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Altered Low Frequency Heart Rate Variability Associated with Agoraphobia in Panic Disorder: A Retrospective Study

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Purpose: This study aimed to compare the clinical features of panic disorder (PD) with comorbid agoraphobia to those of PD alone. We focused on autonomic nervous system (ANS) alterations reflected in heart rate variability (HRV) and executive function deficits reflected in the Stroop test.

Materials and Methods: We retrospectively compared psychometric features, Stroop test results, and resting-state HRV across three groups: a subclinical group with anxiety attack history, a PD group without agoraphobia, and a PD group with agoraphobia. The subclinical group included 10 male and 34 female, the PD without agoraphobia group included 17 male and 19 female, and the PD with agoraphobia group included 11 male and 18 female.

Results: The PD with agoraphobia group had higher Symptom Checklist–95 scores than the other groups. Both PD groups had longer reaction times in the Stroop test than the subclinical group. There were no significant differences in HRV parameters between the PD groups with and without agoraphobia. Compared with the subclinical group, the PD with agoraphobia group showed significantly lower values of the natural logarithm of low-frequency HRV.

Conclusion: Our results do not support that executive function deficits and ANS alterations are more pronounced with comorbid agoraphobia among PD groups. However, PD with agoraphobia patients showed more complex and severe clinical symptoms in their self-reports. Compared with the subclinical group, PD patients with agoraphobia showed specific features in the natural logarithm of low-frequency HRV. Our findings suggest that agoraphobia comorbidity should be considered when evaluating or treating patients with PD.

Key Words: Panic disorder, agoraphobia, executive function, heart rate

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INTRODUCTION

According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), panic disorder (PD) is characterized by repetitive and unexpected panic attacks along with concern and worry about future attacks.[1] More than half of diagnosed PD cases are accompanied by agoraphobia[2,3]: a fear of open or crowded situations, such as public transportation, due to the possibility of experiencing panic-like symptoms with no options for receiving help or escaping.[1] Compared with patients with PD alone, patients with PD and comorbid agoraphobia show an extended illness duration,[4] more frequent comorbidities,[5] more severe panic attacks, and higher levels of emotional symptoms, including depression,[6] indicating that

PD with comorbid agoraphobia has a more severe clinical presentation than PD alone.

Heart rate variability (HRV) is a biomarker for autonomic nervous system (ANS) activity[7] and appears to be related to the pathophysiology of PD.[8,9] HRV could serve as a useful clinical index of objective biological status in addition to subjective symptoms. A previous meta-analysis reported that anxiety disorder is associated with low HRV.[10] PD has also been shown to be associated with low HRV.[11,12] However, several variables are known to affect HRV, including age, sex, lifestyle, and physical activity.[13] Additionally, comorbidity has been found to significantly influence HRV in anxiety disorders.[14] Considering the clinical implications of comorbid agoraphobia and PD, agoraphobia may also affect the relationship between PD and HRV, though few studies have considered agoraphobia when exploring this relationship. Considering the worse clinical features observed in PD with comorbid agoraphobia, compared with PD alone, we suspect that patients with comorbid PD and agoraphobia may also experience more severe ANS alterations, which would be reflected by a lower HRV, relative to PD patients without agoraphobia.

Previous research has suggested that HRV is related to both emotional states and cognitive domains, such as executive function.[15] Executive function is a higher-order cognitive function that plans, monitors, and executes goal-oriented behaviors by controlling and regulating multiple basic cognitive functions.[16] Executive function deficits are regarded as candidate endophenotypes in psychiatric disorders, and researchers have shown that the performance efficiency of executive function is low in anxiety disorders.[17] Previous studies on PD have also suggested an executive function deficit in PD.[18,19] However, others have failed to demonstrate this deficit,[20,21] and some have even shown that patients with PD perform better on task accuracy than controls.[17] These conflicting results may have partly resulted from insufficiently controlled covariates, such as the presence of comorbid conditions, including agoraphobia, and medication history.[22] Also, importantly, executive function includes various cognitive functions, such as executive control, planning, cognitive flexibility, working memory, and decision-making, and the neurocognitive tests that assess executive function respectively target different subdomains of executive function. We speculate that the complexity of the cognitive subdomains of executive function and the variety of tools designed to evaluate them may influence the conflicting results on executive function in PD.

The Stroop test is a neurocognitive test that has been widely used to evaluate executive function. It assesses the "Stroop effect," in which the reaction time to a task varies with attention and cognitive interference.[23] In the Stroop test, colored circles or words are presented to the subject, and the subject is instructed to recognize and name the color of the given stimuli. In the incongruent condition of the Stroop test, cognitive interference occurs because the color and the contents of the stimuli do not match. The Stroop test measures selective attention, cognitive flexibility, and inhibitory control among executive functions.[16] Because these cognitive functions are closely related to anxiety,[24,25] we predicted that it would be clinically meaningful to assess executive functioning among PD patients with the Stroop test. Although previous studies using the Stroop test failed to prove a significant group difference between PD patients and controls,[20,26] the studies were limited by their small sample sizes and lack of consideration of comorbid agoraphobia.

In this study, we compared clinical variables, including 5-minute resting HRV and performance on the Stroop test, between PD patients with and without agoraphobia. As described above, comorbid agoraphobia is associated with more severe clinical features of PD, and we predicted that this would be reflected in the patients' HRV and Stroop test results. We hypothesized that subjects with PD and comorbid agoraphobia would exhibit lower resting HRV and worse performance on the Stroop test than subjects with PD alone, which would provide further evidence that comorbid agoraphobia has a significant impact on ANS alterations and executive function deficits in PD.

MATERIALS AND METHODS

Participants

This study retrospectively analyzed clinical data, including Stroop test results and HRV indices, of subjects who visited a psychiatric outpatient clinic at Yongin Severance Hospital. Ethics approval was obtained from the hospital's Institutional Review Board (9-2021-0128, approved on October 10, 2021). This study targeted adult patients aged 19–60 years who visited an outpatient clinic for anxiety attacks from March 2020 to January 2022. The patients underwent cognitive assessments, including the Stroop test and full-scale intelligence quotient (FSIQ) test. FSIQ scores were measured via the Korean version of the Wechsler Adult Intelligence Scale IV.[27] Each patient underwent a psychometric evaluation of their psychiatric symptoms, including PD symptoms, as well as a 5-minute resting HRV assessment. We selected patients who completed the psychometric evaluation, Stroop test, and HRV assessment as subjects for this study. A total of 129 subjects (49 male and 80 female) were initially reviewed in this study.

Clinical diagnosis information for the study subjects was retrospectively investigated. Certified psychiatrists at the study site confirmed each subject's psychiatric diagnosis according to DSM-5 after the subject had received treatment for more than 3 months. Psychiatric medication history was also evaluated at the time of psychometric evaluation, particularly the types of benzodiazepines the subjects were taking, including alprazolam, clonazepam, lorazepam, diazepam, and etizolam. The types of antidepressants the subjects were taking

were also investigated, including selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, mirtazapine, and vortioxetine.

We excluded 18 subjects (9 male and 9 female) diagnosed with a major psychiatric illness other than PD, such as major depressive disorder, bipolar disorder, or schizophrenia. Two male subjects with an FSIQ score of less than 80 were also excluded. We divided the remaining subjects into three groups according to the attending psychiatrist's diagnosis based on DSM-5 criteria, Panic Disorder Severity Scale (PDSS) score, and Korean Symptom Checklist–95 (KSCL95) score. The subclinical group included those who did not conform to PD on DSM-5 and scored less than 8 on PDSS[28] and below the standard score of 70 on the phobic anxiety–agoraphobia subscale of KSCL95.[29] The PD without agoraphobia group included those who conformed to PD on DSM-5 and scored 8 or higher on PDSS, but below the standard score of 70 on the phobic anxiety–agoraphobia subscale of KSCL95. The PD with agoraphobia group included those who conformed to PD on DSM-5 and scored higher than 8 on PDSS and higher than the standard score of 70 on the phobic anxiety–agoraphobia subscale of KSCL95. Finally, the subclinical group included 44 subjects (10 male and 34 female), the PD without agoraphobia group included 36 subjects (17 male and 19 female), and the PD with agoraphobia group included 29 subjects (11 male and 18 female).

Psychometric measurements

PDSS was used to evaluate PD symptoms. PDSS consists of seven items, each rated on a 0–4 scale, with higher ratings reflecting greater severity. Clinical levels of panic symptoms were defined by a PDSS score of 8 or higher.[30] This study also used KSCL95 to evaluate a broad range of psychiatric clinical symptoms.[29] KSCL95 consists of 95 items, each rated on a 0–3 scale, with higher ratings suggesting greater symptom severity. Among the primary symptom dimensions, this study focused on the phobic scale, which consists of seven items, four of which assess agoraphobia.

In addition to PDSS and KSCL95 scores, all subjects completed several self-report questionnaires that evaluate psychometric characteristics the Anxiety Sensitivity Index (ASI),[31] the Perceived Stress Scale (PSS),[32] the Pittsburgh Sleep Quality Index,[33] the Hospital Anxiety and Depression Scale (HADS),[34] and the State-Trait Anxiety Inventory (STAI).[35] HADS consists of HADS depression (HADS-D) and HADS anxiety (HADS-A) scores, and STAI consists of STAI-state and STAI-trait scores. The Hamilton Anxiety Rating Scale (HAM-A)[36] and the Hamilton Depression Rating Scale (HAM-D)[37] were scored by a certified psychologist.

Stroop test

The Stroop test included in Kim's frontal-executive neuropsychological test II (K-FENT II)[38] was conducted to assess the participants' sustained attention, inhibitory control ability, and processing speed. The Stroop test in K-FENT II consists of a color trial and a color-word trial. In the color trial, a simple colored circle is presented, and in the color-word trial, the name of a color is presented in incongruently colored ink to elicit cognitive interference. In the color trial, participants simply focus on the color dimension, whereas the color-word test requires participants to suppress habitual reactions to a more salient dimension (i.e., simply reading words) and focus on the target dimension (i.e., identifying color). The reaction time and number of errors from each test are converted into a scaled score based on the participant's age; scaled scores of 16–18 (higher than the 95th percentile) are considered very high, 14–15 (85th–95th percentile) are high, 7–13 (15th–84th percentile) are average, 5–6 (5th–14th percentile) are low, and 2–4 (below the 5th percentile) are very low.

HRV measurements

HRV was measured using stress-measuring equipment (SA-3000P, Medicine Co., Ltd., Seoul, Korea). Electrocardiograms (ECG) were performed after the participants rested for 5 minutes. HRV was calculated using R–R variability in the ECG data. HRV analysis was performed using lead II, where the R-peak was most evident. The time-domain HRV parameters used in this study were the standard deviation of normal-to-normal R–R intervals (SDNN) and the root mean square of successive R–R interval differences (RMSSD). Frequency-domain analysis was implemented through a power spectral density analysis in addition to time-domain analysis. The frequency-domain analysis has the strength to provide information on ANS balance.[39] The frequency-domain HRV parameters used in this study were low frequency (LF, 0.04–0.15 Hz), high frequency (HF, 0.15–0.4 Hz), and total power (TP, 0–0.4 Hz). The frequency-domain HRV parameters were logarithmically transformed (lnLF, lnHF, and lnTP).

Statistical analysis

We used SPSS version 22.0 (IBM Corp., Armonk, NY, USA) for all statistical analyses. Analysis of variance and the chi-square test were employed to compare demographic and clinical characteristics between groups. After adjusting for age, sex, and FSIQ scores, the converted scores of the Stroop test and the values of the HRV parameters were analyzed using analysis of covariance (ANCOVA) to compare group differences. The Bonferroni correction was used for post-hoc analysis.

RESULTS

Clinical characteristics

Group differences in demographic and clinical characteristics were examined (Table 1). We found no significant differences in age, sex distribution, or FSIQ scores between groups. Patients in the PD with agoraphobia group were taking more types of

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Table 1. Comparison of Clinical Variables between Groups

	Subclinical group (A) (n=44)	PD without agoraphobia group (B) (n=36)	PD with agoraphobia group (C) (n=29)	F or χ^2	*p* value	Comparison
Age (yr)	41.7±12.0	43.6±11.0	37.7±11.7	F=2.133	0.124	
Sex				χ^2=5.395	0.067	
Male	10 (22.7)	17 (47.2)	11 (37.9)			
Female	34 (77.3)	19 (52.8)	18 (62.1)			
FSIQ	96.9±7.5	99.1±8.9	99.8±8.9	F=1.244	0.292	
PDSS	3.8±0.3	9.6±0.4	11.3±0.4	F=126.023	<0.001	A<B<C
ASI	19.0±1.7	29.8±1.9	34.5±2.1	F=18.383	<0.001	A<B, C
HADS-A	8.4±0.5	10.3±0.6	13.0±0.7	F=14.896	<0.001	A, B<C
HADS-D	8.7±0.6	10.1±0.6	11.6±0.7	F=5.291	0.006	A<C
STAI-State	46.7±1.6	53.8±1.8	58.3±2.0	F=11.239	<0.001	A<B, C
STAI-Trait	46.2±1.5	53.6±1.7	58.8±1.9	F=13.710	<0.001	A<B, C
HAM-A	15.6±1.0	22.6±1.1	23.0±1.2	F=16.530	<0.001	A<B, C
HAM-D	12.7±0.7	16.9±0.8	16.0±0.9	F=8.451	<0.001	A<B, C
PSS	18.4±0.9	22.5±1.0	25.2±1.1	F=12.678	<0.001	A<B, C
PSQI	9.3±0.7	10.2±0.8	11.4±0.8	F=1.810	0.169	
Types of medications	1.6±1.0	2.2±1.0	3.0±1.8	F=11.526	<0.001	A, B<C
Types of benzodiazepines	0.6±0.5	0.8±0.4	1.1±0.7	F=7.297	0.001	A<C
Types of antidepressants	0.8±0.6	1.1±0.4	1.3±0.7	F=8.590	<0.001	A<B, C

ASI, Anxiety Sensitivity Index; FSIQ, full-scale intelligence quotient; HADS-A, Hospital Anxiety and Depression Scale–Anxiety; HADS-D, Hospital Anxiety and Depression Scale–Depression; HAM-A, Hamilton Anxiety Rating Scale; HAM-D, Hamilton Depression Rating Scale; PD, panic disorder; PDSS, Panic Disorder Severity Scale; PSS, Perceived Stress Scale; PSQI, Pittsburgh Sleep Quality Index; STAI, State-Trait Anxiety Inventory.
Data are presented as mean±standard deviation or n (%).

psychiatric medications than those in the other groups and used more types of benzodiazepines than those in the subclinical group. Both the PD with agoraphobia and PD without agoraphobia groups used more types of antidepressants than the subclinical group. The statuses of medications other than benzodiazepines and antidepressants were as follows: aripiprazole (1 subject in the subclinical group, 1 subject in the PD without agoraphobia group, and 2 subjects in the PD with agoraphobia group), propranolol (3 subjects in the subclinical group, 2 subjects in the PD without agoraphobia group, and 6 subjects in the PD with agoraphobia group), buspirone (1 subject in the subclinical group and 1 subject in the PD with agoraphobia group), sleeping pills (zopiclone, doxepin, and zolpidem; 1 subject in the subclinical group, 3 subjects in the PD without agoraphobia group, and 4 subjects in the PD with agoraphobia group), and other drugs for sleep aid purposes (trazodone and quetiapine; 3 subjects in the subclinical group, 3 subjects in the PD without agoraphobia group, and 4 subjects in the PD with agoraphobia group).

No significant differences in ASI, HADS-D, STAI, HAM-A, HAM-D, or PSS scores were observed between the PD with agoraphobia group and the PD without agoraphobia group. However, PDSS and HADS-A scores were significantly higher for the PD with agoraphobia group than for the PD without agoraphobia group. The PD with agoraphobia group showed significantly higher scores than the PD without agoraphobia group on the following KSCL95 subscales: depression, anxiety, phobic anxiety, phobic anxiety–agoraphobia, obsessive-compulsive disorder, posttraumatic stress disorder, aggression, paranoia, schizophrenia, suicide, addiction, and stress vulnerability (Fig. 1 and Supplementary Table 1, only online).

Stroop test results

We assessed group differences in the results of the Stroop test (Table 2) and found no significant differences in the number of errors recorded between groups in the color trial or color-word trial. However, group differences in reaction times were observed for both trials (color trial: F=5.498, *p*=0.005; color-word trial: F=4.628, *p*=0.012). Post-hoc comparisons revealed that both the PD with agoraphobia group and the PD without agoraphobia group had longer reaction times (i.e., lower converted scores) than the subclinical group in both trials.

HRV results

We explored HRV parameters for all three groups (Table 3 and Fig. 2). When examining time-domain parameters, we found no significant differences in RMSSD or SDNN values across groups. When comparing frequency-domain parameters, we found no significant differences in lnTP or lnHF values across groups. However, we did find significant group differences in lnLF values across groups (F=3.394, *p*=0.037). Using pairwise comparisons, we found that lnLF values for the PD with agoraphobia group were significantly lower than those for the subclinical group. Other pairwise comparisons were not statisti-

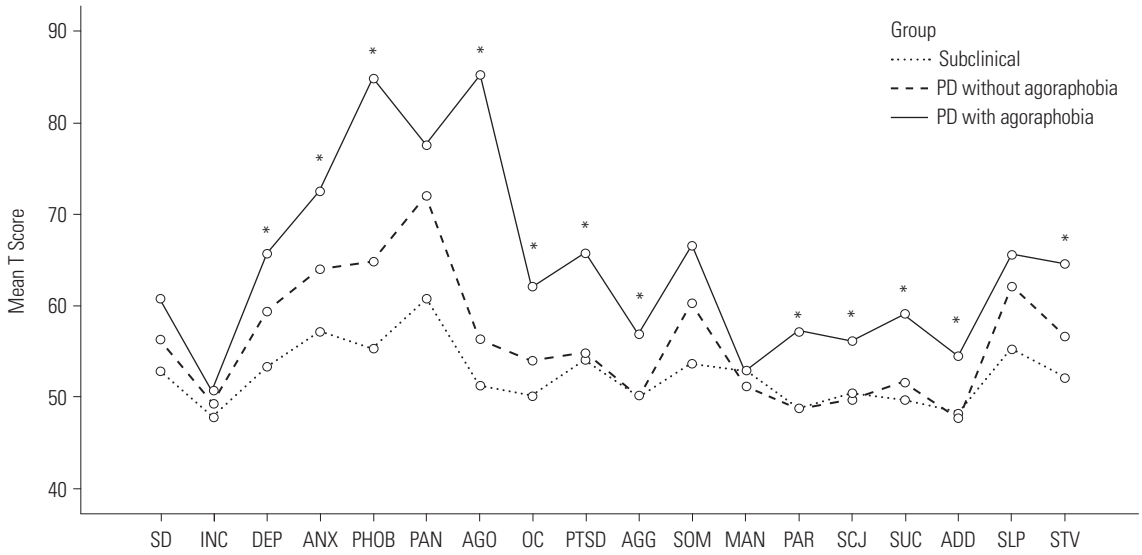

Fig. 1. Korean-Symptom Checklist-95 (KSCL95) profiles in three groups. ADD, addiction; AGG, aggression; AGO, agoraphobia; ANX, anxiety; DEP, depression; INC, inconsistency; INS, interpersonal sensitivity; MAN, manic episode; OC, obsessive-compulsive; PAN, panic attack; PAR, paranoia; PD, panic disorder; PHOB, phobic anxiety; PTSD, posttraumatic stress disorder; SCH, schizophrenia; SD, social desirability; SLP, sleep problem; SOM, somatization; ST-V, stress vulnerability; SUC, suicide. *$p<0.05$, a significant difference between the PD with agoraphobia group and the PD without agoraphobia group in pairwise comparison.

Table 2. Between-Group Comparisons of Converted Scores in the Stroop Test

	Subclinical group (A) (n=44)	PD without agoraphobia group (B) (n=36)	PD with agoraphobia group (C) (n=29)	F	*p* value	Comparison
Color trial						
Reaction time	12.0±0.3	10.7±0.4	10.5±0.4	5.498	0.005	A>B, C
Error	11.7±0.3	11.2±0.4	11.5±0.4	0.583	0.560	
Color-word trial						
Reaction time	12.7±0.4	11.2±0.5	11.0±0.5	4.628	0.012	A>B, C
Error	11.4±0.4	11.5±0.4	11.7±0.5	0.147	0.863	

PD, panic disorder.
Data are presented as mean±standard deviation. Age, sex, and full-scale intelligence quotient were entered as covariates.

cally significant.

Additionally, because various clinical features appeared stronger in the PD with agoraphobia group than in the PD without agoraphobia group, it was necessary to confirm whether other clinical features affected the low lnLF values in the PD with agoraphobia group. Therefore, we performed ANCOVA again by adding several subscales of KSCL95 (depression, anxiety, obsessive-compulsive disorder, posttraumatic stress disorder, aggression, paranoia, schizophrenia, suicide, addiction, and stress vulnerability) to the existing confounders (age, sex, and FSIQ scores). The KSCL95 subscales added as covariates showed significant differences in the PD with agoraphobia group, compared with the other groups, and the phobic anxiety and agoraphobia subscales were excluded from the confounders. Even after additional adjustments, group differences in lnLF remained significant ($F=4.277$, $p=0.017$). We also found that the lnLF values for the PD with agoraphobia group were significantly lower than those for the subclinical group in the pairwise comparisons. Other pairwise comparisons were not statistically significant.

DISCUSSION

In this study, we evaluated the clinical characteristics of individuals with comorbid PD and agoraphobia and compared them with those of individuals with PD alone and a subclinical group of individuals with a history of anxiety attacks. According to the KSCL95 questionnaire evaluation, the PD with agoraphobia group showed features that were more clinically severe than those of the PD without agoraphobia group. In addition to phobic anxiety and agoraphobia, the subscales for various clinical features, including depression, addiction, and suicidal risk–related symptoms, were more prominent in the PD with agoraphobia group than in the PD without agoraphobia group. This finding is consistent with prior studies, which demon-

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Table 3. Differences in Heart Rate Variability Measures between Groups

	Subclinical group (A) (n=44)	PD without agoraphobia group (B) (n=36)	PD with agoraphobia group (C) (n=29)	F	*p* value	Comparison
Time-domain parameters						
SDNN (ms)	38.7±1.9	34.0±2.1	32.1±2.3	2.751	0.069	
RMSSD (ms)	27.6±2.2	23.2±2.4	24.1±2.7	1.027	0.362	
Frequency-domain parameters						
lnTP (ms^2)	6.9±0.1	6.5±0.1	6.5±0.1	2.057	0.133	
lnLF (ms^2)	5.6±0.1	5.3±0.1	5.0±0.2	3.394	0.037	A>C
lnHF (ms^2)	5.2±0.2	4.7±0.2	4.9±0.2	1.972	0.144	

lnHF, natural logarithm of high frequency; lnLF, natural logarithm of low frequency; PD, panic disorder; RMSSD, square root of the mean of the squares of successive normal-to-normal R–R interval differences; SDNN, standard deviation of all normal-to-normal R–R intervals; lnTP, natural logarithm of total power.
Data are presented as mean±standard deviation. Age, sex, and full-scale intelligence quotient were entered as covariates.

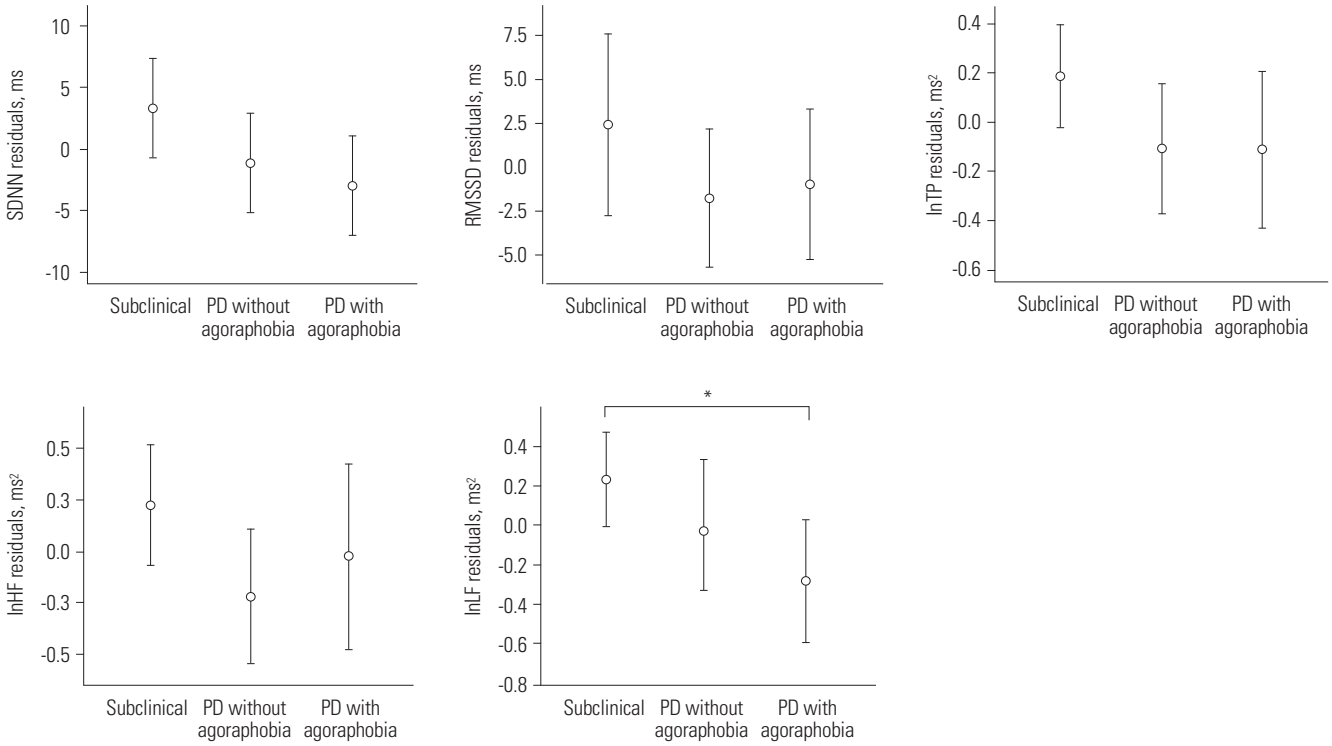

Fig. 2. Heart rate variability (HRV) analysis in three groups. Adjusting for covariates (age, sex, and full-scale intelligence quotient), HRV parameters were regressed onto covariates using linear regression. Calculated non-standardized residuals were used to produce scatter plots. lnHF, natural logarithm of high frequency; lnLF, natural logarithm of low frequency; PD, panic disorder; RMSSD, square root of the mean of the squares of successive normal-to-normal R–R interval differences; SDNN, standard deviation of all normal-to-normal R–R intervals; lnTP, natural logarithm of total power. *$p<0.05$, a significant difference between groups in pairwise comparison.

strated that clinical characteristics worsen when agoraphobia and PD are comorbid.[6,40] However, some points should be considered when interpreting KSCL95 findings: because KSCL95 comprehensively evaluates various psychiatric symptoms through a single self-report questionnaire (multidimensional instrument), it is necessary to exercise caution in determining which specific features show a significant group difference.[41] Further studies using individual scales for each feature are needed to validate the current findings. In addition, there are often discrepancies between self-report questionnaire results and clinician rating scale results.[42] For example, the PD without agoraphobia group and subclinical group showed a significant difference in HAM-D scores but no difference in HADS-D scores. Although the above limitations should be considered, the results of this study on KSCL95 still suggest that the clinical profiles of patients with PD may differ depending on the presence or absence of comorbid agoraphobia. The results of various subscales of KSCL95, which were higher in the PD with agoraphobia group than in the other groups, suggest that complex psychopathology may underlie the comorbidity of PD and

agoraphobia. This interpretation is supported by the finding that the PD with agoraphobia group took more types of psychiatric medications than the other groups.

The main finding of this study is the low lnLF values in the PD with agoraphobia group. Although there was no difference with the PD without agoraphobia group, a statistically significant difference in lnLF values was observed between the PD with agoraphobia group and the subclinical group, and this difference remained significant even after adjusting for other clinical features. Unlike HF-HRV, which is governed by parasympathetic tone, LF-HRV has been found to be affected by both parasympathetic and sympathetic tone.[43] Our findings thus suggest that altered sympathetic tone exists in patients with PD and comorbid agoraphobia. The PD with agoraphobia group would show more persistent avoidant behaviors in anxiety-inducing situations, compared with the subclinical group, and the continuation of these avoidant behaviors may be associated with low levels of threat-related sympathetic activation. Previous studies have also suggested that LF-HRV reflects baroreflex functions,[44] which have been closely linked to fear processing.[45] Thus, our results support the speculation that PD with comorbid agoraphobia can be defined as a coexistent condition, with PD as a distress disorder and agoraphobia as a fear disorder.[46] However, because this interpretation of LF-HRV is controversial,[47] neurobiological features (sympathetic tone or baroreceptor function) associated with low lnLF in the PD with agoraphobia group must be further verified through studies that can directly explore corresponding features.

The PD groups with and without agoraphobia showed no difference in lnHF, compared with the subclinical group. Previous studies measuring HRV in PD reported low levels of HF-HRV,[11,48] but other studies showed no difference in HF-HRV, compared with a control group.[49,50] A meta-analysis study concluded that the differences in individual HRV parameters (LF-HRV or HF-HRV) between PD and control groups were not significant.[9] The meta-analysis study pointed out that different clinical characteristics (comorbidity, disease duration, and severity) of the PD patient group included in each study may produce different results. This study found no significant difference in lnHF between the PD with agoraphobia group and the subclinical group despite the high severity of PD symptoms. Some studies on long-term depression have suggested that parasympathetic tone is not weakened due to the reciprocal effect on homeostasis.[51] In a similar context, chronic manifestation of symptoms in the PD with agoraphobia group may cause a reciprocal effect, resulting in no significant differences in lnHF relative to the subclinical group. However, as this interpretation is based on many assumptions, it seems necessary to re-examine it in future studies.

This study showed no difference in Stroop test error rates between the PD patients and the subclinical group and no group differences in error rates in the color-word trial, in which executive function load is relatively large. In line with our finding, a recent review noted that available research does not support a lack of executive function in PD overall, although specific results were mixed depending on the study design.[22] Furthermore, PD patients in the present study showed longer reaction times than the subclinical group in both the color and color-word Stroop test trials. A recent comprehensive meta-analysis of executive function tasks in anxiety disorders pointed out that although PD patients demonstrated good accuracy, their performance speed was slow.[17] These characteristics of task performance in PD appear to be related to anxiety symptoms, though this association requires a comprehensive comparison with other types of anxiety disorders. On the other hand, the Stroop test results were not significantly different between the PD groups with and without agoraphobia. In other words, our current findings using the Stroop test do not support that comorbid agoraphobia affects executive functioning in PD patients. This is inconsistent with the results of previous studies suggesting an executive function deficit in agoraphobia.[52,53] However, these previous studies included agoraphobia that did not coexist with panic attacks. In addition, previous studies on agoraphobia evaluated non-verbal fluency and task shifting using (e.g., the figural fluency test and the concept shifting test) rather than the Stroop test. Further investigations of the effects of agoraphobia accompanying PD on executive function should combine tests involving multiple subdomains of executive function.

This study has several limitations. First, the subclinical group was composed of subjects with some panic-related symptoms rather than healthy subjects; therefore, interpretation of our study results should consider that the subclinical group may differ from a healthy population. Second, this study analyzed data retrospectively and did not conduct structured interviews to evaluate the subjects' psychiatric diseases. Although the diagnostic judgment of the attending psychiatrist was considered along with the psychometric questionnaire results, there were inevitable limitations due to the study design. In particular, the presence or absence of agoraphobia was evaluated according to a self-report questionnaire, and the subject groups were classified accordingly, which may have affected the results. Third, we had difficulty determining whether findings in the PD with agoraphobia group were due to agoraphobia or other comorbid clinical features. We, therefore, adjusted the main finding (low lnLF in the PD with agoraphobia group) by adding covariates that could reflect other clinical features, but there were still limitations. Future studies must carefully evaluate and consider comorbid psychopathology with larger subject populations. Fourth, we controlled for age and sex, which can affect HRV. However, we did not fully control for other factors known to affect HRV, such as smoking and alcohol consumption.[54,55] In addition, short-term analysis of HRV may produce different results depending on the time of measurement during the day due to the influence of circadian rhythm.[56] Fifth, as mentioned above, this study used only the Stroop test

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to evaluate executive function. Executive function deficits in PD should be explored using a combination of different types of tasks involving the subdomains of executive function.

Despite the above limitations, this study holds several important clinical implications for PD. Slow processing speed in the Stroop test was common in the PD groups with and without agoraphobia. HRV analysis also did not reveal a significant difference between PD patients with and without agoraphobia. However, our findings suggest a significantly lower level of lnLF in PD patients with agoraphobia, compared with the subclinical group. Our results also suggest that self-reported psychometric features differ in cases of comorbid PD and agoraphobia, compared with other groups. Altogether, our findings indicate that agoraphobia should be carefully considered when evaluating and treating PD.

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AUTHOR CONTRIBUTIONS

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