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Alterations of Cortical Thickness in High Suicidality Patients with Panic Disorder and Their Relationship with Symptomatology and Treatment Response

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Objective: Patients with panic disorder (PD) are approximately four times more likely to experience suicidal thoughts and attempts compared to healthy controls (HCs). Despite the elevated risk compared to HCs, the relationship between cortical thickness (CT) in PD and suicidality remains underexplored.
Methods: We recruited 161 right-handed participants, including 82 PD patients and 79 HCs, and assessed them using a comprehensive battery of psychological scales, including the Scale for Suicidal Ideation (SSI), Early Trauma Inventory Self Report-Short Form, Neuroticism-Extraversion-Openness Personality Inventory-Neuroticism (NEO-N), State-Trait Anxiety Inventory-Trait Anxiety (STAI-T), Panic Disorder Severity Scale (PDSS), and Beck Depression Inventory.
Results: In whole-brain vertex-wise group comparison, patients with PD demonstrated significantly lower CT values in the insula, lateral occipital sulcus, and precentral gyrus compared to HCs. Notably, paradoxical significant positive correlations were observed between SSI total scores and CT in the above-mentioned regions within the PD cohort. Pearson's correlation analyses further indicated that CT in these regions may be linked to high levels of early trauma, trait anxiety (e.g., NEO-N, STAI-T), panic symptom severity (e.g., PDSS), and treatment response in patients with PD.
Conclusion: This study suggest that suicidality in PD may be associated with CT in specific EFN regions related to suicidal brain and that CT in these regions could play a critical role in anxiety symptomatology in PD.

KEY WORDS: Panic disorder; Suicide; Fear; Neuroimaging; Treatment outcome.

INTRODUCTION

Suicide constitutes a critical public health concern, accounting for 1.4% of global mortality within the general population [1]. The Republic of Korea reported the highest suicide rate worldwide, with approximately 24.1 deaths per 100,000 individuals in 2020 [2], a figure that more than doubles the global age-standardized suicide rate [3]. Although suicidal ideation frequently arises in depressive states, the progression from ideation to suicide attempt is often precipitated by comorbid psychiatric conditions that exacerbate distress, such as anxiety disorders, including panic disorder (PD), or diminish inhibitory control, such as substance use disorder or personality disorders [4]. Given that suicidal behavior can manifest in the absence of a diagnosable psychiatric disorder, recent evidence supports the recognition of suicidal behavior as an independent diagnostic entity [5]. Notably, individuals with PD are at an elevated risk of suicide, even after controlling for major depression [6,7]. This underscores the necessity of elucidating the relationship between suicide risk and PD and implementing preemptive preventive

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strategies.

The heightened suicidality observed in patients with PD may be attributable to several factors, including pronounced anxiety symptoms, chronic social isolation due to avoidance behaviors, comorbid psychiatric disorders, and a history of early trauma [8]. Recurrent panic attacks can induce significant psychological distress, such as intense anxiety, fear, and a pervasive fear of death, thereby contributing to increased suicidality in PD patients [6]. Additionally, individuals with PD often avoid social interactions due to anticipatory anxiety, leading to increased social isolation, exacerbation of loneliness, and a subsequent rise in suicide risk [9]. Furthermore, a history of suicide attempts in PD patients is associated with poorer pharmacological treatment outcomes, emphasizing the importance of early identification and intervention for suicidality in this population [7].

From the neurobiological perspective, prior research has extensively explored the association between PD and an increased risk of suicide [10]. Neuroanatomical investigations employing structural and functional imaging have suggested that alterations in brain regions associated with mood disorders may be critical in understanding suicidality [11-13]. A review by Schmaal *et al.* [11] that summarized two decades of neuroimaging research on suicidality revealed neurobiological alterations in the ventral prefrontal cortex, dorsal prefrontal cortex, anterior cingulate cortex, insula, mesial temporal lobe, basal ganglia, thalamus, and posterior regions, including the cerebellum and lateral temporal cortex. Specifically, fronto-limbic anatomical abnormalities, including reduced gray matter volumes (GMVs) in the orbitofrontal cortex and amygdala, have been observed in highly suicidal patients with major depressive disorder (MDD) compared to healthy controls (HCs) [14]. We called the above-mentioned regions related to suicidality the "suicidal brain" across our study.

In addition, impairments within the suicidal brain network, notably the extended fear network (EFN)—encompassing the ventral and dorsal prefrontal cortex, insula, anterior cingulate cortex, temporal lobe, precuneus [11], and lateral occipital cortex [15]—may play a pivotal role in precipitating suicidal behavior [16]. Moreover, prior imaging studies in patients with PD have identified white matter hyperintensities in regions such as the internal capsule, splenium of the corpus callosum, superior and posterior corona radiata, thalamic radiations, sagittal stratum, and superior longitudinal fasciculus, which were correlated with elevated suicidality levels [17]. However, to date, no studies have investigated suicide-related neural correlates concerning cortical thickness (CT) in gray matter (GM) regions among patients with PD.

A recent structural connectome study reported that the EFN, potentially implicated in the suicidal brain in patients with PD, is linked to a history of early trauma [18]. In patients with PD who have a history of suicide attempts, white matter alterations in the suicidal brain—such as in the retrolenticular part of the internal capsule, posterior thalamic radiation, sagittal stratum, and superior longitudinal fasciculus—have been associated with depressive symptomatology [17] and showed poor short- and long-term pharmacological treatment responses [7]. Additionally, patients with affective disorders who have a history of suicide attempts demonstrate lower functionality compared to those without such a history [19] and their suicidal behavior reveals a significant correlation with higher trait anxiety [20] and neuroticism [21,22]. Therefore, it is crucial to assess the relationship between suicidal brain alterations, early trauma history, anxiety symptomatology, pharmacological treatment responses in patients with PD.

The present study aimed to evaluate CT differences in patients with PD based on suicidality levels. We hypothesized that: (1) significant differences in CT exist within suicidal brain-related GM regions between patients with PD and HCs; (2) these CT differences in suicidal brain-related GM regions are associated with suicidality in patients with PD; and (3) among patients with PD, there are significant correlations between CT in GM regions implicated in suicide and variables such as early trauma, anxiety symptomatology, pharmacological treatment responses.

METHODS

Participants

A cohort of patients diagnosed with PD was recruited from the Department of Psychiatry at CHA Bundang Medical Center, Seongnam, Republic of Korea, over a 10-year period between December 2013 and December 2023. HCs were recruited from the local community through a combination of online and print advertisements. Trained psychiatrists conducted individual inter-

views to confirm that HCs had no personal history of psychiatric disorders.

The study enrolled 161 participants, comprising 82 patients with PD (34 men and 48 women) and 79 HCs (37 men and 42 women). The diagnosis of PD was established according to the criteria specified in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition-Text Revision (DSM-5-TR), based on evaluations conducted by trained psychiatrists using the Structured Clinical Interview for DSM-5 [23]. Only individuals with a principal diagnosis of PD were included, even if they presented with comorbid depressive disorders. Exclusion criteria included the presence of: (1) major psychiatric comorbidities such as schizophrenia spectrum and other psychotic disorders, MDD with psychotic features, bipolar and related disorders, and substance-related and addictive disorders; (2) neurodevelopmental disorders; (3) neurocognitive disorders; (4) significant medical conditions; and (5) pregnancy.

All patients with PD received pharmacotherapy with antidepressants such as escitalopram, sertraline, or paroxetine (escitalopram equivalence dosage = 10.60 ± 8.30 [mean ± standard deviation] mg/day) [24] and benzodiazepine as alprazolam or clonazepam were primarily permitted on a *pro re nata* (as required) basis. Some patients with PD had pharmacological treatment with antidepressants according to the Korean Medication Algorithm for PD [25]. For evaluating pharmacological treatment response in PD, clinical assessments and interviews were conducted during each patient's visit to the hospital.

The study protocols were reviewed and approved by the Institutional Review Board of CHA Bundang Medical Center (IRB No. 2021-05-055). All procedures were conducted in accordance with the latest version of the Declaration of Helsinki and the principles of Good Clinical Practice. Written informed consent was obtained from all participants.

Suicidality Assessments

Suicidality, defined as the consideration, planning, or contemplation of suicide, is a key predictor of suicidal behavior, including attempts and completed suicide [26]. The Scale for Suicidal Ideation (SSI) was utilized as a self-report measure to quantify the degree of suicidality, assessing specific plans for suicide as well as active or passive suicidal desires [27]. The SSI consists of 19 items, each rated on a 3-point Likert scale ranging from 0 to 2, with total scores ranging from 0 to 38. Higher total scores indicate a greater risk of suicide. The SSI has demonstrated adequate internal consistency, with a Cronbach's alpha of 0.88 [28].

Other Clinical Characteristics Assessments

Trait anxiety was assessed using two established instruments: the Neuroticism-Extraversion-Openness Personality Inventory-Neuroticism (NEO-N) [29,30] and State-Trait Anxiety Inventory-Trait Anxiety (STAI-T) [31]. The NEO-N, a self-report measure, comprises 12 items designed to evaluate neuroticism and the propensity for experiencing negative emotions. This instrument demonstrates strong internal consistency, as indicated by a Cronbach's alpha of 0.93 [32,33]. Similarly, the STAI-T is a self-report instrument consisting of 20 items, scored on a 4-point Likert scale (1 to 4), yielding a total score ranging from 20 to 80. The STAI-T is widely regarded for its robust internal consistency, with a Cronbach's alpha of 0.87 [31,34].

Panic symptom severity was evaluated using the Panic Disorder Severity Scale (PDSS) [35,36]. The PDSS is a 7-item self-report scale, scored on a 5-point Likert scale from 0 to 4, designed to assess the severity of PD symptoms. These include the frequency of panic attacks, levels of distress, anticipatory anxiety, phobic avoidance, and impairment in both occupational and social functioning. The PDSS has demonstrated high internal consistency, with a Cronbach's alpha of 0.89 [37].

The Early Trauma Inventory Self Report-Short Form (ETISR-SF) was employed to assess early trauma experiences [38,39]. The ETISR-SF is a self-reported instrument consisting of 27 items that evaluate physical, emotional, sexual, and general trauma experienced before the age of 18. The ETISR-SF has shown good internal consistency, with a Cronbach's alpha of 0.86 [38].

The treatment response of patients with PD after the commencement of pharmacotherapy was assessed through the follow-up assessments of the PDSS at 8 weeks from the pretreatment baseline. We defined treatment response as a 40% or greater reduction in PDSS score after 8 weeks compared to baseline PDSS score before treatment.

The Korean version of the Beck Depression Inventory (BDI) consisted of 21 items to evaluate the severity of depression, revealing good internal consistency (Cronbach's $\alpha = 0.85$) [40]. The BDI was self-reported a 4-point Likert

measures, and the total scores ranged from 0 to 63 [41]. Based on previous findings depression has been frequently comorbid with PD, and the comorbidity has a greater impact on suicidality. We aimed to measure and control depression in our participants.

Neuroimaging Data Acquisition and Analysis

The CT across the entire brain of all participants was assessed using T1-weighted magnetic resonance imaging (MRI) images, processed via the surface-based pipeline of FreeSurfer (version 7.4.1; https://surfer.nmr.mgh.harvard.edu/). Brain MRI scans were performed on a 3.0 Tesla GE Signa HDxt scanner (GE Healthcare). Structural MRI data were acquired using a three-dimensional T1-weighted fast-spoiled gradient-recalled echo sequence with the following parameters: repetition time = 6.3 ms, echo time = 2.1 ms, flip angle = 12°, field of view = 256 mm, matrix = 256 × 256, and voxel size = 1 × 1 × 1 mm^3. The total MRI scan time for the FSPGR (GE) scan typically requires approximately 4 minutes and 37 seconds. A vertex-wise threshold of $p < 0.001$ (two-tailed) was used to define cluster-forming vertices. Cluster-wise significance was assessed with 10,000 Monte Carlo iterations, cluster-wise probability (CWP) < 0.05, and the surface smoothing kernel applied was 10 mm full-width half-maximum Gaussian. Data preprocessing adhered to FreeSurfer's standard protocol, ensuring proper registration, cortical parcellation, and subcortical segmentation. Cortical parcellation was performed automatically, dividing the cortex into 34 gyral regions per hemisphere using the Desikan-Killiany atlas [42]. The results underwent visual inspection for quality control, with no manual editing deemed necessary.

Statistical Analysis

Sociodemographic variables between patients with PD and HCs were compared using independent *t* tests and chi-square tests. Vertex-wise group comparison were conducted to examine the suicidal brain regions in patients with PD compared to HCs using FreeSurfer. To investigate the relationship between suicidality levels and structural neural correlates, vertex-wise correlational analyses were conducted. The analyses examined the association between SSI total scores and CT across whole brain regions, adjusting for age, sex, and intracranial volume (ICV) as covariates. We used ICV as the covariate, as ICV indexes inter-individual brain size and is less theory-confounded with disease-related regional CT alterations than global/mean CT [43,44]. Multiple comparisons were corrected using a Monte Carlo simulation, applying a CWP.

Regions exhibiting significant correlations with SSI total scores were further analyzed by extracting mean CT values. To address potential bias arising from the comorbidity of MDD, we conducted partial correlation analyses. In these analyses, the presence or absence of MDD were treated as covariates. Additionally, vertex-wise correlation analyses with covariates and multiple regression analyses were performed to control for potential confounders, including illness duration, benzodiazepine use (i.e. lorazepam dosage), and comorbid other anxiety disorders. Pearson's correlation analyses were conducted to assess the linear relationships between mean CT values in regions associated with suicidality and other clinical features (e.g., ETISR-SF, NEO-N, STAI-T, and PDSS) among patients with PD. Statistical significance was set at $\alpha = 0.05$. Moreover, multiple correlation comparisons were based on a false discovery rate (FDR < 0.05). All additional statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) for Windows, version 29.0 (IBM Co.).

RESULTS

Comparisons of Sociodemographic and Clinical Characteristics of Study Participants

Table 1 provides a detailed summary of the sociodemographic and clinical characteristics of the participants diagnosed with PD (n = 82) and HCs (n = 79). Patients with PD exhibited significantly elevated total scores on assessments, including the SSI, ETISR-SF, NEO-N, STAI-T, PDSS and BDI (all $p < 0.001$).

Comparison of CT between Patients with Panic Disorder and Healthy Controls

Figure 1 illustrates the comparison of CT between patients with PD (n = 82) and HCs (n = 79). In the left hemisphere, patients with PD demonstrated significantly reduced CT values predominantly in the insula and lateral occipital sulcus. In the right hemisphere, patients with PD exhibited significantly lower CT values in the lateral occipital sulcus and precentral gyrus (extending into the rostral middle frontal gyrus), compared to HCs. The peak

Table 1. Sociodemographic and clinical characteristics of participants

Variables	Patients with PD (n = 82)	HC (n = 79)	Statistics	
			t or χ^2	p value
Demographics				
Gender (men/women)	34 (41.46)/48 (58.53)	37 (53.84)/42 (46.15)	0.27	0.59
Age (yr)	35.70 ± 12.31	36.02 ± 9.33	0.13	0.89
Intracranial volume (ml)	1,463.95 ± 161.26	1,508.69 ± 125.22	−1.97	0.05
Suicidality				
SSI total score	7.51 ± 7.83	0.59 ± 1.01	7.43	< 0.001
Trait anxiety				
NEO-N total score	8.09 ± 3.04	4.41 ± 2.80	7.82	< 0.001
STAI-T total score	51.17 ± 11.04	34.41 ± 6.02	11.88	< 0.001
Panic symptom severity				
PDSS total score	13.05 ± 6.67	0.08 ± 0.42	17.56	< 0.001
Early trauma				
ETISR-SF total score	5.96 ± 6.05	2.75 ± 2.60	4.38	< 0.001
General	1.42 ± 1.44	0.79 ± 0.95	3.28	0.001
Physical	1.93 ± 1.73	1.34 ± 1.51	2.31	0.022
Emotional	2.09 ± 4.87	0.46 ± 1.00	2.97	0.004
Sexual	0.50 ± 1.04	0.15 ± 0.45	12.60	< 0.001
Depression				
BDI total score	17.79 ± 10.56	3.20 ± 3.14	11.90	< 0.001
Comorbid MDD without psychotic features	9 (10.97)	N/A	N/A	N/A

Values are presented as number (%) or mean ± standard deviation.
PD, panic disorder; HC, healthy control; SSI, Scale for Suicidal Ideation; NEO-N, Neuroticism-Extraversion-Openness Personality Inventory-Neuroticism; STAI-T, State-Trait Anxiety Inventory-Trait anxiety; PDSS, Panic Disorder Severity Scale; ETISR-SF, Early Trauma Inventory Self Report-Short Form; BDI, Beck Depression Inventory; MDD, major depressive disorder; N/A, not available.

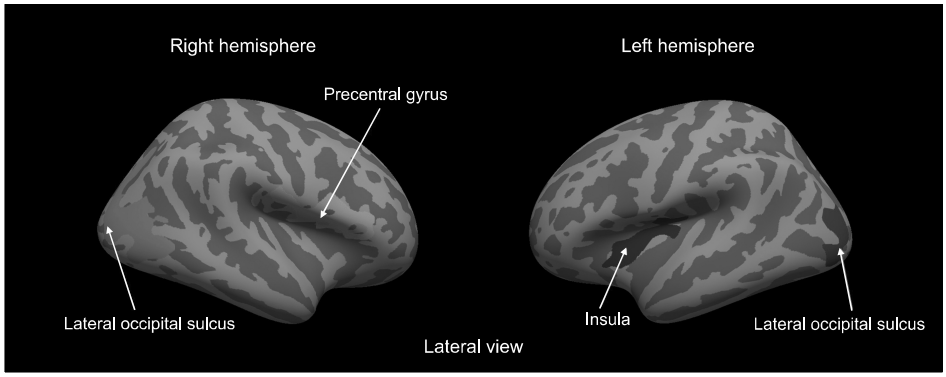

Fig. 1. Patients with panic disorder (n = 82) exhibited significantly reduced CT within the EFN compared to healthy controls (n = 79). Notable reductions in CT were observed in the insula (peak MNI coordinate [−35.0, 0.3, 4.9]; cluster size = 987.2 mm^2), lateral occipital sulcus (right peak MNI coordinate [35.3, −80.5, 2.5]; cluster size = 2,598.9 mm^2, left peak MNI coordinate [−29.4, −83.6, 4.4]; cluster size = 1,104.3 mm^2), and precentral gyrus (peak MNI coordinate [53.5, 0.3, 5.2]; cluster size = 1,999.1 mm^2) according to the Desikan-Killiany atlas. Cluster locations indicate the peak vertex within each cluster (peak MNI coordinates [x, y, z]).
CT, cortical thickness; EFN, extended fear network; MNI, Montreal Neurological Institute.

Montreal Neurological Institute (MNI) coordinates of the brain regions showing significant differences between the groups are detailed in Supplementary Table 1 (available online).

Relationship between Suicidality Levels and CT in Patients with Panic Disorder

Vertex-wise correlation analyses were conducted to explore the relationship between SSI total scores and CT in patients with PD (n = 82). As shown in Figure 2, significant

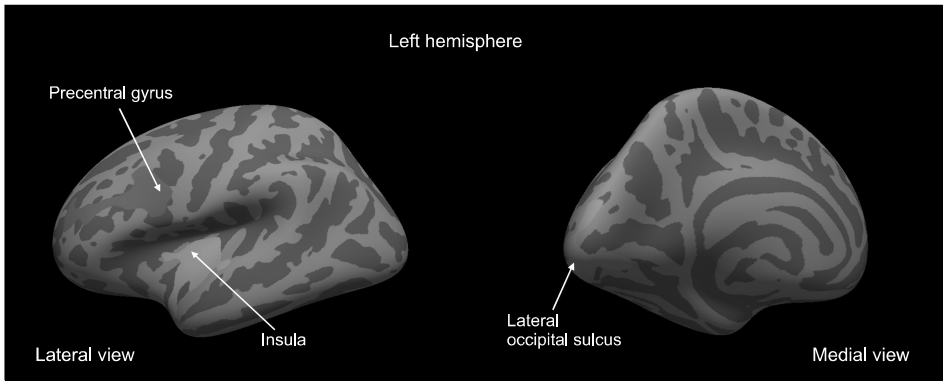

Fig. 2. Vertex-wise correlation analysis revealed a significant positive correlation between CT and suicidal ideation levels. In particular, CT in the precentral gyrus (peak MNI coordinate [−40.0, 2.1, 24.0]; cluster size = 1,448.8 mm^2), insula (peak MNI coordinate [−35.6, −21.6, −2.9]; cluster size = 1,284.0 mm^2), lateral occipital sulcus (peak MNI coordinate [−18.5, −95.1, −11.5]; cluster size = 1,803.2 mm^2) was significantly positively correlated with SSI total scores in patients with panic disorder (n = 82). Cluster locations indicate the peak vertex within each cluster (peak MNI coordinates [x, y, z]).
CT, cortical thickness; MNI, Montreal Neurological Institute; SSI, Scale for Suicidal Ideation.

positive correlations were identified in the insula, lateral occipital sulcus, and precentral gyrus (extended into the rostral middle frontal gyrus) in the left hemisphere (the suicidal brain regions in patients with PD). These correlations remained statistically significant after controlling for age, MRI scan duration, gender, and ICV. In addition, significance were also maintained in those regions after controlling for the potential confounders (e.g., presence or severity of comorbidity [i.e., other anxiety disorders], illness duration, and benzodiazepine use) in multiple regression analyses (Supplementary Table 2; available online). Supplementary Table 3 (available online) presents the peak MNI coordinates of the suicidal brain regions in patients with PD that exhibited significant positive correlations with suicidality levels.

Relationship between CT in Significant Brain Regions and Clinical Measurements in Patients with Panic Disorder

Figures 3 and 4 showed the relationships between CT in significant brain regions and clinical measurements in patients with PD. Pearson's correlation analyses were conducted to examine the relationship between the CT of suicidal brain regions in patients with PD and trait anxiety (NEO-N, STAI-T). The analyses revealed significant correlations between NEO-N total scores and the CT of the insula (r = 0.229, p = 0.045), lateral occipital sulcus (r = 0.263, p = 0.021), and precentral gyrus (r = 0.281, p = 0.013). Additionally, significant positive correlations were observed between STAI-T total scores and the CT of the insula (r = 0.252, p = 0.023), lateral occipital sulcus (r = 0.241, p = 0.030), and precentral gyrus (r = 0.314, p = 0.004). All correlations significantly remained after performing FDR corrections (FDR < 0.05).

Further correlation analyses were performed to evaluate the relationship between the CT of suicidal brain regions and panic symptom severity in patients with PD, as measured by the PDSS. Significant positive correlations were identified between PDSS total scores and the CT of the insula (r = 0.295, p = 0.007), lateral occipital sulcus (r = 0.254, p = 0.021), and precentral gyrus (r = 0.294, p = 0.007). After multiple correction comparisons, all correlations had statistical significance (FDR < 0.05).

Pearson's correlation analyses were performed to examine the association between early trauma using ETISR-SF scores and CT in suicidal brain regions in patients with PD. The analysis revealed that higher physical trauma subtype scores on the ETISR-SF were associated with increased CT in the insula (r = 0.316, p = 0.004, FDR < 0.05).

In terms of treatment response, there were significant differences in the CT of the lateral occipital sulcus between those with a 40% or greater reduction in PDSS after 8 weeks compared to baseline and those without (t = −2.174, p = 0.037).

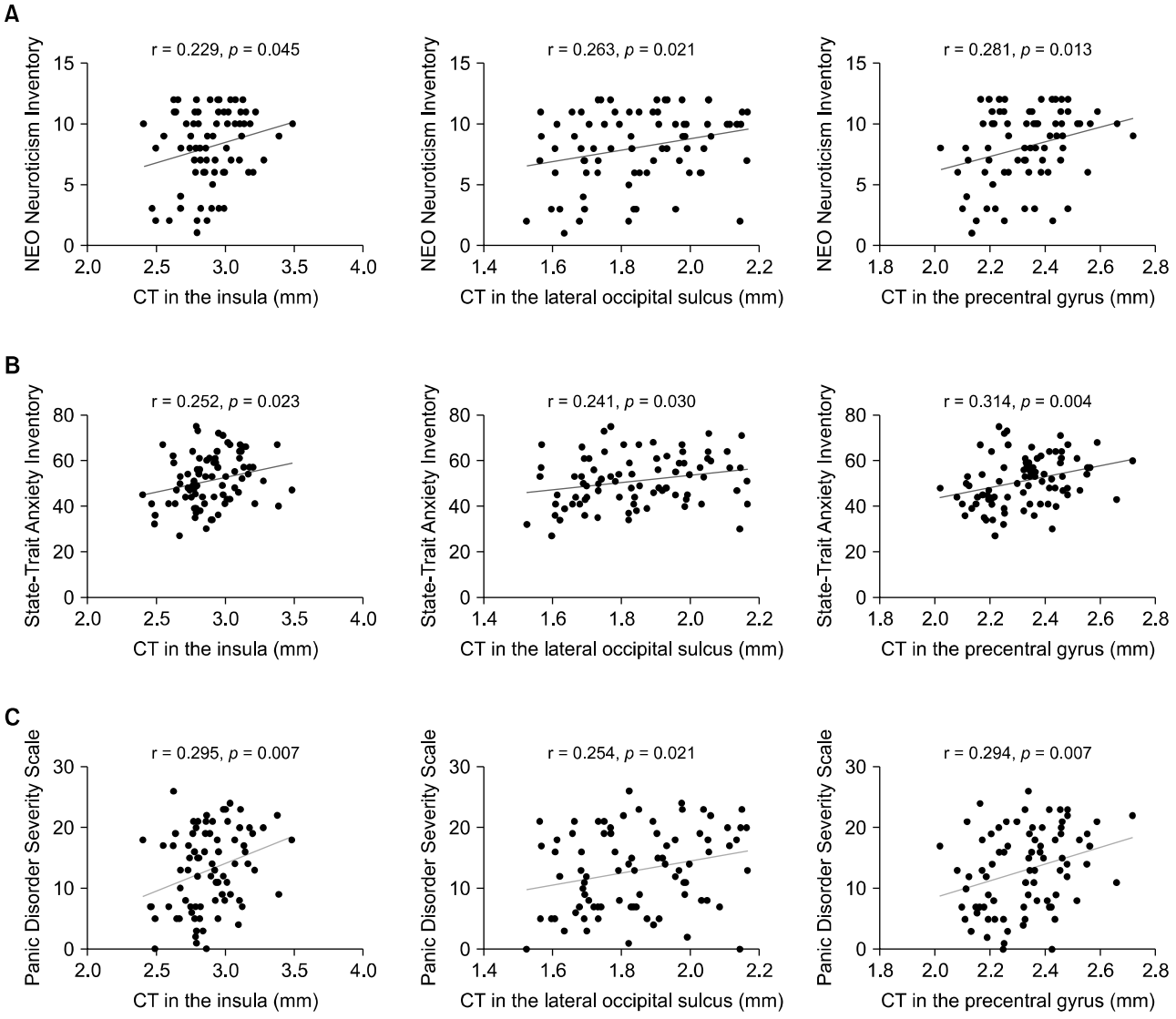

Fig. 3. Pearson's correlation analyses demonstrated significant positive associations between CT in the suicidal brain regions and trait anxiety, panic symptom severity in patients with panic disorder. The significant correlations are as follows: (A) NEO-Neuroticism and the insula, lateral occipital sulcus, precentral gyrus, (B) State-Trait Anxiety Inventory-Trait anxiety and the insula, lateral occipital sulcus, precentral gyrus, (C) Panic Disorder Severity Scale and the insula, lateral occipital sulcus, precentral gyrus.
CT, cortical thickness; NEO-Neuroticism, Neuroticism-Extraversion-Openness Personality Inventory-Neuroticism.

DISCUSSION

To our knowledge, this study represents the first investigation into the relationship between CT in patients with PD and suicidality. Our findings indicate that patients with PD exhibit reduced CT in the insula, lateral occipital sulcus, and precentral gyrus of the EFN compared to HCs. Paradoxically, within the PD patients, we observed that greater CT in those brain regions was correlated with more severe levels of suicidality.

The EFN encompasses the traditional fronto-limbic fear networks and extends to include regions such as the prefrontal cortex, insula, and sensory areas of the occipital, parietal, and temporal cortices [11,45]. In our study, patients with PD demonstrated reduced CT in the insula, and lateral occipital sulcus, precentral gyrus, compared to HCs. These findings align with previous research that has documented reduced CT in the insula, prefrontal cortex, frontal lobe, temporal lobe, and parietal lobe in patients with PD relative to HCs [46,47].

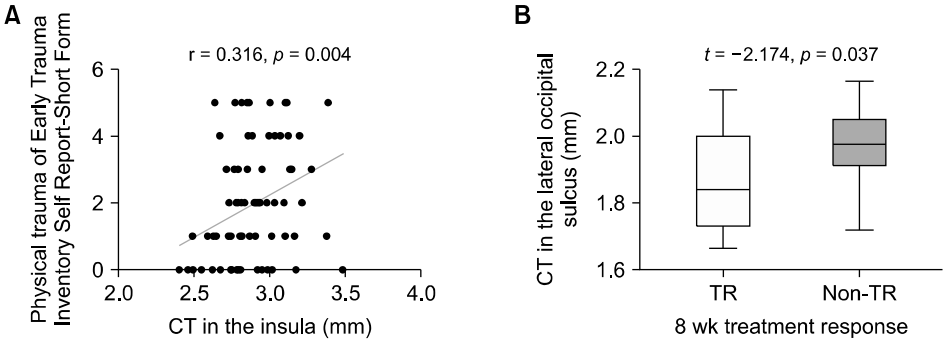

Fig. 4. Relationship between CT in the suicidal brain regions and early trauma, TR in patients with panic disorder. A positive correlation was shown between (A) the CT of the insula and physical trauma subtypes of the Early Trauma Inventory Self Report-Short Form. In addition, a significant group difference was found (B) the CT of the lateral occipital sulcus between those with TR and those without.
CT, cortical thickness; TR, treatment response.

Furthermore, the present study revealed a significant positive correlation between suicidality levels and CT in regions including the insula, lateral occipital sulcus, and precentral gyrus in PD. We called these three subset regions of the EFN strongly correlated with suicidality in our PD cohort "suicidal brain regions in patients with PD." The insula corresponds to both the EFN and the suicidal brain (i.e., the regions identified to be associated with suicidality in clinical samples), and the lateral occipital sulcus and precentral gyrus might be considered part of the brain regions that implied vulnerability regarding fear in PD. This observation is consistent with prior research indicating that the suicidal brain may involve the dorsal prefrontal cortex, insula [11], and lateral occipital cortex [15]. However, our correlation analyses suggest a paradoxical finding: despite overall lower CT in the suicidal brain regions in patients with PD compared to HCs, those PD patients with relatively increased CT in these regions exhibited higher levels of suicidality. This may indicate a "relative overactivity" of the suicidal brain in PD patients with elevated suicidality levels.

The precise mechanism underlying the observed relative increases in CT associated with heightened suicidality in PD remains undetermined to predict causality. However, some explanations may be considered. It is plausible that these findings may be attributable to CT thickening process linked to pathological glial inflammation [48]. This hypothesis is supported by the role of microglia as pivotal mediators of neuroinflammatory processes implicated in the pathogenesis of PD [49-51]. First, compensatory neuroplastic mechanisms in PD may transiently manifest as relative cortical thickening [52]. Similar compensatory responses have been described in neuroimaging studies of anxiety disorders, where divergent regional GMV pattern changes, such as reductions in the temporal poles and lateral orbitofrontal cortex involved in emotional regulation, accompanied by relative increases in the parahippocampal gyrus, cerebellum, middle occipital, supramarginal, and angular cortices, have been interpreted as adaptive responses to heightened stress [53, 54]. Second, the disease stage-specific effects of PD may have contributed to this pattern. Acute disease phases, characterized by neurotrophic or acute inflammatory processes, could lead to transient hypertrophic changes through glial activation. In contrast, chronic processes are more likely to result in neuronal loss or cortical thinning [52,55,56]. This concept may be related to the initial hormetic phase of early stress-related disorders, which may contribute to compensatory plasticity in neurons, glia, and vascular cells [57], showing GMV hypertrophy in brain regions such as the hippocampus [58]. Third, medication-related influences should also be considered. Antidepressant exposure (e.g., sertraline) has been associated with increased CT in the prefrontal and parietotemporal regions [59], possibly mediated by enhanced brain-derived neurotrophic factor expression and synaptic plasticity remodeling [60]. Taken together, these alternative interpretations underscore the need for longitudinal multimodal imaging studies to clarify the significance of the observed mechanisms of cortical thickening.

Furthermore, our results align with previous studies that have demonstrated a positive correlation between the severity of psychiatric symptoms and increased CT, such as in the supramarginal gyrus [61] as well as increased GMVs

in the amygdala [62] and hippocampus [63] among patients with MDD. Interestingly, our study suggested that increased CT in the lateral occipital sulcus may be a potential biomarker for pharmacological treatment responses in patients with PD. The occipital region, one of the components of the EFN, is involved in visual and somatosensory processing [45,64] and has been shown to exhibit heightened sensitivity to fearful stimuli [65] with impaired connectivity to other brain regions due to pathological fear and anxiety [66]. Within top-down regulatory mechanisms, visual processing in the occipital region is modulated by the prefrontal cortex. Disputed top-down modulation may amplify the perception of threat-related cues, which in turn heightens interoceptive awareness, a mechanism implicated in panic attacks [67,68]. Therefore, future investigations employing larger cohorts and prospective longitudinal designs are warranted to elucidate these findings further.

Childhood psychological trauma, including physical, emotional neglect or abuse, and sexual subtypes, has been linked to severe panic symptomatology [69] and an earlier onset of PD [8,70]. Moreover, early trauma constitutes a significant risk factor for suicidality [8,71]. Our study identified a positive correlation between the physical trauma subtype, as measured by the ETISR-SF, and the CT of the insula. Although the mechanisms underlying the association between childhood trauma and suicidality remain to be fully elucidated [8], one plausible hypothesis is that prolonged exposure to stressful situations, such as early trauma-induced allostatic overload, may lead to neurodevelopmental alterations, including neuroinflammation and neuroendocrine dysregulation [18,72]. These findings suggest that early traumatic experiences may contribute to increased CT in suicidality-related brain regions, potentially indicating heightened neural activity in the context of PD.

Previous studies have reported that distinct early trauma subtypes are associated with specific patterns of structural brain abnormalities [73], which may, in turn, contribute to differential psychopathological dysfunction [74]. Reductions in CT or GMVs within the fronto-limbic network (e.g., hippocampus, amygdala) have been associated with early trauma subtypes [73,75-77]. For example, previous studies have linked physical trauma to alterations in the corpus callosum but have neglected GMV reduction in the insula. In contrast, our findings showed a reverse pattern, with an association between physical trauma and increased insular CT in patients with PD. In addition, sexual trauma is associated with CT in the somatosensory cortex [78], whereas emotional trauma is associated with CT in the somatosensory cortex and precuneus [74]. Distinct early trauma subtypes appear to target modality-specific cortical representations.

Neuroticism, characterized by a propensity to experience negative emotions such as worry and tension [79,80], includes panic attacks as a symptomatic manifestation [81]. Neuroticism is recognized as a risk factor for suicidality in MDD [82]. Our results revealed a significant positive correlation between neuroticism levels and CT in suicidality-related brain regions in individuals with PD. These regions correspond with those implicated in neuroticism, such as the insula, lateral occipital sulcus, precentral gyrus [83]. This relationship may be explained by a comprehensive integrative model of suicide, which posits that neuroticism is a clinical factor sequentially influenced by developmental (genetic and early trauma) and neurobiological factors, including neuroendocrine (hypothalamic-pituitary-adrenal axis) and neurochemical (serotonin, norepinephrine, dopamine) markers [84]. Additionally, trait anxiety, as assessed by the STAI-T, may be contextualized within this framework. Trait anxiety reflects a stable personality disposition that becomes pronounced in response to harmful or stressful situations [85,86]. In this study, we found positive correlations between STAI-T levels and CT in suicidal brain regions among PD patients. These findings suggest that alterations in CT in these regions may contribute to the development of vulnerability traits associated with suicidality.

Suicide is not only regarded as unique psychopathology even after controlling for the effects of related mental disorders but also considered as a symptom of psychiatric disorders [5]. Moreover, previous research has demonstrated a significant association between heightened symptom severity and increased suicidality in PD [87,88]. Our findings, which reveal positive correlations between suicidality-related brain regions and panic symptom severity, suggest the potential existence of shared neural correlates between suicidality and symptom severity within the symptomatology of PD. These results align with prior studies indicating that panic symptoms, the frequency of early trauma, and poor response to pharmacological treatment are significantly more pronounced in

PD patients with a history of suicide attempts [7]. The observed relative overactivity in suicidality-related brain regions may be intricately linked to the severity of symptoms.

This study, however, is subject to several limitations. First, the sample size of MRI participants was relatively small, limiting the generalizability of our findings to the broader neurobiology of PD. Nevertheless, our study aimed to investigate suicidality in PD with a larger sample size than that used in previous neuroimaging studies. Second, it is not feasible to establish a causal relationship between structural alterations and severe suicidality or to determine whether regional overactivity precipitates suicidality. Longitudinal studies are therefore necessary to address this gap. Third, individuals who completed suicide were naturally excluded from this study, which may affect the generalizability of the findings.

In conclusion, this study demonstrates that increased CT in specific brain regions, including the insula, lateral occipital sulcus, and precentral gyrus, is associated with suicidality in patients with PD. Furthermore, the altered CT in these suicidality-related regions, potentially linked to early trauma, may contribute to the manifestation of trait anxiety, panic symptom severity, and treatment response.

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■ Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

■ Author Contributions

Conceptualization: Ji-Yoon Ham, Sang-Hyuk Lee. Data curation: Ji-Yoon Ham, Hyun-Ju Kim, Sang-Hyuk Lee. Formal analysis: Ji-Yoon Ham, Hyun-Ju Kim. Investigation: Ji-Yoon Ham, Hyun-Ju Kim, Ji-Eun Kim, Sang-Hyuk Lee. Methodology: Ji-Yoon Ham, Hyun-Ju Kim, Ji-Eun Kim. Software: Hyun-Ju Kim. Supervision: Hyun-Ju Kim, Tai-Kiu Choi, Ji-Eun Kim, Sang-Hyuk Lee. Funding acquisition: Sang-Hyuk Lee. Validation: JI-Yoon Ham, Hyun-Ju Kim, Yeong-Geon Hwang, Tai-Kiu Choi, Ji-Eun Kim, Sang-Hyuk Lee. Visualization: Ji-Yoon Ham, Hyun-Ju Kim. Writing—original draft: Ji-Yoon Ham, Hyun-Ju Kim, Ji-Eun Kim, Sang-Hyuk Lee. Writing—review & editing: Ji-Yoon Ham, Hyun-Ju Kim, Ji-Eun Kim, Sang-Hyuk Lee.

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