

Research paper

High-Gamma: A biological marker for suicide attempt in patients with depression



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ABSTRACT

Background: Quantitative EEG (qEEG) analysis can be used to evaluate brain correlates of human psychology in all aspects. As the gamma oscillations of qEEG rhythms are related to depression, and particularly to treatment resistance, they may also be related to suicidality.

Aim: The present study aimed to identify the neural correlates of suicidal ideation and suicide attempt in depression using qEEG, based on the hypothesis that gamma rhythm in patients with depression would be higher in patients with suicidal ideation and suicide attempt.

Method: qEEG were recorded in 533 participants (276 female). Groups were divided into the following: Non-suicidal ($n = 218$), Suicide Ideation ($n = 211$), Suicide Attempt ($n = 74$), and control ($n = 30$). Results: High-gamma power at the F4, Fz, C4, Cz, O2, F8, T5 and T6 regions was significantly higher in the Suicide Ideation than the other groups.

Conclusion: If confirmed by further studies, high-gamma rhythm has the potential to be used as a biomarker for screening suicidality.

1. Introduction

Suicidal behavior is comprised of suicidal ideation, which means thinking about or planning suicide, and suicide attempt. Although it is well known that not all people with suicide ideation commit suicide, ideation is a significant predictor of suicide attempt and completed suicide. Therefore, predicting which patients with suicide ideation will attempt suicide is challenging in clinical practice and risk assessment solely based on clinical data may be misleading (Wetherall et al., 2018).

Quantitative EEG (qEEG) is computerized processing of digitally recorded EEG used to highlight specific waveform components (e.g. power or frequency) and transform the EEG into a numerical format that enables subsequent statistical analysis and comparison (Iosifescu et al., 2016). qEEG is a useful tool for evaluating neurophysiological changes and predicting mental states. qEEG analysis also helps in the classification of brain electrophysiology in symptomatic and asymptomatic individuals (Iosifescu et al., 2016).

Therefore, qEEG can also be used to evaluate brain correlates of suicidality. Lee et al. (2017) studied the neurophysiological biomarkers of suicide ideation in healthy individuals, using qEEG to examine the absolute and relative theta band of the frontal (Fp1, Fp2, F7, F3, Fz, F4,

and F8) and central midline electrodes (FCz and Cz). They reported that individuals with a high Beck Scale for Suicidal Ideation (BSSI) score had higher theta relative power at F3, Fz, FCz, and Cz than those with a low BSSI score. In addition, theta relative power in the frontocentral region was significantly higher in the high BSSI score group than in the low BSSI group. Likewise, BSSI score was the most powerful predictor of frontocentral theta power. These findings suggest that electrical activity in the frontocentral region might be associated with suicide ideation in young healthy individuals.

Previous studies reported that mental processes, in particular cognitive functions, are closely associated with the gamma rhythm (Danilova, 2008; Strelets et al., 2007). Gamma rhythm may particularly reflect perception, awareness, response to novelty, voluntary and involuntary attention, and memory (Danilova, 2008). A study on the spectral power and synchronization of the gamma rhythm during rest and task performance (arithmetic counting and spatial imagination) in healthy controls and patients with depression by Strelets et al. (2007) reported that gamma power in the frontal and temporal regions of the cortex was significantly higher in patients with depression than in controls. Moreover, resting state gamma rhythm power in patients with depression was higher in the frontal, anterior frontal, and temporal

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regions of the cortex symmetrically (Fp1, Fp2, F3, F4, T3, and T4), and in the central and parietal-temporal regions (C3 and T5) of the left hemisphere than in the controls (Strelets et al., 2007). In a recent study, we found that increased gamma activity was associated with lower response to paroxetine treatment in patients with depression (Arıkan et al., 2018a).

As the gamma oscillations are related to depression, and particularly to treatment resistance, they may also be related to suicidality. Literature especially lacks studies comparing patients with suicide ideation and suicide attempt. As such, the present study aimed to identify the neural correlates of suicide ideation and suicide attempt in patients with depression using qEEG, based on the hypothesis that gamma rhythm in patients with depression would be higher in patients with suicide ideation and suicide attempt and they also may help to identify patients who attempt suicide from those who only have ideations.

2. Materials and methods

2.1. Participants

This retrospective study included 533 participants (276 female and 257 male) whose data were obtained from the outpatient clinic database of Kemal Arıkan Psychiatry Center, Istanbul, Turkey. There were 503 patients aged (15–85) years diagnosed as depression that were divided into the following groups: Non-suicidal group ($n = 218$); Suicide Ideation group ($n = 211$); Suicide Attempt group (people with attempted suicide) ($n = 74$). The study also included a healthy control group ($n = 30$). The demographic characteristics of patients can be found in Table 1. All participants had undergone EEG recordings at their first appointment before starting any pharmacological treatment. Depression was diagnosed according to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) versions of 4 and 5. The patients were interviewed, assessed and qEEG was recorded at outpatient non-emergency settings. For all patients diagnosis was established after agreement between a psychiatrist and a clinical psychologist independently. The controls were diagnosis free.

Suicidal behavior in the patients was determined based on answers to clinical interview questions, including “not currently thinking about suicide”, “currently thinking about suicide”, and “already attempted suicide”. Then, items 2, 4, 7, 10, and 20 of the Beck Scale for Suicidal Ideation (BSSI) (Beck et al., 1979) were administered to the patients. According to interview question and BSSI item responses, the patients were divided into the 3 groups mentioned earlier. All patients were medication free at the time of qEEG acquisition. Patients with comorbid conditions, including epilepsy, organic mental disorders, mental retardation, neurological diseases, any other medical illness, and a history of head injury, were excluded from the study. However patients with psychiatric comorbidities were included. The study protocol was approved by the Uskudar University Ethics Committee.

2.2. Measures

All qEEG data were obtained in a quiet, dimly lit room. Participants sat calmly with eyes closed during the 7-min recording time. In all, 19

Table 1
Demographic characteristics of patients.

	NS	SI	SA	HC
Age (mean)	38,42	35,06	31,36	43,90
Gender(F-M)	107/111	109/102	45/29	15/15

(NS-non-suicidal, SI – Suicide Ideation, SA- Suicide Attempt, HC–Healthy Control)

$P < .001$ (ANOVA) - for age / $P = 0,378$ (Pearson X2) – for gender.

electrodes (FP1, FP2, F3, F4, F7, F8, C3, C4, P3, P4, T3, T4, T5, T6, O1, O2, Fz, Cz, and Pz) were placed on the scalp, based on the international 10–20 system. Linked mastoid electrodes (A1-A2) were used for reference during data acquisition. The data-sampling rate was 500 Hz, and the acquired signals were band-pass filtered at 0.15–70 Hz and notch filtered at 50 Hz. Data artifacts were manually eliminated off-line for each participant. Data were averaged across the recording epochs for each electrode, and the absolute power (percentage of total power) was computed for each of the following bands: delta (1–4 Hz), theta (4–7 Hz), alpha (8–12 Hz), alpha1 (8–10 Hz), alpha2 (10–12 Hz), beta (12–25 Hz), beta1 (12–15 Hz), beta2 (15–18 Hz), beta3 (18–25 Hz), high beta (25–30 Hz), gamma (30–50 Hz), gamma1 (30–35 Hz), gamma2 (35–40 Hz), high gamma (40–50 Hz). Neuroguide Deluxe v.2.5.1 (Applied Neuroscience, Largo, and FL) software was used for qEEG analysis.

2.3. Statistical analysis

Analyses were conducted using SPSS software, Version 24 (IBM Corporation, Armonk, NY, USA) Age of the participants was analyzed with using ANOVA, and gender was analyzed with using Pearson's chi-squared test.

In total, 19 qEEG channels x 14 frequency bands were analyzed via one-way ANOVA and α value for each p was set at .001. Alpha correction level was 0.001 instead of 0.005 to compute conservatively. Thus, the random differences were eliminated. As qEEG data were highly skewed, natural log-transformation was applied. In addition, some qEEG parameters were between 0 and 1, therefore 1 was added to qEEG parameters before natural log transformation. After the normality of data distribution was achieved one-way ANOVA was performed. Assuming that there will be no difference in variance between groups, Fisher's LSD test was used for post-hoc analysis. The level of statistical significance was set at $p < .001$ for post-hoc analysis. For post-hoc testing, if we had applied Bonferroni correction, we should have calculated the p value as $0.05/4 = .0125$ for each electrode. To follow a more conservative approach, we chose to use 0.001 as the significance threshold.

3. Results

According to Pearson's chi-squared test results, gender did not differ significantly between the 4 groups ($p > .05$). ANOVA results showed that the difference in age between the 4 groups was significant. Furthermore, post-hoc analysis showed that, the mean age in Non-suicidal group was significantly higher than Suicide Ideation and Suicide Attempt groups (respectively $p \leq 0.01$, $p < .00$) and lower than HC group ($p < .05$). For Suicide Ideation group the mean age was significantly higher than Suicide Attempt group ($p < .05$) and lower than Non-Suicidal and Healthy Control groups (respectively $p \leq .01$, $p < .01$). The mean age in Suicide Attempt group was lower than all groups (Non-suicidal, Suicidal Ideation and Healthy Control groups), respectively with p values of $p < .01$, $p < .05$, $p < .01$. Age was not used further as a covariate as we did not observe any significant correlation between age and the power values in electrodes showing significant groups difference. qEEG analysis showed that high-gamma absolute power differed between groups at 8 electrode sites (F4, Fz, C4, Cz, O2, F8, T5 and T6). As qEEG data were natural log transformed at the start of the analysis, they were plotted on a graph in 2 steps. First, exponential transformation was applied to the mean of all electrode regions' absolute power, and then 1 was subtracted (see Fig. 1). The electrodes showing significant between group difference on ANOVA were as follows F4 electrode site [$F(3, 529) = 6.22$, $p < .000$], the Fz electrode site [$F(3, 529) = 6.46$, $p < .000$], the C4 electrode site [$F(3, 529) = 6.31$, $p < .001$], the Cz electrode site [$F(3, 529) = 7.19$, $p < .000$], the O2 electrode site [$F(3, 529) = 5.62$, $p < .001$], the F8 electrode site [$F(3, 529) = 7.24$, $p < .000$], the T5 electrode site [$F(3,$

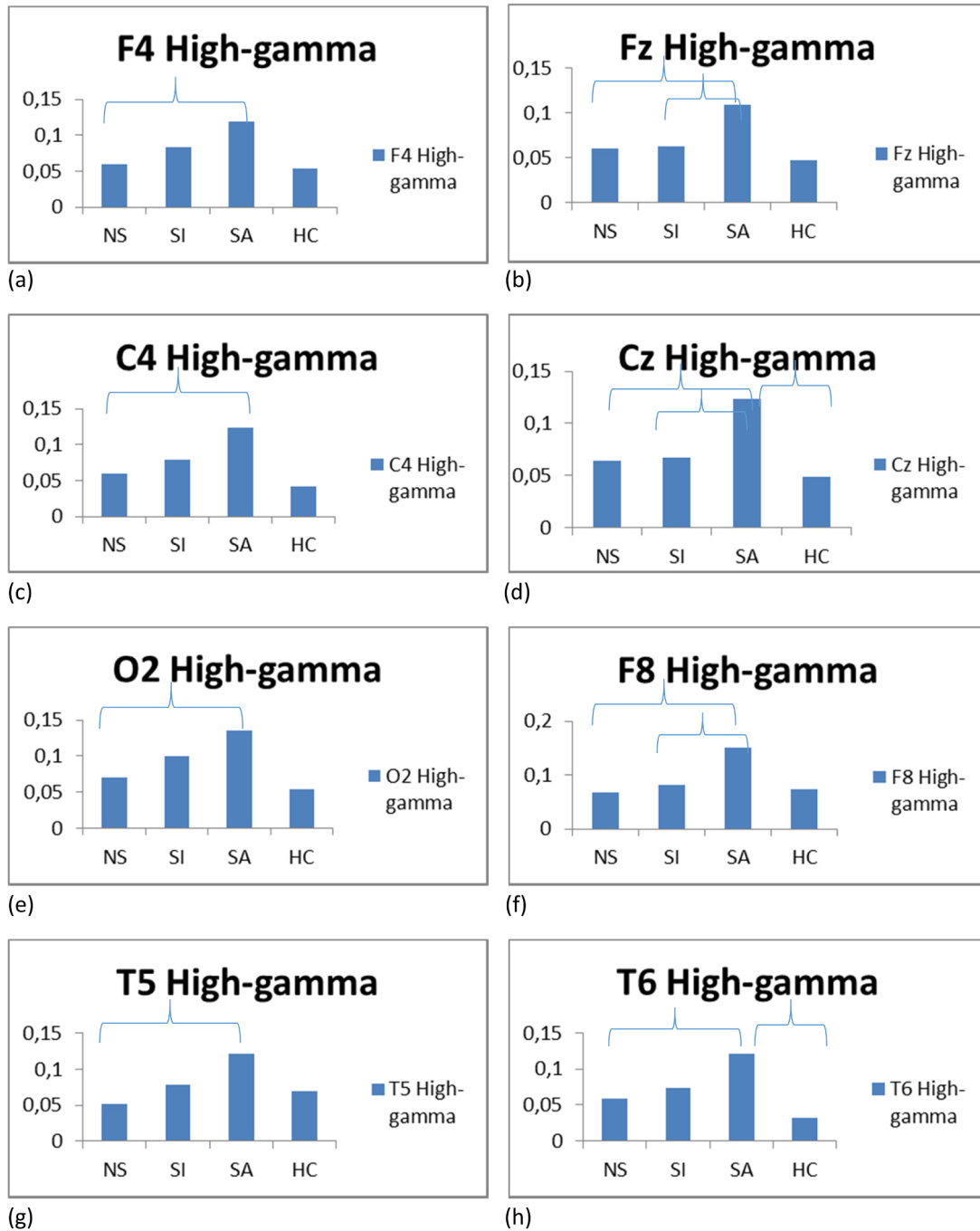


Fig. 1. Fisher's LSD post-hoc results for the different electrode sites according to group. (a) F4, (b) Fz, (c) C4, (d) Cz, (e) O2, (f) F8, (g) T5, (h) T6 . Brackets show significant pairs ($p < .001$).

529) = 5.84, $p < .001$], and lastly the T6 electrode site [F (3, 529) = 6.64, $p < .000$] (see Tables 2 and 3).

Post-hoc comparisons using Fisher's LSD test indicated that the mean high-gamma power at the F4 electrode in the Suicide Attempt group (0.11) was significantly higher than in the Non-suicidal group (0.06) (Fig. 1(a)). Moreover, mean high-gamma power at the Fz electrode in the Suicide Attempt group (0.10) was significantly higher than in the Non-suicidal group (0.06) and Suicide Ideation group (0.06) (Fig. 1(b)). Mean high-gamma power at the C4 electrode in the Suicide Attempt group (0.12) was also significantly higher than in the Non-suicidal group (0.06) (Fig. 1(c)).

On the other hand, mean high-gamma power at the Cz electrode was significantly higher in the Suicide Attempt group (0.12) than in the

Suicide Ideation group (0.07), control group (0.05) and Non-suicidal Group (0.06) (Fig. 1(d)). Mean high-gamma power at the O2 electrode, in the Suicide Attempt group (0.13) was significantly higher than in the Non-suicidal group (0.07) (Fig. 1(e)). Moreover, high-gamma power at the F8 electrode in the Suicide Attempt group (0.14) was significantly higher than in the Non-suicidal group (0.06), and Suicide Ideation group (0.08) (Fig. 1(f)).

In the temporal region mean high-gamma power in the Suicide Attempt group at T5 (0.12) was significantly higher than in the Non-suicidal group (0.05) (Fig. 1(g)). Mean high-gamma power at T6 in the Suicide Attempt group (0.11) was also significantly higher than in the Non-suicidal group (0.06) and control group (0.03) (Fig. 1(h)).

Table 2
Back transformed High Gamma Power values for all electrodes.

Row Labels	NS	SI	SA	HC
C3-HighGamma	0,06	0,06	0,10	0,03
C4-HighGamma	0,06	0,08	0,12	0,04
Cz-HighGamma	0,06	0,07	0,12	0,05
F3-HighGamma	0,06	0,08	0,11	0,07
F4-HighGamma	0,06	0,08	0,11	0,05
F7-HighGamma	0,07	0,10	0,14	0,09
F8-HighGamma	0,06	0,08	0,14	0,07
FP1-HighGamma	0,10	0,13	0,15	0,08
FP2-HighGamma	0,09	0,10	0,12	0,14
Fz-HighGamma	0,06	0,06	0,10	0,05
O1-HighGamma	0,08	0,08	0,11	0,05
O2-HighGamma	0,07	0,10	0,13	0,05
P3-HighGamma	0,06	0,08	0,11	0,04
P4-HighGamma	0,07	0,08	0,12	0,06
Pz-HighGamma	0,07	0,08	0,12	0,08
T3-HighGamma	0,06	0,09	0,10	0,07
T4-HighGamma	0,06	0,10	0,11	0,07
T5-HighGamma	0,05	0,08	0,12	0,07
T6-HighGamma	0,06	0,07	0,11	0,03

(NP-non-suicidal, SI – Suicide Ideation, SA- Suicide Attempt, HC–Healthy Control).

4. Discussion

Worldwide, suicide is a significant public health problem, with an estimated 1 million suicides annually. As such, suicidal behavior is a serious concern among all healthcare professionals (Da Silva et al., 2018). In this study, our aim was to identify neural correlates of suicidal behavior. The present findings show qEEG high-gamma power at several electrodes was different in the Suicide Attempt group than in the other groups. In the Suicide Attempt group high-gamma power at F4, Fz, F8, C4, Cz, O2, T5, and T6 was greater than in the Non-suicidal group. Furthermore, high-gamma power at Fz, Cz, and F8 differed significantly between the Suicide Attempt and Suicide Ideation groups. Suicide Attempt group has higher gamma power than Suicide Ideation group for high-gamma band in each electrode. Previous studies did not report gamma increases in patients with suicidal thoughts (Lee et al., 2017). However this may be due to the fact that gamma range is not frequently analyzed in EEG studies. These findings are clinically important for two reasons.

First, as suicide is the most feared consequence of depression, all clinicians must conduct a “suicide attempt risk” evaluation; however, most relevant instruments for assessing the risk rely on self-reporting. Although self-report scales should be included in the assessment of depression, they have some shortcomings. For instance, they lack sufficient sensitivity and specificity (Runeson et al., 2017), resulting in underrating of suicide ideation. Additionally, overrating of suicide ideation is problematic, as it unnecessarily increases the hospitalization rate and the cost of healthcare. Due to the difficulty in accurately detecting suicide ideation based on self-reporting, additional methods are needed to estimate the risk suicide attempt. Earlier research identified several suicide attempt risk factors, including a family history of suicide, the severity of depression, alcohol and cigarette use, a history of non-suicidal self-injury, hopelessness (Cassidy et al., 2017), borderline personality disorder, and post-traumatic stress disorder (Mellesdal et al., 2015). As compared to the Suicide Attempt risk predictors described above, qEEG has the advantage of being objective. If further confirmed by prospective studies, the data suggest that high gamma power could be used as a marker to identify patients with suicidality.

Second, there is a growing number of studies such as (Wang et al., 2017) showing that there is a relationship between increased gamma

Table 3
ANOVA and post-hoc results of qEEG analysis.

ANOVA	P	Post-Hoc (Fisher's LSD)	P	
F4 High-Gamma	< 0.001	NS	SI	0.02327
			SA	0.00006
			HC	0.75555
			NS	0.02327
			SA	0.01709
			HC	0.15126
		SI	NS	0.00006
			SI	0.01709
			HC	0.00548
			NS	0.75555
			SI	0.15126
			SA	0.00548
Fz High-Gamma	< 0.001	NS	SI	0.74868
			SA	0.00006
			HC	0.45074
			NS	0.74868
			SA	0.00016
			HC	0.36225
		SI	NS	0.00006
			SI	0.00016
			HC	0.00149
			NS	0.45074
			SI	0.36225
			SA	0.00149
C4 High-Gamma	< 0.001	NS	SI	0.08310
			SA	0.00007
			HC	0.41628
			NS	0.08310
			SA	0.00604
			HC	0.09527
		SI	NS	0.00007
			SI	0.00604
			HC	0.00133
			NS	0.41628
			SI	0.09527
			SA	0.00133
Cz High-Gamma	< 0.001	NS	SI	0.73795
			SA	0.00002
			HC	0.44155
			NS	0.73795
			SA	0.00007
			HC	0.35058
		SI	NS	0.00002
			SI	0.00007
			HC	0.00087
			NS	0.44155
			SI	0.35058
			SA	0.00087
O2 High-Gamma	< 0.001	NS	SI	0.01903
			SA	0.00031
			HC	0.54047
			NS	0.01903
			SA	0.05324
			HC	0.07640
		SI	NS	0.00031
			SI	0.05324
			HC	0.00514
			NS	0.54047
			SI	0.07640
			SA	0.00514
F8 High-Gamma	< 0.001	NS	SI	0.24281
			SA	0.00001
			HC	0.77494
			NS	0.24281
			SA	0.00019
			HC	0.76945
		SI	NS	0.00001
			SI	0.00019
			HC	0.00933
			NS	0.77494
			SI	0.76945
			SA	0.00933

(continued on next page)

Table 3 (continued)

ANOVA	P	Post-Hoc (Fisher's LSD)	P		
T5 High-Gamma	<0.001	NS	SI 0.02571		
			SA 0.00005		
			HC 0.47328		
		SI	NS 0.02571		
			SA 0.01347		
			HC 0.69601		
		SA	NS 0.00005		
			SI 0.01347		
			HC 0.05797		
		Healthy controls	NS 0.47328		
			SI 0.69601		
			SA 0.05797		
		T6 High-Gamma	<0.001	NS	SI 0.17886
					SA 0.00007
					HC 0.22369
SI	NS 0.17886				
	SA 0.00263				
	HC 0.06039				
SA	NS 0.00007				
	SI 0.00263				
	HC 0.00037				
Healthy controls	NS 0.22369				
	SI 0.06039				
	SA 0.00037				

(NP-non-suicidal, SI – Suicide Ideation, SA- Suicide Attempt, HC–Healthy Control).

power and cognitive impairment. Wang et al. (2017) observed that patients with Alzheimer disease exhibited increased gamma rhythm power dominantly in the midline frontal, central-parietal, and occipital regions. Our previous studies showed that increased gamma was related to treatment resistance in depression and lack of insight in schizophrenia (Arıkan et al., 2018b). Interestingly, lack of insight could also be considered as a cognitive problem. All in all our results, together with the literature might indicate that cognitive problems could be the mediating factor between gamma oscillations and lack of insight, suicidality and resistance. However, this speculation needs to be tested in future studies.

5. Limitations and future directions

The present study has some limitations, including its retrospective design and the fact that only 5 items were used to evaluate suicidal behavior. Subsequent research would benefit greatly from use of standardized scales for evaluation of suicidal behavior. In addition, to validate the predictive value of gamma oscillations, longitudinal studies that include high-risk depressed individuals with a high BSSI score, a family history of suicide, bipolar disorder, and borderline personality disorder will be needed. Methodical screening and analysis of such populations using qEEG to predict suicide attempt risk may confirm the role of high gamma power as a biomarker for suicidal behavior. Current study merely shows that the individuals with a history of suicide attempt have increased gamma oscillations any strong claim on predictive power of gamma oscillations for suicide should be avoided. Nevertheless, subsequent studies may also show that gamma oscillations are a trait marker in depression as it has already been shown in one study analyzing evoked oscillations in patients with remitted depression (Shaw et al., 2013). In addition, there were differences between the mean age of participants in four groups. This difference arised mainly due to the retrospective design in which controlling for age is not possible. Such problems could be resolved again by employing a prospective design. Finally, the relationship between suicidal behavior and gamma should not necessarily implicate any causality and such correlations may also arise due to the common third variable

effects. For instance in a previous study we have observed that patients with increase gamma show diminished response to paroxetine treatment (Arıkan et al., 2018a). As such, the groups with suicidal behavior might also include more of individuals with treatment resistance and thus might have increased gamma. In addition, the individuals with suicidality might also have more severe depression and this could also be a confounding factor affecting the absolute power values. As stated above lack of insight and cognitive problems could be other mediators between depression and suicidality. The latent variables mediating the effect between gamma and suicidality should be assessed further in future studies

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Conflict of interest

The authors declare there are no conflicts of interest—financial or otherwise—related to the material presented herein.

CRedit authorship contribution statement

Mehmet Kemal Arıkan: Conceptualization, Data curation, Writing - original draft. **Mehmet Guven Gunver:** Formal analysis. **Nevzat Tarhan:** Conceptualization, Data curation. **Baris Metin:** Data curation, Writing - original draft.

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Supplementary materials

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