies between the different depression groups (p>0.05).

Adolescents with depression who received standardized treatment had short MMN latency

To explore whether different treatment statuses affect cognitive function in adolescents with depression, they were regrouped according to various treatment statuses. The latencies of the N2, P3, and MMN in different groups of participants were compared. The results are summarized in Table 4. The MMN latency (202.88±16.74 ms) of participants in the standard treatment group was shorter than that of participants in the no previous treatment group and the nonstandard treatment group (p<0.05). However, no significant difference was observed between the no previous treatment and nonstandard treatment groups (p>0.05). In addition, no significant differences were identified in the N2 and P3 latencies among the three groups (p>0.05).

The latency of MMN was positively correlated with the severity and duration of depression

To further explore the influence of different factors on cognitive function in adolescents with depression, the correlation between various factors and the latencies of N2, P3, and MMN was analyzed (Table 5). Correlation analysis dis-

Table 4. The comparison between participants with different treatment status

Variable	No previous treatment group (a) (n=14)	Nonstandard treatment group (b) (n=16)	Standard treatment group (c) (n=11)	p	Post-test†
Age (yr)	15.79±1.71	16.31±1.30	16.00±1.73	0.656	
Sex, male	9 (64.3)	8 (50.0)	4 (36.4)	0.389	
With psychotic symptoms or not, yes	7 (50.0)	11 (68.8)	4 (36.4)	0.247	
The course of depression (mo)	17.07±11.74	15.41±9.75	22.36±8.71	0.222	
P300					
N2 (ms)	273.71±25.73	265.00±18.28	264.56±24.62	0.517	
P3 (ms)	363.29±39.35	361.73±29.10	350.06±27.13	0.483	
MMN (ms)	219.71±11.10	215.82±12.73	202.88±16.74	0.006**	a–b (0.49) a–c (0.002**) b–c (0.02*)

Values are presented as mean±standard deviation or number (%). Chi-square test was used to detect the differences of categorical variables between different groups. One-way ANOVA was used to detect the differences of continuous variables between different groups. *p<0.05; **p<0.01; †pairwise comparisons were adjusted for multiple testing using LSD correction. ANOVA, analysis of variance; LSD, least significant difference; MMN, mismatch negativity

Table 5. The correlation between different factors and P300 or MMN

Variable	P300		MMN
	N2	P3	
Age	-0.109	-0.095	0.028
Sex†	0.095	0.122	0.056
Family history of mental disorders†	0.052	0.021	0.002
Depression levels†	0.012	0.248	0.465**
With psychotic symptoms or not†	0.079	0.182	-0.095
Treatment status†	-0.143	0.003	-0.170
The course of depression	-0.021	0.347*	0.479**

Values listed in the table were r for Pearson correlation. *p<0.05; **p<0.01; †r for Spearman's correlation. MMN, mismatch negativity

played that the severity of depression was positively correlated with the delay in MMN (r=0.465, p<0.01), indicating that adolescents with severe depression had long MMN latency. In addition, the course of depressive disorder was positively correlated with P3 latency and MMN latency (correlation coefficients were 0.347 and 0.479, respectively) (p< 0.05), indicating that adolescents who had a long course of depressive disorder had long P3 or MMN latency.

DISCUSSION

The results of this study demonstrated that only 26.8% of the 41 participants with adolescent depression had previously received standardized treatment. The latency of the P300 (either N2 or P3) and MMN in adolescent participants with depression was longer than that in healthy controls, suggesting that adolescent participants with depression have a certain degree of cognitive impairment. Moreover, severe depression was associated with a long MMN latency, indicating that compared to healthy controls cognitive function was more impaired in adolescents with depression. However, standardized treatment seems to shorten the latency of MMN to some extent, implying a reduction in the severity of cognitive impairment. Similarly, when exploring the influence of different factors on cognitive impairment in adolescents with depression, we identified that the severity and duration of depressive symptoms were positively correlated with the degree of cognitive impairment.

Previous studies established that most adolescents with depression have varying degrees of cognitive impairment significantly impacting their social function [21]. Therefore, multiple interventions for adolescents with depression to relieve their depressive symptoms and reduce the damage to their cognitive functions have a positive effect on their comprehensive rehabilitation. Many relevant studies have also indicated that various interventions such as drug therapy [21], physical therapy [22,23], and behavioral therapy [24] have positive effects in alleviating depressive symptoms and reducing the degree of cognitive impairment in adolescents with depression. However, interventions that have proven to be effective in previous studies are only helpful if the patient receives them for a sustained period. In other words, the effectiveness of these interventions was time-dependent. This requires patients to adhere to treatment rather than arbitrarily interrupting it. However, this study identified that only 26.8% of the adolescents with depression received standardized treatment. This means that only a small proportion of depressed adolescents adhere to the various types of antidepressant treatments directed by their physicians. In other words, this phenomenon undoubtedly suggests that a large proportion of adolescents with depression are not treated properly or do not receive proper treatment, thereby their recovery process is hindered. In addition to focusing on the effectiveness of different treatment modalities for adolescent depression, future studies should appropriately shift their focus to altering the treatment of adolescent depression through comprehensive interventions (such as reducing the rate of treatment discontinuation and more comprehensive personalized treatment). Only when their relevant treatment status improves can adolescents with depression truly benefit from comprehensive intervention strategies and achieve better rehabilitation outcomes.

Depressive disorder has a negative impact on cognitive function [25], including attention [10], executive function [26], and processing speed [26,27]. The results of this study are consistent with those of previous studies. The results suggest that cognitive impairment is more significant in adolescents with depression than in healthy controls. Cognitive impairment can further affect the social functioning of depressed adolescents [6] and is detrimental to their recovery. Therefore, it is a crucial aspect to consider.

Previous studies have demonstrated that antidepressant treatment can, to some extent, reduce the degree of cognitive impairment in patients with depression. The underlying mechanism may be related to a series of physiological regulatory mechanisms induced by antidepressants, such as changes in neurotransmitter levels, brain structure, or brain function [28]. A previous study demonstrated that antidepressant treatment can reduce negative affective bias in patients with depression and that a change in affective bias can lead to cognitive and psychological reconsolidation [29]. Over time, this effect may lead to increased responsiveness and improvement in mood, which, in turn, reduces the patients' social withdrawal. Similarly, the results of the present study suggest that the greater the severity of depression in adolescents, the greater their cognitive impairment. Additionally,

the duration of depression negatively impacts cognitive function. After receiving standardized treatment, the duration of depression in adolescents may be moderately reduced and their cognitive impairment may be milder than that of those who do not receive standardized treatment and/or have a long duration of depression. Therefore, reducing the severity of depression and shortening its course in adolescents may be key points that must be considered in the future development of treatment strategies.

In recent years, the Chinese government has implemented numerous policies aimed at safeguarding the mental well-being of adolescents. These policies endorse the establishment of a comprehensive mental health service model that integrates schools, communities, families, media, and medical and health institutions. They also promote the implementation of preventive and intervention measures for addressing psychological and behavioral issues and mental disorders among adolescents. Additionally, efforts have been made to improve psychological counseling services for vulnerable groups. This lays an important foundation for improving adolescent health and well-being. However, knowledge of depressive disorders among the Chinese population is relatively rudimentary, and knowledge of adolescent depression is low. This leads to low detection and treatment rates of adolescent depression. Therefore, the popularization of depression-related knowledge remains crucial. The popularization of depressive disorder-related knowledge, especially adolescent depression-related knowledge, is conducive to improving public awareness of this mental disease. Furthermore, the popularization can also improve the detection rate of adolescent patients with depression, reduce the physical and psychological damage caused by the disorder, help individuals get rid of depressive disorder, and promote comprehensive physical and psychological rehabilitation.

Limitations

The present study had some limitations. First, this study included a limited number of participants with adolescent depression (n=41). The treatment of depression was categorized based on the extent to which adolescents with depression adhered to their doctors' prescribed treatment and rehabilitation interventions, rather than on the specific impact of their treatment on cognitive function. In addition, other potential confounders such as intelligence quotient and attention were not included in the analysis. Therefore, the results of the present study are preliminary.

CONCLUSION

Changes in cognitive function are evident in adolescents with depression. However, only a small proportion receive standardized treatment to manage depression. The severity, duration, and treatment of depression have a significant impact on cognitive function in adolescents with depression. Therefore, in future research and clinical practice, reducing the severity of depression in adolescents, shortening the course of depression, and allowing more adolescents with depression to receive standardized treatment is key to reducing cognitive impairment and promoting comprehensive rehabilitation.

Availability of Data and Material

The datasets used and/or analyzed in the current study are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Nannan Pan, Ziyan Fang. Data curation: Nannan Pan. Formal analysis: Nannan Pan, Penghui Cao, Junjie Tan. Funding acquisition: Nannan Pan, Ziyan Fang. Investigation: Xuezhen Liao, Jinwei Wang, Lihuan Chen. Methodology: Nannan Pan, Ziyan Fang. Project administration: Nannan Pan, Ziyan Fang. Resources: Nannan Pan, Ziyan Fang. Supervision: Nannan Pan, Ziyan Fang. Writing—original draft: Nannan Pan, Ziyan Fang, Penghui Cao. Writing—review & editing: Nannan Pan, Ziyan Fang, Penghui Cao.

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