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Smoking affects global and regional brain entropy in depression patients regardless of depression: Preliminary findings

Halil Aziz Velioglu [a,b,1], Sultan Yıldız [c,d,1], Ece Ozdemir-Oktem [e], Seyda Cankaya [e], Anton Kjell Lundmark [f], Ahmet Ozsimsek [e], Lütfü Hanoglu [g], Burak Yulug [e,*]

[a] Center for Psychiatric Neuroscience, Feinstein Institute for Medical Research, Manhasset, NY, USA
[b] Functional Imaging and Cognitive-Affective Neuroscience Lab (fINCAN), Health Sciences and Technology Research Institute (SABITA), Istanbul Medipol University, Istanbul, Turkey
[c] School of Engineering and Natural Sciences, Istanbul Medipol University, Istanbul, Turkey
[d] Program of Neuroscience Ph.D., Graduate School of Health Sciences, Istanbul Medipol University, Istanbul, Turkey
[e] Department of Neurology, School of Medicine, Alanya Alaaddin Keykubat University, Alanya, Turkey
[f] Stockholm Region Health Care, Stenhamra Primary Care Center, Stockholm, Sweden
[g] Department of Neurology, School of Medicine, Istanbul Medipol University, Istanbul, Turkey

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ABSTRACT

Objective: This study examines the effect of smoking on global and regional brain entropy in patients with Major Depressive Disorder (MDD), aiming to elucidate the relationship between smoking habits and brain network complexity in depression.

Methods: The study enrolled 24 MDD patients, divided into smokers and non-smokers, from Alanya Alaaddin Keykubat University and Istanbul Medipol University. Resting-state fMRI data were acquired and processed. The complexity of neuronal activity was assessed using dispersion entropy, with statistical significance determined by a suite of tests including Kolmogorov–Smirnov, Student's t-test, and Mann–Whitney *U* test.

Results: The smoking cohort exhibited higher global brain entropy compared to the non-smoking group ($p = 0.033$), with significant differences in various brain networks, indicating that smoking may alter global brain activity and network dynamics in individuals with MDD.

Conclusion: The study provides evidence that smoking is associated with increased brain entropy in MDD patients, suggesting that chronic smoking may influence cognitive and emotional networks. This underscores the importance of considering smoking history in the treatment and prognosis of MDD. The findings call for further research to understand the mechanistic links between smoking, brain entropy, and depression.

1. Introduction

The brain is composed of topologically complex networks (Damoiseaux et al., 2006; van den Heuvel and Hulshoff Pol, 2010) with diverse functions (Laird et al., 2011). A brain network system contains linear and non-linear properties results from integrations, differentiations, feedback loops and regulatory mechanisms of brain (Lipsitz and Goldberger, 1992; Sokunbi et al., 2014). Brain signals and their variations are generated by individual neurons and their interactions over space and time. By utilizing functional segregation, the brain maximizes information transfer by extracting specialized information from neuron inputs (Cieri et al., 2021; Shew and Plenz, 2013). Simultaneously, it fosters correlations between different cell groups or brain regions through functional integration, ensuring the production of mutual information between these areas. The coexistence of these two systems indicates that the brain possesses a complexity capable of integrating information (Sporns et al., 2005). In other words, brain complexity can be defined as the difficulties faced in describing or predicting a brain signal (Lu et al., 2008; Sokunbi et al., 2014).

Entropy measures the randomness and predictability of brain signals, reflecting their non-linear properties (Wang et al., 2017). High entropy is indicating more irregularity while less entropy means high order and

* Corresponding author. Department of Neurology, School of Medicine, Alanya Alaaddin Keykubat University, Kestel Mahallesi, Üniversite Caddesi, No:80 PK:07425, Alanya, Turkey.
E-mail address: burak.yulug@alanya.edu.tr (B. Yulug).
[1] **Equal contribution:** These authors contributed equally to this work.

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less complexity using probability distributions. If the brain system has high entropy or irregularity, to predict the system states is impossible (Rostaghi and Azami, 2016a; Shannon, 1948). Generally, a loss of complexity, often associated with pathological conditions or aging, suggests diminished adaptability to environmental changes (Escudero et al., 2015).

Entropy analysis quantifies the complexity in the brain in a computational manner, while impaired brain complexity is associated with various mental disorders. Successful applications of entropy analysis in functional MRI signals have revealed insights into disorders ranging from schizophrenia (Sokunbi, 2014) to dementia (Wang, 2020). Notably, many of these disorders are characterized by altered brain entropy. For instance, several mental disorders have been associated with increased brain network entropy (Lin et al., 2019).

Major depressive disorder (MDD) is a devastating mental illness and a leading cause of morbidity and mortality worldwide (Moussavi et al., 2007). Evidence indicates that individuals with depression have decreased entropy in critical brain networks, and these changes are associated with specific clinical aspects (Lin et al., 2019). To be more specific, the severity of late life depression is negatively associated with increased entropy of the frontoparietal network activity suggesting the role of resting state temporal-spatial complexity in specific clinical aspects of depression. Interestingly, the same study also highlighted the role of decreased and increased entropy in networks implicated in affective processing (Lin et al., 2019).

It's notable how demographic elements influence the structural and functional changes in the brain associated with MDD (Ancelin et al., 2019; Cusi et al., 2012; Moussavi et al., 2007). Smoking, due to its involvement in both vascular and mental health disorders (Dalby et al., 2010), has received significant attention. Epidemiologically, there is a reported elevated prevalence of smoking among MDD patients (Boden et al., 2010; Chaiton et al., 2009; Taylor et al., 2014). But it remains a matter of debate if smoking, given the central stimulatory effects of nicotine, acts as a compensatory tool that potentially elevates mood and cognition in those with MDD. While nicotine's positive effects on mood and cognition are evident in healthy individuals (Stein et al., 1998), depression is distinct, involving metabolic and inflammatory elements. The combined effects of smoking might modify the trajectory of MDD, further compounded by both conditions being identified as cardiovascular disease risk factors (Dhar and Barton, 2016).

Research posits that depression might be intertwined with metabolic and vascular risk factors, especially those linked to neuroinflammation severity (Glassman and Shapiro, 1998; Katon et al., 2004; Nicholson et al., 2006). The overlap between high smoking prevalence in patients with mental health challenges and cardiovascular issues (Dhar and Barton, 2016)hints at a possible connection between neuroinflammation and MDD. Interestingly, while many studies suggest smoking is tied to depression, some have reported inconsistent outcomes, possibly due to nicotine's varied effects on nicotinergic receptors among healthy and depressed populations (Koob and Volkow, 2010; Li et al., 2016; Nestler, 2002; Volkow and Li, 2004).

To the best of our knowledge there is a scarce of functional data indicating a link between smoking and brain network alterations in MDD smokers. A good example is a recent novel work by Janes et al. revealing that nicotine normalizes dysfunctional cortico-striatal communication in unmedicated non-smokers with MDD (Janes et al., 2018). Recent findings highlighted that smoking induced noticeable alterations in brain entropy in healthy subjects, unrelated to its immediate vascular impact (Li et al., 2016). Notwithstanding these intriguing findings, there remains a gap in understanding the relationship between smoking and changes in brain entropy among MDD patients. This study aims to bridge that gap, focusing on computing both global and regional entropy values within specific brain networks for depressed patients, categorizing them based on their smoking histories.

2. Methods

2.1. Participants

Twenty-four individuals (Age Mean - SD: 28.33 ± 7.44; 6 Male) diagnosed with MDD were recruited from the Neurology and Psychiatry Department at Alanya Alaaddin Keykubat University and Istanbul Medipol University. According to the Center for Disease Control and Prevention (CDC) criteria for being smoker ("NHIS - Adult Tobacco Use - Glossary," n.d.), MDD patients were separated into smoker (Mean age ± SD: 28.18 ± 6.9 years; 2 males) and non-smoker (Mean age ± SD: 28.46 ± 8.15 years; 4 males) groups (Table 1). The study received approval from the local ethics committee (Ethical report: 10840098-772.02) for scientific research at Istanbul Medipol University, and all participants provided written informed consent. Inclusion in the study required participants to meet the criteria outlined in the Diagnostic and Statistical Manual, Fourth Edition (DSM-IV). Two experienced psychiatrists using the mini-international neuropsychiatric interview (Sheehan et al., 2010) further confirmed their diagnoses. Participants with cognitive impairments, a history of chronic or acute neurological diseases, or systemic illnesses were excluded. After these assessments, all participants underwent functional magnetic resonance imaging (fMRI) at the radiology department.

2.2. Image acquisition and data preprocessing

Resting-state fMRI of the patients was conducted using the Signa Explorer MR device (General Electric Company, United States). Once the patient was positioned and calibrated within the MR device, resting-state activity was captured for functional imaging. During this phase, patients were instructed to keep their eyes open and remain motionless. To minimize head movement, sponge pads were placed between the patient's temples and the coil. A pillow positioned under the legs helped reduce potential z-axis artifacts from leg movement.

The resting-state fMRI recording spanned approximately 12.5 min, capturing 255 vol with parameters set at TR 3000 ms, TE 30 ms, FA 90° (TR/TE: 3000/30 ms), FOV 256 x 256 × 156 mm (FH x AP x RL), voxel size 4 x 4 × 4 mm, flip angle 90°, and comprising 39 slices. The anatomical T1 sagittal section image parameters included 156 slices, with TR/TE set at 1/3.7, FOV 256 x 256 × 156 mm (FH x AP x RL), and the voxel size of 1 x 1 × 1 mm.

For the fMRI data analysis, we utilized the FMRIB FSL software tools on the Linux Mint 18.3 Sylvia operating system (version 6.0.0). The raw DICOM single slice images from the MR device were converted to NIFTI format using the dcm2niix command-line tool (version V1.0.20170724). The FSL "fsl_anat" script facilitated brain extraction. Preprocessing, which included image alignment to the center and motion correction, was executed collectively for all participants using the FSL FEAT tool. A high-pass filter with a time constant of 150 s was applied, targeting the 0.01–0.1 Hz frequency range typical of resting-state networks. The smoothing kernel FWHM was set at 5 mm.

ICA was conducted with the FSL "melodic" tool. To purge the functional data of artifacts -including those from body/head movement,

Table 1
MDD patient demographics.

MDD Patients	Smokers N = 11, 2M, 9F		Non-smokers N = 13, 4M, 9F		
	Mean	SD	Mean	SD	p value
Age (years)	28.2	6.89	28.5	8.15	0.929
HDRS	20.7	3.49	19.1	4.14	0.073
Duration of depression (months)	11.7	1.61	11.5	1.25	0.425
Average amount of cigarettes per day	13.2	3.52	–	–	–

N: Number, **M:** Male, **F:** Female, **SD:** Standard Deviation.

respiratory and cardiovascular origins, and device-dependent signal fluctuations- ICA components were manually labeled based on their time course, frequency content, and spatial distribution. Artifact-related ICA components were excised from the functional data via the FSL "fsl_regfilt" tool. Post-preprocessing, individual cleaned functional data was aligned to the MNI152 standard brain (Mazziotta et al., 1995) using the FSL "applywarp" tool, and the "dual_regression" tool was then used for time-series calculations based on the Schaefer parcellation map (Schaefer et al., 2018).

2.3. Complexity analysis of neuronal activity

For the complexity analysis of signals, we employed the "dispersion entropy (DE)" method. Dispersion entropy is an innovative approach grounded in Shannon entropy (Azami et al., 2017; Rostaghi and Azami, 2016b). Notably, it offers superior computational efficiency and remains robust even with the presence of noise in the signal (Liu et al., 2020). Compared to multiscale methods, this method provides a more reliable means to assess the underlying neuronal spatiotemporal variability (Liu et al., 2019, 2020).

Dispersion entropy reveals dispersion patterns using normal cumulative distribution function (NCDF). Every point of the signal $x_i = \{x_1, x_2, \ldots, x_N\}$ is mapped to number of class (c). The dispersion pattern series (z_i) is created by mapping with class (range from 1 to c).

$$z_i = round(c * y_i + 0.5)$$

Where c is class number and NCDF maps time series of signal into $y_i = \{y_1, y_2, \ldots, y_N\}$ from 0 to 1 (Azami et al., 2017; Rostaghi and Azami, 2016b).

The embedding dimension (m) is a sliding window length which is used to bin sequence z_i into dispersion patterns as $[z_i, \ldots, z_{i+m}]$. Time delay (τ) is defined as the step length of sliding window. After getting dispersion patterns, the probability "p" of each detected dispersion pattern to calculate the dispersion entropy:

$$EN = -\sum_{i}^{c^m} p_i \ln p_i$$

For reliable calculations, it is suggested that the number of potential dispersion patterns (c^m) should be smaller than length of the signal (Rostaghi and Azami, 2016b). For all analysis, we fixed the parameter m = 2, c = 6 and $\tau = 1$. It provides $c^m < L$ (L: length of the signal).

We first extracted time series in each of region of interests (ROI) using Schaefer 100 parcellation (Schaefer et al., 2018). The name list of ROIs was given in the supplementary documents Table S1.

Before proceeding with entropy calculations, the parceled time series were standardized using z-scoring. This z-score standardization brings the parceled data into a consistent range, ensuring uniformity (Gopal et al., n.d.; Koh et al., 2022). Such an approach is especially suitable for data that maintains a temporally invariant mean and standard deviation (Faskowitz et al., 2020).

For every participant, we computed the dispersion entropy (DE) for individual ROIs as well as larger brain networks. The entire brain was categorized into seven distinct networks based on the Yeo parcellation: these include the Default Mode Network (DMN), Control (CON), Somatomotor (SM), Visual (VIS), Dorsal Attention Network (DAN), Salience/Ventral Attention Network (VAN), and Limbic (Thomas Yeo et al., 2011). The mean DE values for these brain networks were derived by averaging the DE across all ROIs encompassed within each network.

2.4. Statistical analysis

Descriptive statistics and illness duration analyses were conducted using SPSS 21 (SPSS Inc., Chicago, IL, USA). We assessed the normality of continuous variable distributions using the one-sample Kolmogorov–Smirnov test. Means and standard deviations of these variables were also calculated. To compare the "non-smoker with MDD" and "smoker with MDD" groups, we employed Student's t-test, Mann–Whitney *U* test, Pearson $\chi 2$, and Fisher's exact test where suitable. A p-value less than 0.05 was deemed statistically significant.

For the analysis of DE values, we used an independent *t*-test in a Matlab environment. To correct for multiple comparisons in all entropy calculation phases, we applied False Discovery Rate (FDR) controls (Groppe, 2022).

3. Results

In this study, we compared smokers with major depressive disorder (MDD) to their non-smoking counterparts. The smoker group comprised 11 patients, with a mean illness duration of 11.73 ± 1.62 months and a mean age of 28.18 ± 6.90 years. The non-smoker group had 13 patients, averaging an illness duration of 11.3 ± 0.85 months and an age of 28.46 ± 8.15 years.

We observed no statistically significant differences between the groups concerning age (p = 0.92) or MDD duration (p = 0.42 However, we observed that Hamilton Depression Rating Scale (HDRS) scores were not statistically significant between smoker mean of HDRS 20.7 ± 3.5 and non-smoker 17.7 ± 4.27 groups (p = 0.073) suggesting an effect of smoking on the brain entropy regardless of depression average amount of cigarettes that were being smoked per day was 13.2 ± 3.52 (Table 1).

DE of each ROIs was calculated using parameters m = 2 and c = 6. Fig. 1 depicts the average DE values for the whole brain of both groups. Each subject's whole network entropy was derived by averaging DE across all individual ROIs. Notably, smokers displayed higher mean DE values for the entire brain following FDR correction (p = 0.033) (refer to Fig. 1 and Supplementary Table S2).

Fig. 2 displays significant differences and the average DE of each ROI between smokers and non-smokers, with a comprehensive list of these mean DE values in Supplementary Table S3. Our findings highlight elevated DE in several ROIs, specifically within the somatomotor, default mode network, dorsal attention network, control network, and salience/ventral attention network, for smokers.

The average DE for each resting-state networks across all subjects is presented in Fig. 3 and Supplementary Table S4. Higher DE values in the somatomotor, control, and dorsal attention network were observed in smokers compared to non-smokers. This suggests that neuronal activity in these regions for non-smokers is more regular (indicating less complexity) than in their smoking counterparts.

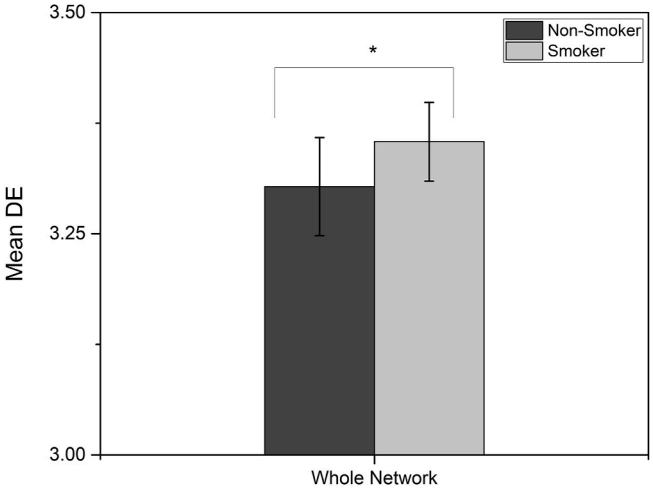

Fig. 1. The mean DE of groups of whole the network. Error bars and "*" represent standard deviation and significant differences respectively.

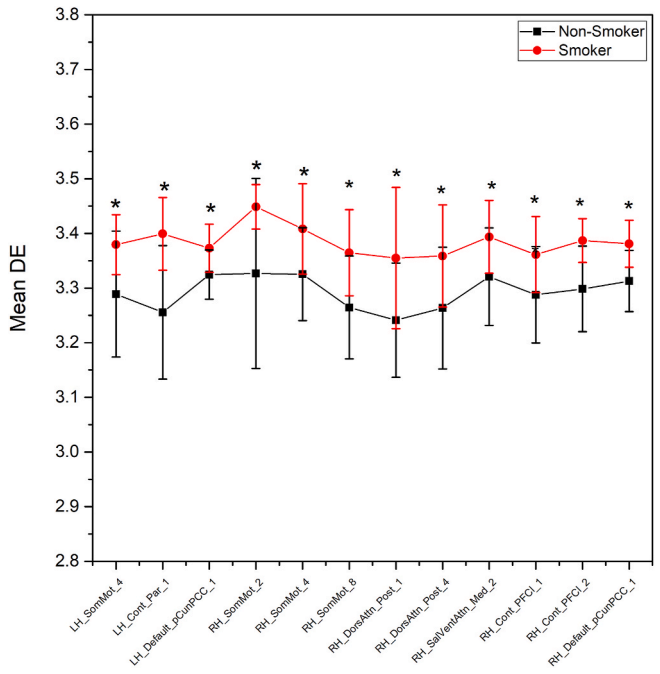

Fig. 2. Significant differences of DE between smoker and non-smoker groups at $p < 0.05$ after applying FDR correction. For details, see TableS3.

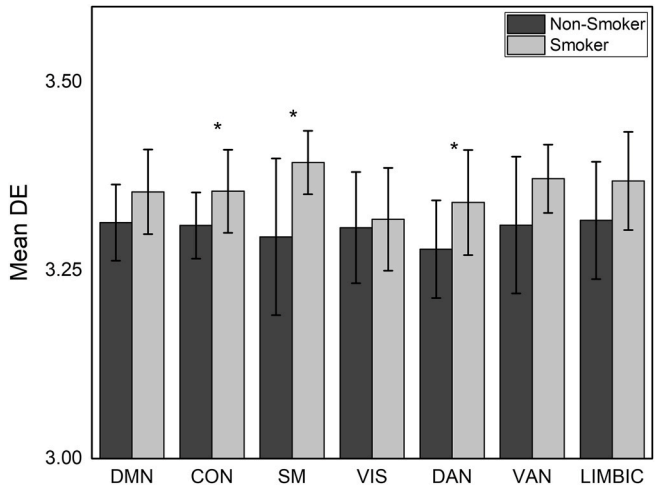

Fig. 3. The mean DE of each resting-state network across all groups. "*" represents significant differences between the groups at $p < 0.05$ after applying FDR correction. DMN, default mode network; CON, control network; SM, somatomotor; VIS, visual network; DAN, dorsal attention network; VAN, salience/visual attention network and LIMBIC, limbic. For details, see TableS4.

4. Discussion

The results of this study showed increased global and regional brain entropy in depressed patients with a history of smoking compared to those with no such history. Additionally, the study data showed that brain entropy was not associated with depression. Smokers exhibited globally increased brain entropy compared to non-smokers, demonstrating more irregularly fluctuating resting brain activity, reflecting a possible alteration of global brain activity due to chronic smoking. This may be related to the stimulatory effect of nicotine on endogenous nicotinic, dopaminergic, and glutamatergic receptors (nAchRs) (Koob and Volkow, 2010; Nestler, 2002; Ray et al., 2008). This may partly explain the ability of nicotine to alter several cognitive and emotional networks, including those involved in reward, mood, and attention (Benowitz, 2010; Koob and Volkow, 2010; Nestler, 2002; Ray et al., 2008; Volkow and Li, 2004).

It is also reasonable to conclude that chronic smoking may disrupt the functional dynamics and the integrity of skilled networks, leading to greater entropy in the resting brain. This is suggested by the fact that higher entropy indicates greater irregularity and inefficient coherence dynamics in the brain (Li et al., 2016; Sandler and Sandler, n.d.), although a recent study observed that increased global entropy was associated with successful antidepressant therapy in depression (Roy et al., 2021). Similarly, our results complement previous findings concerning the stimulatory role of smoking on cognitive networks (Knott et al., 2009) by revealing increased entropy in regional networks, especially those associated with attention and mood. However, on the contrary, a previous study showed that increased latent brain entropy among cognitively impaired patients compared to healthy individuals, suggesting a detrimental role of increased entropy in the development of mental illness, such as Alzheimer's disease (Wang, 2020).

Based on these findings, the lower entropic values in the non-smokers in the present study may indicate a beneficial effect of non-smoking on specific networks, facilitating the maintenance of adaptive network integrity, and suggesting a beneficial role of "balanced stability" (decreased entropy) in the brain. We therefore hypothesized that the decreased complexity in the non-smoking MDD group in the present study may reflect a healthy and already completed "ready to use" adaptive process capable of responding in a rapid and specific manner to unpredictable hazardous stimuli and of remaining healthy during depression. Considering the hazardous effects of smoking on brain network integrity (Jørgensen et al., 2015) it also appears reasonable to assume that this process can be potentialized through non-smoking in individuals with depression. As briefly described above, our findings may also indicate a dynamic entropy process, and that a final decreased entropy stage (and hence the stability of the healthier brain characterized by condensed networks) may be seen after a higher entropy stage consisting of creating more alternatives to any fixed internal or external consciousness states (such as rumination), (Dennis and Vander Wal, 2010; Deveney and Deldin, 2006; Friston et al., 2012) transiently associated with a successful period of antidepressant therapy in non-smokers. Such a potential different antidepressant response profile is suggested by our data showing no difference in terms of treatment type and duration between the groups.

Our study has several limitations. First, due to ethical concerns, all the participants were receiving antidepressant therapy at the time of data collection. It was therefore difficult to exclude a medication effect, although we found no differences in terms of duration of antidepressant therapy and response rates between the smoker and non-smoker groups, thus appearing to exclude potential bias related to antidepressant therapy. Similarly, an isolated effect of smoking on network integrity could not be evaluated (either in the form of changes to counter the effect of nicotine or self-adaptive changes to depression or medication). Another limitation is the lack of serum nicotine and metabolite collection, which would provide additional information on level/amount of nicotine exposure and how that affects brain connectivity in MDD that could be another area of future investigation. Our findings appear to suggest that smoking exhibited different effects among our MDD patients, where the effects of smoking were attributed to higher entropy values in specific brain networks regardless of depression severity. Despite the small sample size and lack of healthy group that could be considered as a limitation, the major strength of this pilot study that this study results provide preliminary evidence for a possible adaptive process in the non-smoker MDD group supporting to conduct a larger study including a control group.

In conclusion, our study reveals that entropy analysis is a more beneficial and dynamic approach than conventional imaging analysis methods since it provides more resting-state information regarding the temporal–spatial complexity network and hence adaptive variability in

combatting depressive states. Although the findings of the present study suggest a potential beneficial role of decreased entropy in non-smoking individuals with MDD, further longitudinal studies are now needed to confirm the existence of a mechanistic link between smoking, entropy, and depression.

Ethical approval

All methodologies employed in this research involving human subjects strictly adhered to the ethical guidelines established by both the institutional and national research committee. Furthermore, the study was conducted in full compliance with the principles set forth in the 1964 Helsinki Declaration and its subsequent amendments.

Informed consent

Written informed consent was secured from every participant included in this research.

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CRediT authorship contribution statement

Halil Aziz Velioglu: Writing – original draft, Visualization, Formal analysis, Conceptualization. **Sultan Yıldız:** Writing – original draft, Investigation, Formal analysis. **Ece Ozdemir-Oktem:** Methodology, Investigation, Data curation. **Seyda Cankaya:** Supervision, Investigation, Data curation. **Anton Kjell Lundmark:** Writing – review & editing, Writing – original draft, Supervision. **Ahmet Ozsimsek:** Investigation, Data curation. **Lütfü Hanoglu:** Writing – review & editing, Writing – original draft, Supervision. **Burak Yulug:** Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of competing interest

All contributing authors have declared no potential conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2024.07.002.

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