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ORIGINAL ARTICLE

Observational Study

Sleep disturbances and psychomotor retardation in the prediction of cognitive impairments in patients with major depressive disorder

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Abstract

BACKGROUND

Symptoms of depression and comorbid anxiety are known risk factors for cognitive impairment in major depressive disorder (MDD). Understanding their relationships is crucial for developing targeted interventions to mitigate cognitive impairments in MDD patients. We expect that the severity of sleep disturbances and other depressive symptoms will be positively correlated with the degree of cognitive impairments. We also hypothesize that anxiety symptoms, especially psychic anxiety, is a key factor in predicting cognitive performance in MDD patients and may indirectly contribute to cognitive impairment by affecting sleep disturbances and other potential factors.

AIM

To determine which dimension of the depressive and anxiety symptoms predicts cognitive impairment during a depressive episode.

METHODS
A comprehensive neurocognitive test battery assessed executive function, attention, processing speed, and memory in 162 medication-free MDD patients and 142 matched healthy controls. The 24-item Hamilton Depression Rating Scale was used to assess depressive symptoms, and the 14-item Hamilton Anxiety Scale was used to assess anxiety symptoms. Linear regression analyses and mediation analyses were conducted to evaluate the impact of depressive and anxiety symptoms, as well as their interactions, on cognitive impairments.

RESULTS
Among the depressive symptoms, sleep disturbances were associated with poorer executive function (P = 0.004), lower processing speed (P = 0.047), and memory impairments (P < 0.001), and psychomotor retardation (PR) was associated with lower processing speed in patients with MDD (P = 0.019). Notably, PR was found to mediate the impact of sleep disturbances on the processing speed. Regarding anxiety symptoms, psychic anxiety, rather than somatic anxiety, was associated with cognitive impairments in all aspects. Sleep disturbances mediated the effect of psychic anxiety on executive function [β = -0.013, BC CI (-0.027, -0.001)] and memory [β = -0.149, BC CI (-0.237, -0.063)], while PR mediated its effect on processing speed (β = -0.023, BC CI (-0.045, -0.004)].

CONCLUSION
Sleep disturbances may be a key predictor of poorer executive function, lower processing speed, and memory loss, while PR is crucial for lower processing speed during a depressive episode. Psychic anxiety contributes to all aspects of cognitive impairments, mediated by sleep disturbances and PR.

Key Words: Major depressive disorder; Cognitive impairment; Depressive symptoms; Anxiety symptoms; Sleep disturbance; Psychomotor retardation

Core Tip: In this study, four major cognitive domains were assessed in 162 patients with major depressive disorder and 142 healthy controls *via* a comprehensive cognitive battery. Linear regression analyses and mediation analyses revealed that sleep disturbances independently contributed to executive function, processing speed, and memory, whereas psychomotor retardation (PR) symptoms independently contributed to processing speed. PR symptoms completely mediated the effect of sleep disturbances on processing speed. Psychic anxiety symptoms contributed to impairment in all four cognitive domains. Sleep disturbances mediated the effect of psychic anxiety symptoms on executive function, and PR symptoms mediated the effect of psychic anxiety symptoms on processing speed.

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INTRODUCTION

Cognitive impairment is a well-established feature of major depressive disorder (MDD). Numerous studies have shown that cognitive impairments, mainly poor executive function, attention deficit, low processing speed, and memory loss, are overrepresented in patients with acute depression[1-4], and such symptoms have been reported to be associated with the outcomes[5-7], recurrence[8] and psychosocial functioning[9-11] of these patients. However, in previous years, the primary focus was on addressing mood and somatic symptoms in patients with depression rather than on cognitive symptoms, although improvements in cognitive symptoms have been observed as positive side effects of antidepressant treatment[12]. Nonetheless, an increasing number of studies have reported long-term cognitive impairments following depressive episodes[13]. The lack of effective treatment for cognitive impairments during depressive episodes might be a leading cause of residual cognitive symptoms. Notably, identifying the association between depressive symptoms and cognitive impairments not only helps provide insight into the cause of cognitive impairments but also facilitates efforts to identify targets of antidepressant treatment regarding cognitive function.

Some studies have addressed the association between the severity of depression and cognitive performance. Previous epidemiological studies demonstrated that high levels of depressive symptoms are associated with cognitive decline in older adults[14-16]. A meta-analysis by McDermott and Ebmeier[17] revealed that the severity of current depressive symptoms was significantly associated with executive function, processing speed, and episodic memory in patients with MDD. A later meta-analysis investigating the impairment of executive function in patients with MDD suggested a significant correlation between the severity of depression and executive dysfunction[18]. Additionally, more severe

current depressive symptoms, rather than the duration of illness, contributed to impaired processing speed in unmedicated adult patients with MDD[2]. The above findings suggest that the severity of depression is a core risk factor for poor cognitive function during acute depressive episodes. However, the limited research focusing on individual depressive symptoms, rather than overall severity, has hindered the understanding of the relationship between depressive symptoms and cognitive performance in patients with MDD.

Anxiety symptoms are another critical factor to consider, as they are a common comorbidity in patients with MDD. A study revealed that up to 78.0% of patients with MDD met the criteria for "anxious distress specifiers"[19]. In addition, comorbid anxiety symptoms have been reported as a predictor of a poor prognosis of MDD, including poorer outcomes [20,21], higher rates of insomnia[22] and sleep problems[23], increased suicidal ideation[24] and attempts[25], and poorer psychosocial functioning[19]. Furthermore, previous findings also indicated a negative effect of comorbid anxiety on cognitive function[26-28]. Comorbid anxiety, especially psychic anxiety, is associated with poor executive function, attention deficit, lower processing speed, and memory loss in patients with MDD with "anxious distress"[29]. However, it is still unclear whether the impact of anxiety symptoms on cognitive function is direct or just mediated by specific factors. For example, comorbid anxiety was found to be predictive of both sleep disturbances and cognitive impairments, whereas some previous studies also reported that patients with insomnia performed poorer on various cognitive tests[30, 31]. Thus, the effect of sleep disturbances on the association of comorbid anxiety with cognitive impairments remains to be explored.

To investigate these unresolved issues, we explored the influence of different depressive and anxiety symptoms on cognitive impairments in medication-free patients with MDD during depressive episodes *via* a comprehensive battery of neurocognitive tests. We expected that the severity of sleep disturbances and other depressive symptoms would be positively correlated with the degree of cognitive impairment. We also hypothesized that anxiety symptoms, especially psychic anxiety symptoms, may be key factors in predicting cognitive performance in patients with MDD and may indirectly contribute to cognitive impairment by affecting sleep disturbances and other potential factors.

MATERIALS AND METHODS

Participants

A total of 162 patients with MDD were recruited from the inpatient and outpatient departments of Zhumadian Psychiatric Hospital (Henan, China), and 142 healthy controls were recruited from nearby communities from 2013 to 2018. All participants were aged between 18 and 55 years, were right-handed, and had at least 6 years of education. Additional inclusion criteria for patients with MDD were as follows: (1) Diagnosed with MDD by well-trained attending psychiatrists *via* the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, fourth edition; (2) Currently experiencing a major depressive episode, with a total score ≥ 20 on the 24-item Hamilton Depression Rating Scale (HAM-D_{24}); and (3) Not using psychotropic medications for at least 2 weeks (6 weeks for fluoxetine) before enrollment. Individuals with any other psychiatric comorbidities (except generalized anxiety disorder) or major physical illnesses, alcohol or drug abuse or dependence, a history of head injury or neurological illnesses, or color-blindness, pregnant and breastfeeding women, and individuals who had undergone similar neurocognitive assessments within the past 12 months were excluded.

This study was approved by the Medical Ethics Committees of the Second Xiangya Hospital of Central South University and the Zhumadian Psychiatric Hospital. All the participants signed written informed consent forms before study initiation.

Assessments

A self-designed demographic information form was used to collect demographic information, and a structured clinical interview was conducted to collect relevant information about the patients' medical conditions.

Depressive symptoms were evaluated *via* the HAM-D_{24}, which includes 7 dimensions: Psychomotor retardation (PR) (including 4 items: Depressed mood, work and activities, retardation symptoms, and genital symptoms), cognitive disturbances (including 6 items: Feelings of guilt, suicide, psychomotor agitation, depersonalization and derealization, paranoid symptoms, and obsessional symptoms), sleep disturbances (including 3 items: Early insomnia, middle insomnia, and late insomnia), anxiety/somatization (including 6 items: Psychic anxiety, somatic anxiety, gastrointestinal symptoms, general somatic symptoms, hypochondriasis, and insight), weight loss (including 1 item: Loss of weight), diurnal variation (including 1 item: Diurnal variation), and hopelessness (including 3 items: Helplessness, hopelessness, and worthlessness). Anxiety symptoms were evaluated *via* the 14-item Hamilton Anxiety Rating Scale (HAM-A), which includes the dimensions of psychic anxiety symptoms (including 7 items: Anxious mood, tension, fears, insomnia, intellectual symptoms, depressed mood, and behavior during the interview) and somatic anxiety symptoms (including 7 items: Somatic-muscular, somatic-sensory, cardiovascular, respiratory, gastrointestinal, genitourinary, and autonomic symptoms).

Executive functions, attention, processing speed, and memory were assessed *via* a comprehensive battery of neuropsychological tests[2,29]. Executive function was assessed *via* the digit span backward test from the Wechsler Adult Intelligence Scale-Revised (WAIS-R), the color-word interference condition of the Stroop test, the categories completed and preservative errors on the Wisconsin Card Sorting Test, Part B of the Trail-Making Task (TMT)-B, and the Semantic Verbal Fluency (animals) test; attention was assessed *via* the digit span forward test from the WAIS-R and the word condition of the Stroop test; processing speed was assessed *via* part A of the TMT-A and the color condition of the Stroop test; and memory was assessed *via* the Visual Memory Test, Intelligent Memory Test, and Associative Memory Test from

the Wechsler Memory Scale-Revised.

Statistical analysis

To group different subsets into different cognitive domains, raw scores were converted to standardized z scores, and the average composite z score was calculated as a measure for each domain. The z scores were calculated *via* the equation $X_{individual}$-$X_{controls}$/$\sigma_{controls}$, where $X_{individual}$ represents the raw score of each individual, $X_{controls}$ represents the mean score of the controls, and $\sigma_{controls}$ represents the standard deviation of the controls. This conversion was based on our previous research [29]. To standardize z scores across all subtests, we reversed scores for the subtests where lower raw values (TMT-A and perseverative errors on the WCST) indicated better performance. The internal consistency of different tests in each cognitive domain was assessed *via* Cronbach's alpha. All variables were tested for normality *via* the Kolmogorov-Smirnov test or Shapiro-Wilk test, and log or square root transformation was performed for variables that were not normally distributed.

Linear regression analysis was used to assess the impact of depressive and anxiety symptoms on cognitive function. Mediation analysis was also conducted to assess the associations between depressive and anxiety symptoms and each cognitive domain. The CI of the indirect effect was a bias-corrected bootstrapped CI based on 5000 bootstrap samples (BC CI). In this test, a significant indirect effect and a significant direct effect (with the CI excluding zero, $P < 0.05$) indicated partial mediation, and a significant indirect effect alongside a nonsignificant direct effect (with CI including zero, $P \geq 0.05$) indicated complete mediation. Mediators were defined as factors with a significant indirect effect (*i.e.*, with the CI excluding zero).

The level of statistical significance was set at $P < 0.05$ (two-tailed). All the statistical analyses were conducted *via* SPSS 24.0 software, and the mediation analyses were performed *via* Process Tool version 3.3.

RESULTS

Demographic and clinical characteristics

The demographic and clinical characteristics of the patients with MDD are presented in Table 1. The mean HAM-D score was 31.56 points, and the mean HAM-A score was 18.33 points, indicating that the patients experienced moderate-to-severe depression with obvious comorbid anxiety symptoms.

Impact of depressive symptoms on cognitive performance in the MDD group

The Cronbach's alpha values for executive function, attention, processing speed, and memory were 0.732, 0.655, 0.778, and 0.763, respectively, indicating high internal consistency of the tests for the four cognitive domains. Using regression models with the scores for the seven subdomains of the HAM-D as independent variables, sleep disturbance was found to be an independent factor for impaired executive function ($P = 0.004$), lower processing speed ($P = 0.047$), and memory loss ($P < 0.001$), whereas PR was an independent factor for lower processing speed only ($P = 0.019$) (Table 2).

The mediating effect of PR on the association between sleep disturbances and cognitive performance in the MDD group

Mediation analysis was conducted to investigate whether PR mediated the relationship between sleep disturbances and processing speed. In the mediation model, sleep disturbances, PR, and processing speed served as the predictor, mediator, and outcome variables, respectively, and PR partially mediated the effect of sleep disturbances on processing speed, as there was a significant indirect effect [β = -0.021, BC CI (-0.051, -0.002)] and a nonsignificant direct effect [β = -0.075, BC CI (-0.150, 0.0001)] (Table 3).

Impact of anxiety symptoms on cognitive performance in the MDD group

In regression models with psychic anxiety symptoms and somatic anxiety symptoms as independent variables, higher HAM-A scores for psychic anxiety symptoms were associated with poor executive function (β = -0.343, $P < 0.001$), attention deficit (β = -0.278, $P = 0.004$), lower processing speed (β = -0.215, $P = 0.025$), and memory loss (β = -0.238, $P = 0.012$); however, the HAM-A score for somatic anxiety symptoms was not associated with any cognitive impairment (all $P > 0.05$) (Table 4).

The mediating effect of depression severity on the association between anxiety symptoms and cognitive performance in the MDD group

To further investigate whether sleep disturbances mediate the effect of psychic anxiety symptoms on different cognitive domains, mediation analyses were conducted with psychic anxiety symptoms, sleep disturbances, and cognitive domains as the predictor, mediator, and outcome variables, respectively (Table 5). The results showed that sleep disturbances mediated the effect of psychic anxiety symptoms on executive function [β = -0.013, BC CI (-0.027, -0.001)] and memory [β = -0.149, BC CI (-0.237, -0.063)] but did not mediate the effect of psychic anxiety symptoms on processing speed [β = -0.018, BC CI (-0.042, 0.007)]. In the mediation model with psychic anxiety symptoms, PR, and processing speed as the predictor, mediator, and outcome variables, respectively, PR completely mediated the effect of psychic anxiety symptoms on processing speed (β = -0.023, BC CI (-0.045, -0.004)].

Table 1 Demographic and clinical characteristics of patients with major depressive disorder, mean (SD)

Characteristics	MDD (*n* = 162)
Age (years)	35.1 (9.55)
Male/female	72/90
Education (years)	10.45 (3.41)
Age of onset (years)	31.94 (9.71)
Number of episodes (*n*)	2.15 (1.51)
Total illness duration (months)	40.36 (50.64)
HAM-D score	31.56 (7.28)
Retardation	8.08 (2.94)
Cognitive disturbances	4.73 (2.32)
Sleep disturbances	4.13 (1.98)
Anxiety/somatization	6.44 (2.31)
Weight loss	0.86 (0.79)
Diurnal variation	1.07 (0.82)
Hopelessness	6.25 (2.26)
HAM-A score	18.33 (6.31)
Psychic anxiety symptoms	12.47 (3.52)
Somatic anxiety symptoms	5.76 (3.49)

MDD: Major depressive disorder.

DISCUSSION

This study investigated the impact of depressive and anxiety symptoms on cognitive functions during a depressive episode in patients with MDD *via* a comprehensive battery of cognitive assessments. Generally, the severity of depression has been regarded as the main risk factor for cognitive impairments. It has been reported that more severe current symptoms of depression are predictive of poor cognitive function[17,18]. The findings of the present study support this notion and further demonstrate that comorbid anxiety symptoms are also a risk factor for poor cognitive performance. Specifically, we found that not all depressive symptoms were linked to cognitive impairments, with only sleep disturbances being related to poor executive function, lower processing speed and memory loss. Additionally, PR was associated with lower processing speed and mediated the effects of sleep disturbances on processing speed. Comorbid anxiety is also regarded as a risk factor for cognitive impairment in patients with MDD[26-29]. Our study revealed that among all types of anxiety symptoms, psychic anxiety symptoms were associated with impairment in all four cognitive domains, whereas somatic anxiety symptoms showed no such associations. Sleep disturbances were found to mediate the effects of psychic anxiety symptoms on executive function and memory, whereas PR was found to mediate the effect of psychic anxiety symptoms on processing speed, indicating that the impact of comorbid anxiety symptoms on cognitive functions was mediated mainly by sleep disturbances and PR in patients with MDD. To our knowledge, this is the first study to explore the impact of depressive symptoms and comorbid anxiety symptoms on cognitive functions in patients with MDD, revealing that sleep disturbances might be a core predictor of poor cognitive performance and that PR might be a major influencing factor of lower processing speed during a depressive episode.

Sleep disturbances are among the most common symptoms of MDD; they usually appear before the onset of depression and persist during remission[32]. A three-year prospective study revealed that sleep problems were reported by approximately 85% of patients with MDD during major depressive episodes and 39% of patients with MDD during remission[33]. McClintock *et al*[34] reported that up to 94.6% of patients with MDD who failed to achieve clinical remission after 12 weeks of antidepressant treatment experienced residual sleep problems. Previous studies identified insomnia as a risk factor for MDD[35,36]. A meta-analysis suggested that individuals with insomnia are twice as likely to develop depression as those without sleep difficulties[37]. Moreover, a STAR*D report showed that insomnia was predictive of increased depressive symptom severity[36]. Insomnia also greatly impacts patients' cognitive functions. A recent meta-analysis on the impact of insomnia on cognitive function that included 48 studies revealed that both subjective and objective cognitive functions were significantly impaired in patients with insomnia[31]. By investigating the cognitive function of older adults with depression and sleep symptoms, Biddle *et al*[38] reported that poor sleep efficiency was associated with impaired executive function and decreased response speed but not with the severity of depression. On the basis of previous studies, the present study is the first to demonstrate that sleep disturbances predict poor cognitive performance and mediate the effect of comorbid anxiety on cognitive functions in patients with MDD.

Table 2 Results of multiple linear regression analyses for the impact of depressive symptoms on different cognitive domains

		β	*t*	*P* value	R^2	*F*	*P* value
Executive function	Retardation	-0.023	-0.850	0.396	0.096	20.31	0.029
	Cognitive disturbances	0.049	0.605	0.546			
	Sleep disturbances	-0.235	-20.94	0.004			
	Anxiety/somatization	0.076	0.901	0.369			
	Weight loss	-0.017	-0.215	0.830			
	Diurnal variation	-0.087	-10.10	0.273			
	Hopelessness	-0.086	-0.959	0.339			
Attention	Retardation	-0.01	-0.110	0.912	0.080	10.89	0.075
	Cognitive disturbances	0.113	10.37	0.172			
	Sleep disturbances	-0.256	-30.17	0.002			
	Anxiety/somatization	-0.028	-0.324	0.746			
	Weight loss	-0.008	-0.102	0.919			
	Diurnal variation	0.091	10.14	0.256			
	Hopelessness	-0.053	-0.585	0.560			
Processing speed	Retardation	-0.218	-20.37	0.019	0.095	20.30	0.029
	Cognitive disturbances	-0.006	-0.076	0.940			
	Sleep disturbances	-0.160	-20.00	0.047			
	Anxiety/somatization	-0.036	-0.428	0.670			
	Weight loss	-0.001	-0.015	0.988			
	Diurnal variation	0.083	10.05	0.297			
	Hopelessness	0.001	0.007	0.995			
Memory	Retardation	-0.113	-10.27	0.207	0.165	30.77	< 0.001
	Cognitive disturbances	0.067	0.843	0.401			
	Sleep disturbances	-0.352	-40.52	< 0.001			
	Anxiety/somatization	-0.045	-0.546	0.586			
	Weight loss	0.052	0.670	0.504			
	Diurnal variation	-0.062	-0.334	0.739			
	Hopelessness	0.047	0.542	0.589			

Table 3 Simple mediation analysis for the relationship between sleep disturbances and processing speed

Mediating variable (M)	Independent variable (X)	Dependent variable (Y)	X→M	M→Y	Indirect effect[1]	Direct effect[1]
Retardation	Sleep disturbances	Processing speed	0.204[a]	-0.105[b]	-0.021 [-0.051, -0.002][1]	-0.075 [-0.150, 0.0001]

[a]$P < 0.05$.
[b]$P < 0.01$.
[1]Significant point estimates ($P < 0.05$) as determined by the exclusion of zero from the confidence interval.

This may be due to the overlapping neural mechanism of sleep disturbances and cognitive impairments. It has been demonstrated that sleep disturbances are linked with 5-HT and glutamate abnormalities, as well as hypothalamic-pituitary-adrenal (HPA) axis dysfunction[39,40], and these abnormalities are also involved in changes in cognitive functions[41,42].

Another important finding of the present study is that PR may be a major influencing factor of lower processing speed. Specifically, PR not only is an independent influencing factor of lower processing speed but also mediates the effect of psychic anxiety symptoms on processing speed. PR encompasses a series of symptoms related to low energy, especially

Table 4 Results of multiple linear regression analysis for the effect of anxiety symptoms on different cognitive domains

		β	*t*	*P* value	R^2	*F*	*P* value
Executive function	HAMA-psychic symptoms	-0.343	-30.67	< 0.001	0.081	60.84	< 0.001
	HAMA-somatic symptoms	0.158	10.69	0.094			
Attention	HAMA-psychic symptoms	-0.278	-20.96	0.004	0.053	40.41	0.014
	HAMA-somatic symptoms	0.140	10.48	0.140			
Processing speed	HAMA-psychic symptoms	-0.215	-20.27	0.025	0.040	30.32	0.039
	HAMA-somatic symptoms	-0.027	0.282	0.778			
Memory	HAMA-psychic symptoms	-0.238	-20.54	0.012	0.060	50.03	0.008
	HAMA-somatic symptoms	-0.011	-0.116	0.908			

Table 5 Simple mediation analysis for the relationship between psychic anxiety symptoms and cognitive performance

Mediating variable (M)	Independent variable (X)	Dependent variable (Y)	X→M	M→Y	Indirect effect[1]	Direct effect[1]
Sleep disturbances	HAMA-psychic symptoms	Executive function	0.285[c]	-0.048	-0.013 [-0.027, -0.001][1]	-0.027 [-0.054, 0.001]
Sleep disturbances	HAMA-psychic symptoms	Processing speed	0.285[c]	-0.063	-0.018 [-0.042, 0.007]	-0.037 [-0.086, 0.012]
Sleep disturbances	HAMA-psychic symptoms	Memory	0.285[c]	-0.522[c]	-0.149 [-0.237, -0.063][1]	-0.075 [-0.232, 0.081]
Retardation	HAMA-psychic symptoms	Processing speed	0.241[c]	-0.097[a]	-0.023 [-0.045, -0.004][1]	-0.031 [-0.077, 0.014]

[a]$P < 0.05$.
[c]$P < 0.001$.
[1]Significant point estimates ($P < 0.05$) as determined by the exclusion of zero from the confidence interval.

psychomotor slowing. Although few studies have explored the relationship between PR and processing speed, it has been proposed that lower processing speed in patients with MDD might be related to psychomotor slowing[43-45]. Previous neuroimaging studies have shown that decreased processing speed may be attributed to prefrontal white matter hyperintensities and fronto-striatal disconnection[46,47], whereas white matter hyperintensity was found to be the structural basis of psychomotor slowing in individuals with late-life depression[48]. Functional magnetic resonance imaging studies have also reported that psychomotor slowing in individuals with depression is related to a decrease in BOLD signals in the dorsolateral prefrontal cortex, left prefrontal cortex, angular gyrus, and anterior cingulate cortex[49, 50]. The above evidence is in line with the neuroimaging findings on processing speed, which provides a basis for the association between psychomotor slowing and lower processing speed in patients with depression.

Unexpectedly, we did not find any significant independent influence of cognitive disturbances, anxiety/somatization, weight loss, diurnal variation, or hopelessness on the four cognitive domains. The subdomain of cognitive disturbances in the HAM-D_{24} is related mainly to "hot cognition" rather than neurocognitive function; however, the relationship between these two aspects of cognition is still unclear. The anxiety/somatization subdomain included 6 items: Psychic anxiety, somatic anxiety, gastrointestinal symptoms, general somatic symptoms, hypochondriasis, and insight. In the present study, anxiety symptoms (assessed *via* the HAM-A), especially psychic anxiety symptoms, were associated with broad cognitive impairments, but no such association was found regarding anxiety/somatization. We speculate that this may be related to the more detailed anxiety symptom information provided by the HAM-A, as this level of detail may aid in a more precise analysis of the specific links between anxiety symptoms and cognitive functions. Weight loss is also a common symptom for patients with depressive episodes. Hidese *et al*[51] reported that patients with MDD and obesity performed worse on working memory, processing speed, and executive function tests than did those without obesity. Nonetheless, there is still a lack of evidence to support that weight loss directly affects cognitive function in patients with MDD. Similarly, although previous studies have revealed an association between diurnal variation changes (related to the HPA axis) and global cognitive impairments in individuals of advanced age[52], as well as a relationship between suicidal ideation and cognitive dysfunction[53-55], there is still a lack of direct evidence in patients with MDD. Therefore, prospective studies and more specific assessment tools are needed to explore the factors affecting cognitive function. Despite the strength of our comprehensive assessment of the relationships among depressive symptoms, anxiety symptoms, and cognitive impairments in a relatively large sample of medication-free patients with MDD, two main limitations should be noted. First, the cross-sectional design of the present study makes it difficult to make accurate causal inferences; thus, prospective and longitudinal studies with larger sample sizes are needed. Second, the dimensions of depressive and anxiety symptoms included in the HAM-D_{24} provide only limited information, indicating the need for assessment tools for more specific symptoms (*e.g.*, the Insomnia Severity Index).

CONCLUSION

In summary, the present study investigated the impact of different depressive and anxiety symptoms on the cognitive functions of patients with MDD. These findings indicate that sleep disturbances and PR are responsible for cognitive impairments in patients with MDD during a depressive episode, which provides evidence for factors affecting cognitive performance in patients with MDD as well as potential targets for the treatment of residual cognitive symptoms. Our results suggest that sleep disturbances should receive more attention from patients with executive dysfunction and memory loss, whereas early intervention for PR symptoms is likely to benefit patients with lower processing speed.

FOOTNOTES

Author contributions: Li LJ and Liu J codesigned the study; Liu BS, Ju YM, Dong QL, Lu XW, Sun JR, Zhang L, Guo H, Zhao FT, Li WH, Zhang L, Li ZX, Liao M and Zhang Y were responsible for participant recruitment and data collection; Chen WT and Wang M performed the statistical analyses; Chen WT wrote the initial draft of the manuscript. Wang M and Wang HT made substantial revisions to the manuscript. All the authors have approved the final version of this manuscript. In this study, both corresponding authors provided critical guidance and supervision at different stages. Li LJ played a central role in the early stages of study design and project initiation, being responsible for the construction of the study concept and the overall supervision of manuscript writing. Liao M, on the other hand, provided crucial support in the later stages of the study, particularly during the revision process, where she was responsible for data analysis and made significant contributions to the revision and refinement of the manuscript. The contributions of both corresponding authors are complementary and indispensable, and their joint designation as corresponding authors is a fair reflection of their sustained contributions.

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