Relationship between symptom severity, glutamate levels, and *N*-methyl-D-aspartate receptor target microRNA expression in patients with panic disorder

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Background **Glutamate, an excitatory neurotransmitter in the central nervous system, plays a role in neurodevelopment, learning, and memory. It is thought to interact with the GABAergic system in the development of panic symptoms; however, the relationship between blood glutamate levels and panic disorder severity remains unclear. While research on miRNAs is increasing, studies on their role in panic disorder are limited. This study aimed to evaluate blood glutamate levels and the expression of miR-138-2-3p, which affects glutamate receptors, in panic disorder.**

Methods **The study included 46 panic disorder patients and 46 healthy controls. All participants completed sociodemographic, Panic Disorder Severity Scale (PDSS), Anxiety Sensitivity Index-3 (ASI-3), and Somatosensory Exaggeration Scale (SSAS) forms. Peripheral venous blood was collected for genetic and biochemical analysis. MicroRNA expression was assessed by real-time PCR, and glutamate levels were measured using ELISA.**

Results **Patients with panic disorder exhibited significantly lower plasma glutamate levels compared with healthy controls, with median values (25–75% percentiles) of 96.7 nmol/ml (51.39–133.62) versus 209 nmol/ml (95.6–521.9, $P < 0.001$). Moreover, glutamate levels were negatively associated with symptom severity as measured by the PDSS, ASI-3, and SSAS. In parallel, miR-138-2-3p expression was significantly reduced in patients relative to controls, with median ratios (25–75% percentiles) of 0.27 (0.14–0.57) versus 0.48 (0.23–0.98, $P = 0.034$), corresponding to a 1.77-fold higher expression in controls.**

Conclusion **Altered miR-138-2-3p expression and reduced peripheral glutamate levels may contribute to the pathophysiology and clinical severity of panic disorder.** ***Psychiatr Genet*** **35: 171–176**

Psychiatric Genetics 2025, **35**:171–176

Keywords: glutamate, microRNA, panic disorder

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Received 28 June 2025 **Accepted** 8 October 2025.

Introduction

Panic disorder is characterized by recurrent panic attacks, intense fear, and anticipatory anxiety (Torpy *et al*., 2011). Its lifetime prevalence is 2–5% (Kaplan & Sadock, 2005), and it has the highest familial inheritance among anxiety disorders (Baxter *et al*., 2013). Several neurotransmitters are involved in panic disorder, including glutamate, the brain's primary excitatory neurotransmitter. Glutamate is known to affect neurodevelopment, learning, and memory, and it is believed to interact with the GABAergic system in panic symptom formation (Hettema *et al*., 2001). Evidence suggests glutamatergic neurotransmission plays a role in stress and anxiety responses, making it a potential target for new treatments (Barkus *et al*., 2010).

Recent studies have focused on microRNAs (miRNAs), which regulate gene expression and have potential diagnostic and therapeutic roles in psychiatric disorders. While many miRNA studies were initially conducted on animals or postmortem samples, recent research has shifted toward human peripheral blood. miRNAs are increasingly recognized for their roles in neuron development and neurodegenerative conditions; however, their direct involvement in psychiatric disease etiology remains unclear (Martino *et al*., 2009; Im & Kenny, 2012).

Limited studies have explored miRNA expression in panic disorder. Some found upregulation of miRNAs regulating GABA-A genes, while others identified polymorphisms in miRNAs such as miR-22, miR-138-2, and miR-491 associated with panic disorder (Muiños-Gimeno *et al*., 2011; Kim *et al*., 2015; Çökmüş *et al*., 2019). This study aimed to assess glutamate levels and miR-138-2-3p expression in patients with panic disorder and healthy controls, exploring their relationship with disease severity. The hypotheses were: glutamate levels differ significantly between patients with panic disorder and controls; miR-138-2-3p expression is significantly altered in panic disorder; and both measures correlate with the clinical severity of panic disorder.

1473-5873 DOI: 10.1097/YPG.0000000000000402

Materials and methods

The study group size was determined using G-Power 3.1 software, α = 0.05, power = 80, and the number of participants was determined as 46 patients and 46 healthy volunteers. Panic disorder was diagnosed using the DSM-V Structured Clinical Interview. Conducted in psychiatry, medical biochemistry, and medical genetics laboratories, the study received ethical approval from the relevant institutional ethics committee (Approval for the research was received from the Clinical Research Ethics Committee of Balikesir University Faculty of Medicine on 30 March 2022, with the decision number 2022/53). All participants were thoroughly informed about the procedures and provided written consent.

The Sociodemographic Data Form, Panic Disorder Severity Scale (PDSS) (Shear *et al*., 1997), Anxiety Sensitivity Index-3 (ASI-3) (Taylor & Cox, 1998), and Somatosensory Exaggeration Scale (SSAS) (Taylor *et al*., 2007) were administered to all participants. Individuals with intellectual disability, pregnancy, severe head trauma, substance use disorder, psychotic disorders, bipolar disorder, moderate-to-severe depression or anxiety, neurological, oncological or autoimmune diseases, severe endocrinopathy, active infections, or immunosuppressant use were excluded.

Collection and evaluation of biological materials

Measurement of microRNA expression levels

MiRNAs were isolated from EDTA-anticoagulated venous blood of panic disorder patients and healthy controls using the SanPrep Column MicroRNA Mini-Prep Kit (SK8811). cDNA synthesis was performed in two steps using the miRNA All-In-One cDNA Synthesis Kit (G898). Real-Time PCR was conducted with Qiagen Rotor-Gene Q using BlasTaq 2X qPCR MasterMix (G891, G892). Each sample was analyzed in triplicate using U6-2 (MPH00001) and hsa-miRNA-138-2-3p (MPH02174). Gene expression was quantified with Rotor-Gene Q Software v2.3.4, normalized to Actin Beta (ACTB), and calculated using the $2^{-\Delta\Delta Ct}$ method. Ratios greater than 1 indicate upregulation and less than 1 indicate downregulation.

Glutamate (nmol/ml) level measurement

Blood samples from panic disorder patients and healthy controls were collected in EDTA tubes. After 10 min of centrifugation at 2000 rcf, the plasma supernatant was stored at -40 °C in Eppendorf tubes. Before analysis, samples were gradually thawed at +4 °C and room temperature. Glutamate levels were measured using the ELISA method with a Human Glutamate ELISA kit (Catalog No: 201-12-5405; SunRed Biotechnology, Shanghai, China), with a sensitivity of 2.358 nmol/ml and a range of 2.5–700 nmol/ml.

Statistical analysis

Data were analyzed using SPSS 25.0 (IBM, Armonk, NY, USA). Descriptive statistics are presented as number (*N*), percentage (%), SD, median (*M*), and percentiles. For nonnormally distributed data, median values and 25–75% percentiles were reported; normally distributed data are presented as mean and SD. An independent samples *t* test was used for normally distributed data, while the Mann–Whitney *U* test was applied for nonnormally distributed data. Spearman and Pearson correlation coefficients were used to assess relationships between quantitative variables, depending on the distribution. The χ^2 test was used for categorical data. Receiver operating characteristic (ROC) analysis was performed to evaluate the diagnostic performance of glutamate and miR138-2-3P, and the results were evaluated at a confidence interval of 95%, with significance at *P* less than 0.05. Fold changes were calculated using median values of $2^{-\Delta\Delta Ct}$ ratios.

Results

The study included 46 patients with panic disorder and 46 age- and gender-matched healthy controls. The mean age of the patients with panic disorder was 38.70 ± 9.33 years, while the mean age of the controls was 38.82 ± 11.42 years. Thirty-three (68.8%) were female and 15 (31.3%) were male. Of the control group, 34 (73.9%) were female and 12 (26.1%) were male; of the patients, 32 (69.6%) were female and 14 (30.4%) were male. No significant difference was found between the groups in terms of age or gender.

Of the 46 patients diagnosed with panic disorder, 10 (21.7%) were medication-free at the time of blood sampling, whereas 36 (78.3%) were receiving pharmacological treatment with selective serotonin reuptake inhibitors or serotonin–noradrenaline reuptake inhibitors.

Evaluation of glutamate (nmol/ml) levels and microRNA expression rates

The median value of the glutamate level in the patient group (25–75% percentile) was 96.7 (51.39–133.62), and the median value of the control group (25–75% percentile) was 209 (95.6–521.9). A statistically significant difference was found between the glutamate values of the patient and healthy volunteers ($P < 0.001$). The median value of the miRNA ratio in the patient group (25–75% percentile) was 0.27 (0.14–0.57), and the median value of the control group (25–75% percentile) was 0.48 (0.23–0.98). When evaluated statistically, significance was found between the patient and control groups in terms of miRNA ratios ($P = 0.034$). When the control group and panic disorder patients were evaluated in terms of miRNA fold change, it was found to be 1.77 times higher in controls.

When patients were divided into two groups as panic disorder accompanied by agoraphobia and panic disorder without agoraphobia, no significant difference was found in glutamate levels ($P = 0.419$), while a significant difference was found in miRNA ratios ($P = 0.042$) (Table 1).

Table 1 Glutamate levels and microRNA expression rates of patients according to the presence of agoraphobia

	Glutamate (nmol/ml), median (25–75% percentile)	*P* value
Patient group		
Agoraphobic (*N* = 25)	86.20 (69.90–123.20)	0.419
Nonagoraphobic (*N* = 21)	100.90 (83.37–138.95)	
	miRNA-138-2-3p, median (25–75% percentile)	*P* value
Patient group		
Agoraphobic (*N* = 25)	0.20 (0.14–0.43)	0.042
Nonagoraphobic (*N* = 21)	0.35 (0.17–0.82)	

miRNA, microRNA.

Table 2 Correlation between glutamate levels and scale scores

	Spearman correlation	Glutamate
PDSS	r_s	-0.404
	P	<0.001
PDSS-1	r_s	-0.352
	P	0.001
PDSS-2	r_s	-0.451
	P	<0.001
PDSS-3	r_s	-0.347
	P	0.001
PDSS-4	r_s	-0.295
	P	0.007
PDSS-5	r_s	-0.352
	P	0.001
PDSS-6	r_s	-0.369
	P	0.001
PDSS-7	r_s	-0.378
	P	<0.001
SSAS	r_s	-0.338
	P	0.002
ASI-3	r_s	-0.348
	P	0.001
ASI-3 physical	r_s	-0.367
	P	0.001
ASI-3 social	r_s	-0.355
	P	0.001
ASI-3 social	r_s	-0.327
	P	0.003

ASI-3, Anxiety Sensitivity Index-3; PDSS, Panic Disorder Severity Scale; PDSS-1, frequency of panic attacks; PDSS-2, stress during panic attacks; PDSS-3, severity of anticipatory anxiety; PDSS-4, agoraphobic fear/avoidance; PDSS-5, fear/avoidance of sensations associated with panic attacks; PDSS-6, impairment/disruption in work functioning due to panic disorder; PDSS-7, impairment/disruption in social functioning due to panic disorder; r_s, Spearman correlation coefficient; SSAS, Somatosensory Amplification Scale.

Correlation of glutamate (nmol/ml) values and microRNA expression rates with clinical characteristics of participants

When the relationship between the participants' glutamate levels and the PDSS, SSAS, and ASI-3 scale scores was analyzed using Spearman correlation analysis, a statistically significant negative correlation was observed (r_s = -0.404, $P < 0.001$; r_s = -0.338, $P = 0.002$; r_s = -0.348, $P < 0.001$) (Table 2).

When the relationship between the participants' miRNA ratios and PDSS was examined using Spearman correlation analysis, a statistically significant negative correlation was found (r_s = -0.258, $P = 0.018$), while no statistically significant correlation was found between the miRNA ratios and SSAS and ASI-3 scale scores, respectively (r_s = -0.084, $P = 0.452$; r_s = -0.189, $P = 0.087$) (Table 3) No statistically significant correlation was found between glutamate levels and miRNA ratios (r_s = -0.106, $P = 0.354$) (Table 3).

Receiver operating characteristic curve evaluation of glutamate (nmol/ml) and microRNA levels

ROC curve analysis determined the cut-off values for glutamate and miR138-2-3P based on statistically significant differences between patient and control groups. For glutamate, a sensitivity of 68.3% and specificity of 73.8% were found at a threshold of 126.5 nmol/ml. For miR138-2-3P, sensitivity was 63.4% and specificity was 62.8% at a cut-off of 0.36 (Table 4).

Discussion

This study investigated blood glutamate levels and miR-138-2-3p expression, a regulator of glutamate receptor activity, in patients with panic disorder. We found that glutamate levels were significantly lower in patients compared with healthy controls and were negatively correlated with symptom severity as measured by the PDSS, ASI-3, and SSAS. In addition, miR-138-2-3p expression was significantly reduced in patients, indicating coordinated alterations in glutamatergic signaling associated with panic disorder.

Panic disorder has been shown to have the highest familial inheritance rate among anxiety disorders, supporting a genetic etiology (Hettema *et al.*, 2001). Given the role of glutamate in modulating the GABAergic system and its involvement in the biological mechanisms underlying stress and anxiety-related disorders, this study aimed to investigate the regulation of target miRNA that acts on glutamate receptors, influencing glutamate levels and gene expression in patients with panic disorder and healthy controls. The study further aimed to explore the relationship between miRNA-138-2-3p expression, glutamate levels, and clinical severity in individuals diagnosed with panic disorder. We hypothesize that significant correlations exist between serum miRNA-138-2-3p expression, glutamate levels, and the severity of panic disorder. It is proposed that both glutamate and miRNA-138-2-3p believed to influence the *N*-methyl-D-aspartate (NMDA) receptor, play crucial roles in the pathophysiology and clinical presentation of panic disorder. These findings may provide a foundation for future research with larger sample sizes, contributing to the evaluation of miRNA-138-2-3p and glutamate as potential biomarkers and therapeutic targets in panic disorder.

Anxiety disorders, including generalized anxiety disorder, panic disorder, and specific phobias, are significantly more prevalent in women than in men (Hantsoo & Epperson, 2017). In our study, conducted with patients

Table 3 Correlation between microRNA ratios and scale scores

	Spearman correlation	miRNA
PDSS	r_s	-0.258
	P	0.018
PDSS-1	r_s	-0.216
	P	0.050
PDSS-2	r_s	-0.212
	P	0.055
PDSS-3	r_s	-0.265
	P	0.015
PDSS-4	r_s	-0.286
	P	0.009
PDSS-5	r_s	-0.203
	P	0.066
PDSS-6	r_s	-0.185
	P	0.094
PDSS-7	r_s	-0.225
	P	0.041
SSAS	r_s	-0.084
	P	0.452
ASI-3	r_s	-0.189
	P	0.087
ASI-3 physical	r_s	-0.255
	P	0.020
ASI-3 social	r_s	-0.233
	P	0.034
ASI-3 social	r_s	-0.113
	P	0.308

ASI-3, Anxiety Sensitivity Index-3; miRNA, microRNA; PDSS, Panic Disorder Severity Scale; PDSS-1, frequency of panic attacks; PDSS-2, stress during panic attacks; PDSS-3, severity of anticipatory anxiety; PDSS-4, agoraphobic fear/avoidance; PDSS-5, fear/avoidance of sensations associated with panic attacks; PDSS-6, impairment/disruption in work functioning due to panic disorder; PDSS-7, impairment/disruption in social functioning due to panic disorder; r_s, Spearman correlation coefficient; SSAS, Somatosensory Amplification Scale.

Table 4 Scale scores of the participants in the study

	Mean	SD
PDSS (patient group)	12.02	5.62
	Median (25–75% percentile)	
PDSS-1 (patient group)	2 (1–3)	
PDSS-2 (patient group)	2 (2–4)	
PDSS-3 (patient group)	2 (1–2.5)	
PDSS-4 (patient group)	1 (0–2.5)	
PDSS-5 (patient group)	1 (1–2)	
PDSS-6 (patient group)	1 (1–2)	
PDSS-7 (patient group)	1 (1–2)	

	Mean	SD	*P* value
SASS (patient group)	28.0	9.32	<0.001
SASS (control group)	14.09	4.17	
	Median (25–75% percentile)		*P* value
ASI-3 (patient group)	35 (22–48.50)		$P < 0.001$
ASI-3 (control group)	3.00 (0–6)		

ASI-3, Anxiety Sensitivity Index-3; PDSS, Panic Disorder Severity Scale; PDSS-1, frequency of panic attacks; PDSS-2, stress during panic attacks; PDSS-3, severity of anticipatory anxiety; PDSS-4, agoraphobic fear/avoidance; PDSS-5, fear/avoidance of sensations associated with panic attacks; PDSS-6, impairment/disruption in work functioning due to panic disorder; PDSS-7, impairment/disruption in social functioning due to panic disorder; SSAS, The Somatosensory Amplification Scale.

diagnosed with panic disorder at a psychiatry outpatient clinic, 75.6% were female and 24.4% male. Literature suggests that women more frequently seek psychiatric care due to physical symptoms of anxiety, whereas men present because of its social consequences (Sheikh *et al*., 2002). Although gender-based differences in the physical, cognitive, and social subdimensions of the ASI were not statistically significant in our sample, women exhibited higher subscale scores than men. This finding may reflect the limited sample size and gender distribution imbalance; statistical significance may emerge in studies with larger, more balanced samples.

A study in Korea examining miR-491 and miR-*22* polymorphisms in panic disorder patients with and without agoraphobia reported that the miR-*22* rs8076112C/rs6502892C and miR-491 rs4977831G/rs2039391G and rs4977831A/rs2039391A haplotypes were significantly more frequent in patients than in healthy controls. In addition, miR-*22* rs6502892 was significantly associated with ASI scores in the agoraphobic subgroup (Kim *et al*., 2015). In our study, miRNA expression levels were significantly higher in patients without agoraphobia compared to those with agoraphobia.

A statistically significant difference was found in our study between patients with panic disorder and healthy controls in terms of miRNA-138-2-3p expression rates, and the miRNA expression rate in patients with panic disorder was 1.7 times higher than in the healthy control group; however, miRNA expression rates were found to be below one in both the patient group and the control group, and it was interpreted that miRNA expression was downregulated in both groups. While the expression rate below one in healthy individuals and the patient group generally indicates decreased miRNA 138-2-3p activity, the relatively high expression rate in patients may indicate a possible irregularity in panic disorder.

A study investigating the association between disease severity and miRNA expression during sertraline treatment in patients with panic disorder found significant upregulation of miR-451a, miR-144-5p, miR-25-3p, and miR-660-5p, and downregulation of miR-1 and miR-148-5p posttreatment. Notably, changes in miR-25-3p were positively correlated with PDSS-3 and PDSS-7 scores (Min *et al*., 2019). In our study, miRNA expression levels were significantly higher in patients receiving active psychiatric treatment compared to those not receiving treatment, suggesting a regulatory effect of psychotropic medication on miRNA expression. This interaction may influence the clinical severity of panic disorder. PDSS items 3 and 4, assessing anticipatory anxiety and agoraphobic avoidance – core symptoms of panic disorder – along with item 7, showed a significant negative correlation with miR-138-2-3p in our sample.

Hsa-miR-4717-5p has been shown to strongly influence RGS2, a key regulator of G-protein-mediated signaling pathways implicated in fear and anxiety, and also targets two additional candidate genes for anxiety disorders, CNR1 and IKBKE (Hommers *et al*., 2015). In patients with generalized anxiety disorder, miR-4505 and miR-663 levels were found to be negatively correlated with total

hamilton anxiety rating scale (HAMA) scores (Chen *et al*., 2016). In our study, miR-138-2-3p expression showed a significant negative correlation with the physical and social subscales of the ASI-3, though no significant association was observed with total ASI-3 scores.

We investigated the expression of miRNAs targeting the glutamate receptor gene, along with plasma glutamate levels. miRNAs are known to regulate glutamate synthesis and receptor expression. For instance, miR-124 has been shown to influence synaptic plasticity and neuroprotection by targeting the GluR2 subunit of α-Amino-3-Hydroxy-5-Methyl-4-Isoxazolepropionic acid (AMPA) receptors (Hou *et al*., 2015). Similarly, miR-138 has been reported to regulate the expression of the NMDA receptor subunit NR2A (GRIN2A), a critical component of synaptic transmission and plasticity. miR-138 may also exert neuroprotective effects by modulating proteins involved in glutamate-induced excitotoxicity (Maza *et al*., 2022). Given these findings, it has been hypothesized that miR-138 may contribute to the pathophysiology of panic disorder through its role in glutamate signaling. Accordingly, our study examined the correlation between miR-138-2-3p expression and plasma glutamate levels, analyzing the patient group and the overall sample separately. No statistically significant association was identified in either group. To our knowledge, no previous studies have explored the relationship between peripheral glutamate levels and miRNA expression.

There are no studies specifically examining peripheral glutamate levels in anxiety disorders; however, existing studies on other psychiatric conditions, including major depressive disorder, schizophrenia, and autism spectrum disorder, have generally reported elevated peripheral glutamate levels in patient groups compared with healthy controls (Song *et al*., 2014; Zheng *et al*., 2016; Inoshita *et al*., 2018). In contrast, our findings indicate higher glutamate levels in the control group than in the patient group, diverging from the current literature. This discrepancy may be attributed to variability in neurotransmitter imbalances implicated in psychiatric disorders, as well as participant-related factors such as age, sex, biological differences, medication use, and comorbid conditions. Notably, psychotropic medication use was not an exclusion criterion in our study; including this in future exclusion criteria may yield more definitive results. Our study identified a statistically significant difference in glutamate levels between the patient and control groups, with higher levels detected in the control group ($P < 0.001$). A significant negative correlation was found between glutamate levels and PDSS scores. Similarly, glutamate levels were negatively correlated with SSAS and ASI-3 scores, suggesting that elevated glutamate levels may be associated with reduced panic disorder severity; however, it is important to consider that factors such as psychotropic and nonpsychotropic medication use, as well as comorbid physical illnesses, may influence glutamate levels. The diagnostic performance of glutamate and miR-138-2-3p levels was assessed using ROC analysis. Glutamate demonstrated a sensitivity of 68.3% and specificity of 73.48% at a threshold of less than 126.5 nmol/ml, while miR-138-2-3p showed a sensitivity of 63.4% and specificity of 62.8% at a threshold greater than 0.36. Although these findings suggest potential utility of glutamate and miR-138-2-3p as biomarkers, their diagnostic value may vary depending on the disorder and factors such as medication effects on miRNA expression. Further studies with larger samples and controlled confounding variables are warranted.

Several limitations should be acknowledged. Glutamate and miR-138-2-3p levels were measured peripherally, and their ability to accurately reflect central nervous system activity remains uncertain. Although participants with other psychiatric diagnoses were excluded, subthreshold symptoms of comorbid anxiety or depressive disorders may still have influenced miRNA expression. Medication use also represents a potential confounding factor, as most patients were receiving pharmacological treatment at the time of blood sampling. Moreover, the cross-sectional design limits causal inferences, and a larger sample size may have provided greater statistical power, potentially yielding more robust and generalizable conclusions. Collectively, these limitations highlight the need for future studies employing longitudinal designs, larger cohorts, and direct assessments of central nervous system biomarkers.

Conclusion

In conclusion, our study draws attention to the fact that changes in the levels of glutamate and miRNA-138-2-3p may be factors that contribute to the etiology of panic disorder and affect the clinical severity of the disorder. In this context, it is thought that future studies will encourage the study of miRNAs and glutamate in larger and different populations.

Acknowledgements

We would like to thank all participants who participated and contributed to the study.

This research project was supported by Balikesir University Scientific Research Projects Unit with project code 2022/054.

T.T.A. and N.D.: Concept and design. Ö.B., H.B., and A.S.A.: Materials, data collection or processing, and analysis or interpretation. T.T.A., N.D., and T.K.: Writing.

Approval for the research was received from the Clinical Research Ethics Committee of Balikesir University Faculty of Medicine on 30 March 2022 with the decision number 2022/53. During the implementation phase, the participants were briefly informed

about the purpose of the study, verbal and written consents were obtained from those who agreed to participate in the study.

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflicts of interest

There are no conflicts of interest.

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