

ORIGINAL RESEARCH

# MicroRNA-135a and MicroRNA-221 in First-Episode and Recurrent Depression: Associations with Serum Markers and Cognitive Impairment

Zhenzhen Yang, MM; Yi Chen, MM; Wen Xu, MM; Xiaofei Sui, MM

## ABSTRACT

**Objective** • This study aimed to compare miR-135a and miR-221 levels among patients with first-episode depression and recurrent depression, examining their association with cognitive performance.

**Method** • A total of 97 first-episode depression patients, 104 recurrent depression patients hospitalized from April 2019 to December 2021, and 60 healthy individuals as a control group underwent cognitive function assessment using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). Serum inflammatory cytokine levels and miR-135a and miR-221 levels were measured. The correlation between miR-135a, miR-221, cognitive function, and inflammatory cytokines in depression patients was analyzed.

**Results** • Significant differences were observed in immediate memory, speech function, visual span, delayed memory, attention, and total RBANS scores among the three groups ( $P < .05$ ). Both first-episode and recurrent depression groups scored lower than the control group across all cognitive function measures ( $P < .05$ ), with the

recurrent depression group exhibiting lower scores than the first-episode depression group ( $P < .05$ ). Inflammatory markers (hs-CRP, TNF- $\alpha$ , IL-6) showed substantial variations among the groups ( $P < .05$ ). miR-135a and miR-221 levels significantly differed among the three categories ( $P < .05$ ). Correlation analyses revealed a negative association between miR-135a and IL-6, TNF- $\alpha$ , hs-CRP ( $P < .05$ ), and a positive correlation with cognitive function. MiR-221 demonstrated significant connections with inflammatory markers and negative correlations with immediate memory, verbal function, visual span, delayed memory, attention, and RBANS total score ( $P < .05$ ).

**Conclusion** • Patients with depression exhibit cognitive impairment, with recurrent depression associated with more severe impairment. The downregulation of miR-135a and upregulation of miR-221 may play a role in the cognitive impairment process by regulating inflammatory responses. The findings suggest a potential link between microRNA expression and cognitive dysfunction in depression. (*Altern Ther Health Med*. [E-pub ahead of print.]

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## INTRODUCTION

Depression, marked by persistent negative emotions, poses a significant public health concern due to its high prevalence and associated risks like suicide and disability.<sup>1</sup> Extensive research indicates that depression not only impacts emotional well-being but also profoundly influences cognitive processes such as attention, memory, and linguistic abilities.<sup>2,3</sup> Studies further suggest that individuals with persistent

depression experience more significant cognitive decline and heightened levels of inflammation compared to those experiencing their first-episode of depression. The severity of cognitive impairment appears closely linked to inflammation and recurrence frequency.<sup>4</sup> Inflammatory cytokines are critical mediators of the pathophysiology of cognitive dysfunction. Excessive release of inflammatory factors can hinder cerebral blood flow, damage nerve synapses, induce apoptosis of nerve cells, and impair patients' cognitive function.<sup>5-6</sup>

MicroRNAs (miRNAs) are crucial in regulating neuronal synaptic plasticity and immune and inflammatory responses. Scholars believe that abnormal miRNA expression is closely connected with neurological diseases.<sup>7</sup> Animal studies have shown that miR-135a<sup>8</sup> can alleviate depression in mice by inhibiting toll-like receptor 4 in the hippocampus; miR221 may promote the incidence and progression of depression by controlling the Wnt2/CREB/BDNF signaling axis.<sup>9</sup> The object of this study is to investigate the impact of miRNAs on

cognitive impairment in individuals with both first-episode and recurrent depression. This will be achieved by comparing the levels of miR-135a and miR-221 in the serum and evaluating their association with cognitive function.

## DATA AND METHODS

### Clinical Data

A total of 97 individuals experiencing their first-episode of depression and 104 individuals with a history of recurrent depression who were admitted to the hospital between April 2019 and December 2021 were selected for the study. In addition, 60 healthy individuals who underwent examinations during the same time frame were included as the control group.

### Inclusion and Exclusion Criteria

Criteria for participants with depression who were eligible to be included in the study included (1) individuals who met the diagnostic criteria of the 10<sup>th</sup> edition of the *International Classification of Diseases & Related Health Problems (ICD-10)* for depression, specifically those diagnosed with first-episode depression; (2) patients who have experienced an acute episode; (3) patients who have scored more significant than 20 points on the Hamilton Depression Scale (HAMD, 24 items), indicating mild or moderate depression, and  $\geq 35$  points indicating severe depression; (4) age range from 18 and 60; (5) hold at least a junior high school diploma; (6) patients who have not taken antidepressants, antipsychotics, or other medications that may affect cognitive function in the 2 weeks before enrollment; and (7) patients who voluntarily signed the study's consent form.

To be eligible for participation in the control group, participants were required to (1) have no history of mental illness with a HAMD score of less than 8 points; (2) be between the ages of 18 and 60; (3) have completed at least a junior high school education; and (4) not have a history of nervous system or other chronic diseases.

On the other hand, participants were excluded if they met any of the following criteria: (1) have mental disorders caused by drugs or organic diseases, (2) have disorders that affect brain function and structure, (3) or being a female during pregnancy or lactation.

### Assessment of Cognitive Function

The Repetitive Neuropsychological State Test (RBANS) scale includes 5 components: immediate memory, verbal function, visual span, delayed memory, and attention. The test consists of a total of 12 items. The score for each component was determined by referencing the original scores of the included items. The total score was obtained by summing up the scores of the five components. A lower score indicates poorer cognitive function in the subject.

RBANS was administered in accordance with standardized procedures. The test is widely recognized for its reliability and validity in evaluating cognitive performance across various domains. During the study, participants underwent the RBANS test as part of a comprehensive

cognitive assessment. The RBANS manual provides a detailed protocol for administration and scoring criteria. This well-accepted neuropsychological test has been utilized in diverse clinical and research settings to assess cognitive function across different populations.

### Detection of Serum Inflammatory Cytokines

In the morning, the researchers extracted 3ml of the fasting venous blood from each of the 3 groups. After separating the serum through centrifugation, the researchers identified the cytokines interleukin-6 (IL-6), tumor necrosis factor (TNF), and high-sensitivity C-reactive protein (hs-CRP), the study employed an enzyme-linked immunoassay (ELISA), a laboratory test to detect antibodies in the blood. The procedure strictly followed the instructions provided with the kit.

### Comparison of miR-135a and miR-221

Fasting venous blood samples (5 ml) were collected from participants in all 3 groups in the morning. The blood was collected in sterile test tubes without anticoagulant and then centrifuged at 4°C to separate the serum. The isolated serum was subsequently stored at -80°C until further analysis. To extract RNA, the samples were treated with TRIzol (Invitrogen, USA), and the purity and concentration of the extracted RNA were assessed using a UV spectrophotometer.

The researchers used 20 µg of RNA to synthesize cDNA through an M-MLV reverse transcriptase (Takara, Japan) in a 20 µl reaction system. The serum miR-135a and miR-221 expressions were determined using real-time PCR with specific primers (refer to Table 1 for primer sequences). The PCR reaction conditions involved 40 cycles of denaturation at 95°C for 15 s, annealing at 65°C for 20 s, and extension at 75°C for 15 s. The  $2^{-\Delta\Delta C_t}$  method quantified the expressions of miR-135a and miR-221, with  $\beta$ -actin acting as the internal standard. Throughout the process, the researchers followed established protocols and implemented quality control measures to ensure accurate and reliable results.

### Statistical Analysis

Data processing and analysis were conducted using SPSS 25.0. An analysis of variance was employed to compare three groups of measurement data, and a *t* test was utilized for two groups. The enumeration data between the three groups were compared using the rank sum and chi-square tests. Statistical significance was considered if  $P < .05$ . No corrections for multiple comparisons were applied in this analysis.

**Table 1.** Primer Sequences

Primer	Sequence
miR-135a	Forward Primer: 5'-GCGCCGGTATGGCTTTTATTCCAT-3'
	Reverse Primer: 5'-GTCGTATCCAGTGCAGGGTCCGAGG-3'
miR-221	Forward Primer: 5'-GCTAGCGCTGATGTCGAAATGACT-3'
	Reverse Primer: 5'-TACCTGTGGCGCAACGTGTACGCAT-3'
$\beta$ -actin	Forward Primer: 5'-TGTCACCTTCCAGCAGATGT-3'
	Reverse Primer: 5'-GCTCAGTAACAGTCCGCCTAG-3'

**Table 2.** Comparison of General Data

Group	Number of Cases	Gender		Age (Years, ±s)	BMI (kg/m <sup>2</sup> , ±s)	Years of Education (Years, ±s)
		Male	Female			
First-episode Depression Group	97	45	52	30.42±6.08	23.52±2.11	12.96±2.26
Recurrent Depression Group	104	46	58	31.14±5.83	23.24±2.49	13.17±2.46
Control Group	60	27	33	30.29±6.028	23.21±3.02	13.18±2.83
F	-	1.191		0.518	0.432	0.225
P value	-	.551		.596	.650	.799

**Table 3.** Comparison of Cognitive Function of Three Groups of Subjects (Points, ±s)

Cognitive Function	First-episode Depression Group (n=97)	Recurrent Depression Group (n=104)	Control Group (n=60)	F	P value
Immediate Memory	81.39±10.95	71.61±12.72	99.05±12.55	94.747	.000
Speech Function	85.69±11.46	78.52±9.80	101.38±12.31	59.706	.000
Visual Span	89.84±11.20	80.84±9.84	92.83±12.30	26.883	.000
Delayed Memory	85.87±10.92	75.28±11.35	101.40±10.95	89.893	.000
Attention	97.26±12.42	88.64±13.06	110.98±15.28	47.749	.000
Total RBANS Score	440.04±26.17	398.41±32.14	506.20±25.80	257.984	.000

**RESULTS**

**General Data Comparison**

Among the three groups, there were no appreciable differences in gender ( $P = .551$ ), BMI ( $P = .650$ ), age ( $P = .596$ ), or education ( $P = .799$ ) (Table 2).

**Cognitive Function Comparison**

The three groups exhibited notable variations in immediate memory, speech function, visual span, delayed memory, attention, and total RBANS scores ( $P < .05$ ). In comparison to the control group, both the first-episode and recurrent depression groups' scores demonstrated significantly lower scores across all cognitive function dimensions ( $P < .05$ ). Additionally, the recurrent depression group's scores on these dimensions seemed to be lower than those of the first-episode depression group ( $P < .05$ ) (Table 3).

**Inflammatory Cytokines Comparison**

The inflammatory factors IL-6, TNF-, and hs-CRP levels exhibited significant variations across the three categories ( $P < .05$ ). Both the first-episode (IL-6: 118.49±20.37; TNF-α: 5.22±1.41; hs-CRP: 9.87±1.62) and recurrent depression groups (IL-6, 134.56±19.28; TNF-α: 6.49±1.72; hs-CRP: 14.10±2.19) had higher index values than the control group (IL-6; 35.47±10.21; TNF-α: 2.81±0.69; hs-CRP: 2.27±0.64) ( $P < .05$ ). Additionally, the recurrent depression group had significantly higher indexes than the first-episode depression category group had noticeably higher indexes than the first-episode depression category ( $P < .05$ ) (Table 4).

**miR-135a and miR-221 Comparison**

The statistical significance of miR-135a and miR-221 was observed in the three groups ( $P < .05$ ). In comparison to the control group (1.049±0.221), miR-135a levels were significantly lower in the first-episode (0.792±0.115) and recurrent depression groups (0.544±0.083) ( $P < .05$ ). On the other hand, miR-221 levels were significantly higher in both the first-episode (2.237±0.354) and recurrent depression groups (3.174±0.336) compared to the control group

**Table 4.** Comparison of Inflammatory Cytokines among Three Groups (±s)

Group	Number of Cases	IL-6 (ng/L)	TNF-α (µg/L)	hs-CRP (mg/L)
First-episode Depression Group	97	118.49±20.37	5.22±1.41	9.87±1.62
Recurrent Depression Group	104	134.56±19.28	6.49±1.72	14.10±2.19
Control Group	60	35.47±10.21	2.81±0.69	2.27±0.64
F	-	329.390	91.368	430.101
P value	-	.000	.000	.000

**Table 5.** Comparison of miR-135a and miR-221 in Three Groups

Group	Number of Cases	miR-135a	miR-221
First-episode Depression Group	97	0.792±0.115	2.237±0.354
Recurrent Depression Group	104	0.544±0.083	3.174±0.336
Control Group	60	1.049±0.221	1.092±0.125
F	-	195.964	875.301
P value	-	.000	.000

**Table 6.** Correlation Analysis

Index		Immediate Memory	Speech Function	Visual Span	Delayed Memory	Attention	Total RBANS Score	IL-6	TNF-α	hs-CRP
		miR-135a	r	0.584	0.530	0.354	0.540	0.426	0.721	-0.687
	P value	.000	.000	.000	.000	.000	.000	.000	.000	.000
miR-221	r	-0.607	-0.573	-0.371	-0.642	-0.522	-0.806	0.792	0.644	0.861
	P value	.000	.000	.000	.000	.000	.000	.000	.000	.000

(1.092±0.125). Additionally, miR-135a levels were lower in the recurrent depression category compared to the first-episode depression category ( $P < .05$ ), while miR-221 levels were significantly higher.

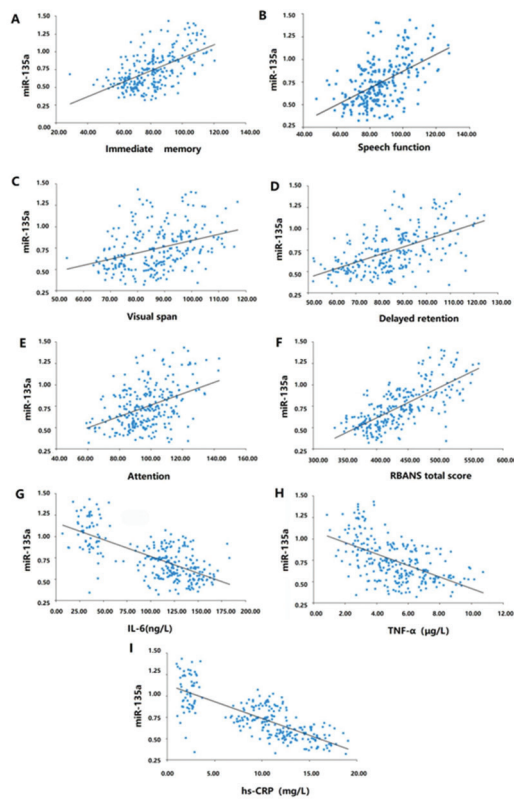
**Correlation Analysis**

MiR-135a correlated favorably with immediate memory, visual span, speech function, attention, delayed memory, and RBANS total score ( $P < .05$ ). On the other hand, it exhibited a negative correlation with IL-6, TNF-, and hs-CRP ( $P < .05$ ). In depressed individuals, IL-6, TNF-, and hs-CRP were found to be positively associated with miR-221 ( $P < .05$ ), while immediate function, visual span, delayed verbal function, memory, attention, and RBANS total score were negatively correlated with miR-221 (Table 6, Figure 1, Figure 2).

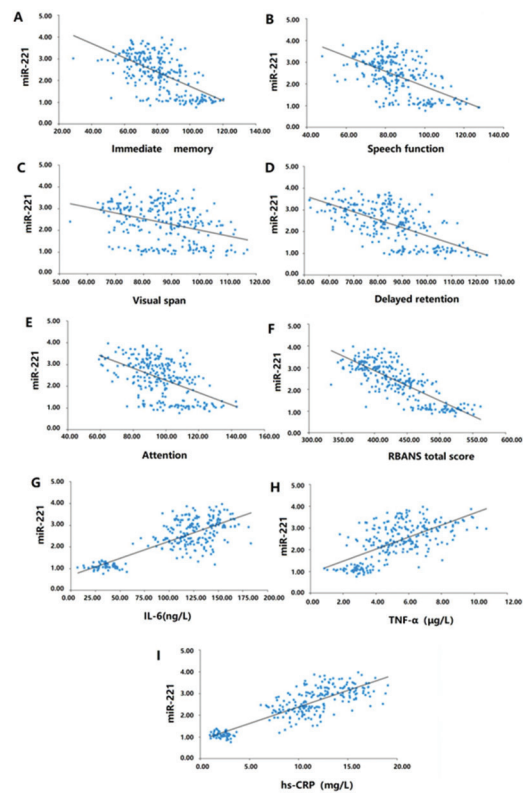
**DISCUSSION**

Depression is a condition that poses a significant threat to mental well-being, physical health, quality of life, and social function. Individuals with this illness experience feelings of sadness and often exhibit various levels of cognitive dysfunction in addition to emotional disorders.<sup>10</sup> Recent studies have indicated that individuals with depression frequently experience impairments in cognitive performance, memory retention, and information processing speed.<sup>11,12</sup> These impairments can persist throughout the entire duration of depression, even after the clinical symptoms have subsided. Consequently, researchers have increasingly focused on the cognitive impairment experienced by individuals with depression. While prior studies have predominantly examined either first-episode or recurrent depression, separately,<sup>13</sup> this study directly compared individuals with first-episode depression to those with recurrent depression.

**Figure 1.** Correlation Analysis of miR-135a with Cognitive Function and Inflammatory Cytokines. A: miR-135a was positively correlated with immediate memory,  $r = .584, P = .000$ ; B: miR-135a was positively correlated with speech function,  $r = .530, P = .000$ ; C: miR-135a was positively correlated with visual span,  $r = .354, P = .000$ ; D: miR-135a was positively correlated with delayed memory,  $r = .540, P = .000$ ; E: miR-135a was positively correlated with attention,  $r = .426, P = .000$ ; F: miR-135a was positively correlated with an RBANS total score of:  $r = .721, P = .000$ ; G: miR-135a was negatively correlated with IL-6,  $r = -0.687, P = .000$ ; H: miR-135a was correlated with TNF- $\alpha$  was negatively correlated,  $r = -0.545, P = .000$ ; I: miR-135a was negatively correlated with hs-CRP,  $r = -0.772, P = .000$ .



**Figure 2.** Analysis of Correlation Between miR-221 with Cognitive Function and Inflammatory Cytokines. A: miR-221 was negatively correlated with immediate memory,  $r = -0.607, P = .000$ ; B: miR-221 was negatively correlated with speech function,  $r = -0.573, P = .000$ ; C: miR-221 was negatively correlated with visual span. Negative correlation,  $r = -0.371, P = .000$ ; D: miR-221 was negatively correlated with delayed memory,  $r = -0.642, P = .000$ ; E: miR-221 was negatively correlated with attention,  $r = -0.522, P = .000$ ; F: miR-221 was negatively correlated with RBANS total score,  $r = -0.806, P = .000$ ; G: miR-221 was positively correlated with IL-6,  $r = 0.792, P = .000$ ; H: miR-221 was positively correlated with TNF- $\alpha$ ,  $r = 0.644, P = .000$ ; I: miR-221 was positively correlated with hs-CRP,  $r = 0.861, P = .000$ .



The findings of this study uncovered significant variations in immediate memory, speech function, visual span, delayed memory, attention, and total RBANS scores among the three groups. The scores of individuals with first-episode and recurrent depression were consistently lower across all cognitive function measures compared to those in the control group. Furthermore, the recurrent depression group displayed notably lower scores in all cognitive dimensions compared to the first-episode depression group. These findings support earlier studies<sup>14,15</sup> that suggest individuals experiencing both first-episode and recurrent depression exhibit diminished cognitive functions, including memory, language, and attention. Notably, patients with recurrent depression appear to have more severe cognitive impairments than those with first-episode depression. Consequently, it is crucial to pay closer attention to the

cognitive function impairments of patients during the clinical treatment of depression.

Research has consistently demonstrated that microRNAs (miRNAs) are abundantly expressed in brain tissue, with a primary expression in hippocampal tissue.<sup>16</sup> The miR-135a-5p molecule plays a pivotal role in promoting the growth of neural stem cells in the dentate gyrus, facilitating the regeneration of nerve cells. Simultaneously, it inhibits the synaptic nucleoprotein theory, exerting a neuroprotective function.<sup>17</sup> Scholars have reported positive effects of miR-135a in preventing the pathological aging of brain tissues, underscoring its significant diagnostic potential in conditions such as Alzheimer's disease and cognitive impairment.<sup>18,19</sup>

This study conducted a comparative analysis of miR-135a alterations in individuals with depression. The focus was on understanding its direct impact on patients' cognitive

function. The results indicated that miR-135a expression in both first-episode and recurrent depression groups was significantly lower than in the control category. Furthermore, within the depression cohorts, the recurrent depression category exhibited even lower miR-135a expression compared to the first-episode depression group. These findings suggest that miR-135a expression is inhibited in patients with depression. Further research indicates that the decrease in miR-135a may contribute to neuronal apoptosis and cognitive dysfunction, potentially representing one of the mechanisms underlying cognitive impairment in depression patients. Notably, the reduction in miR-135a expression was more pronounced in individuals with recurrent depression.

Another microRNA, miR-221, has diverse effects on biological processes. Studies have shown that when miR-221 is up-regulated, it stimulates oncogenes in various malignant tumor types. Overexpression of miR-221 has been linked to increased proliferation, invasion, and tumor growth in cancer cells.<sup>20,21</sup> Importantly, miR-221 is also implicated in both the occurrence and progression of depression.<sup>22</sup> The levels of miR-221 were significantly higher in both the first-episode and recurrent depression groups compared to the control group. Moreover, within the depression cohorts, the recurrent depression group exhibited significantly elevated miR-221 levels compared to the first-episode group. This suggests that individuals with depression have an overexpression of miR-221, with a more pronounced overexpression seen in those with recurrent depression. Overall, these findings emphasize the intricate regulatory roles of miR-135a and miR-221 in depression.

Moreover, the outcomes of the correlation analysis revealed noteworthy associations between miR-135a and cognitive function scores, indicating a positive correlation and an inverse relationship with inflammatory factor levels. Conversely, miR-221 exhibited a negative correlation with cognitive function scores while demonstrating a significant positive correlation with inflammatory factor levels in patients with depression. Previous studies have underscored the close connection between inflammatory cell levels and the severity of cognitive impairment in individuals with depression.<sup>23,24</sup>

In summary, patients with depression exhibited evident cognitive impairment, which was more pronounced in those with recurrent depression. The expression levels of miR-135a were inversely correlated with cognitive impairment, while miR-221 expression levels displayed a positive correlation. These findings suggest that the impact of miR-135a and miR-221 on cognitive function in depression patients may be linked to the modulation of pathways regulating inflammatory cells.

To elaborate further on these findings, it is essential to discuss the broader implications and clinical relevance of miR-135a and miR-221 in the context of depression. Such exploration will provide a deeper understanding of their potential roles as biomarkers or therapeutic targets, which may contribute to the overall understanding of the mechanisms involved in cognitive impairment associated with depression.

## CONCLUSION

Patients who suffer from depression often experience significant cognitive impairment, particularly those who have recurring episodes. The levels of miR-135a are inversely correlated with cognitive impairment, while miR-221 expression levels are positively correlated. These microRNAs may influence cognitive impairment processes by regulating inflammatory responses, affecting cognitive function. These findings underscore the importance of considering cognitive function in the clinical treatment of depression.

## AUTHOR CONTRIBUTIONS

Zhenzhen Yang and Yi Chen contributed equally to this work.

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