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Abnormal frontal generator during auditory sensory gating in panic disorder: An MEG study

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ABSTRACT

Patients with panic disorder (PD) exhibit abnormalities in early-stage information processing, even for the nonthreatening stimuli. A previous event-related potential study reported that PD patients show a deficit in sensory gating (SG), a protective mechanism of the brain to filter out irrelevant sensory inputs. However, there is no clear understanding about the neural correlates of SG deficits in PD. Moreover, whether SG deficits, if any, are associated with clinical manifestations remain unknown. In this study, 18 patients with PD and 20 age- and gender-matched healthy controls were recruited to perform auditory paired-stimulus paradigm using magnetoencephalographic (MEG) recordings. Results showed that PD patients demonstrated significantly higher M50 SG ratios in the right inferior frontal gyrus (RIFG) and higher M100 SG ratios in both RIFG and right superior temporal gyrus (RSTG) than those of the control group. It was important to note that in the RIFG, the M50 SG ratios correlated significantly with the scores of Body Sensation Questionnaire (BSQ) and Distractibility scale of Sensory Gating Inventory among patients with PD. In conclusion, this study suggests that PD patients exhibited a deficient ability to filter out irrelevant information, and such a defect might lead to cognitive misinterpretation of somatic sensations and distractibility.

1. Introduction

Panic disorder (PD) is characterized by recurrent anxiety attacks, accompanied by physiological symptoms such as palpations, trembling, sweating, and shortness of breath. It has been suggested that patients with PD are relatively sensitive to trivial somatic sensations and exhibit dysfunctional cognitive processes, including widespread catastrophic thinking (Clark, 1986; Chambless et al., 2000). These symptoms suggest that individuals with PD engage in the maladaptive allocation of attention, probably originating from the disturbances of sensory information processing. In addition, clinical observation indicates that complex environments with high sensory load would lead to or trigger heightened anxiety, possibly due to the failure in the modulation of sensory inputs (Street et al., 1989).

Although evidence from several sources converge to indicate that individuals with PD manifest apparent defects in the processes of threatening or affective stimuli (Pauli et al., 2005; Pillay et al., 2006; Lueken et al., 2015), it is scientifically and clinically important to examine whether brain responses to nonthreatening stimuli exhibit an abnormal pattern in the regular environment. Since patients with PD generally manifest attentional bias, it is more objective to investigate the sensory information processing in a pre-attentive state. Sensory gating (SG), an attenuation of neural response to the second identical stimulus, is conceptualized as an automatic processing in the central nervous system to filter out repetitive sensory inputs (Boutros and Belger, 1999; Kisley et al., 2004; Cheng et al., 2016b, 2017, 2018). The paired-stimulus paradigm, in which two auditory stimuli in close succession are delivered, has been widely applied in basic research and psychiatric population, such as aging (Cheng and Lin, 2013; Cheng et al., 2015a, b), schizophrenia (Smith et al., 2010; Hamilton et al., 2018), post-traumatic stress disorder (Ghisolfi et al., 2004; Holstein et al., 2010), and bipolar disorder (Olincy and Martin, 2005; Cheng et al., 2016a). The event-related P50 and N100, recorded by electroencephalography (EEG), are two major components that can be used to

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assess the functional integrity of SG. Quantitatively, SG is measured by the amplitude ratio of Stimulus 2 over Stimulus 1 (S2/S1), and a lower S2/S1 ratio, i.e., more suppression of S2 with respect with S1, indicates better SG function.

Till date, only one event-related potential (ERP) study has been conducted to examine the SG function in patients with PD and demonstrated that these patients exhibited deficient SG evidenced by higher P50 S2/S1 ratios than those of healthy controls (Ghisolfi et al., 2006). However, these findings do not indicate which neural substrates might be associated with these SG changes in PD. It is also still unclear whether this neurophysiological alteration is a trait or a state marker. Therefore, to address the neural mechanisms underlying SG in PD, this study aimed at using a whole-head magnetoencephalography (MEG), which possesses excellent temporal resolution and reasonable spatial resolution, to elucidate the cortical activation of neuromagnetic counterparts of P50 (M50) and N100 (M100). Minimum norm estimate (MNE) is a strategy of distributed source imaging that can reconstruct a number of local and distributed neural generators even overlapping in time (Hamalainen and Ilmoniemi, 1994). Hence, MNE is considered to be a preferred method for analyzing multiple sources compared with other strategies (Lin et al., 2006a,b).

To be more specific, the aims of the present study were two-fold. First, we attempted to assess whether the M50 and M100 SG ratios at the cortical level would be higher in patients with PD than in healthy controls. Our second aim was to explore the relationships between SG function and psychological and clinical assessments, including State-Trait Anxiety Inventory (STAI), Hamilton Scale for Anxiety (HAM-A), Panic Disorder Severity Scale (PDSS), Body Sensation Questionnaire (BSQ), and Sensory Gating Inventory (SGI).

2. Methods

2.1. Subjects

A total of 18 outpatients with PD (11 females, aged 28–59 years, mean age = 47.8 years) were recruited in this study. Psychiatric diagnoses were made by board-certified psychiatrists according to the DSM-5 criteria (American Psychiatric Association, 2013). Antidepressant treatment was given to 3 patients, whereas 15 patients were on combined treatment with antidepressants and benzodiazepines. The detailed demographic information of each patient with PD is presented in Table 1. A total of 20 gender- and age-matched healthy adults (13 females, aged 33–59 years, mean age = 45.0 years) with no history of neurological or psychiatric disorders were recruited through local advertisements. All the subjects refrained from smoking at least 12 h before the MEG recordings to avoid tobacco-related confounding effects (Brinkmeyer et al., 2011).

All study procedures were approved by the Institutional Review Board of Chang Gung Memorial Hospital (Linkou, Taiwan) and were performed in accordance with approved guidelines and regulations. All participants provided the written informed consent after receiving complete explanation about the experimental protocol.

2.2. Symptom severity and neuropsychological assessments

Before MEG recordings, patients with PD completed the assessments of HAM-A (Hamilton, 1959), PDSS (Shear et al., 1997), BSQ (Chambless et al., 1984), and STAI (Spieberger et al., 1983). For a better understanding of the perceptual experiences in the real life, the short form of SGI, including three categories of perceptual modulation, distractibility, and over-inclusion (Kisley et al., 2004; Hetrick et al., 2012; Sable et al., 2012), was also administered to patients with PD.

2.3. Auditory stimulation and MEG recordings

Auditory stimuli were 800-Hz click-like tones (duration = 20 ms with 5 ms of rise and fall times) that were binaurally presented through plastic earphones at an intensity of 60–70 dB sound pressure level above the subjects' threshold. There was no significant between-group difference in the stimulus intensity. The paired-stimulus paradigm was delivered with an inter-stimulus interval (ISI) of 500 ms and an inter-pair interval of 6 s. During the MEG recordings, all participants were instructed to watch a silent movie with subtitles and to ignore the auditory stimuli. The available movies were emotionally neutral to avoid overt affective reactivity.

Auditory evoked fields (AEFs) were obtained from participants in a sitting position using the 306-channel MEG device (Vectorview, Elekta Neuromag, Helsinki, Finland). The data from planar gradiometers of this device, which detect the most robust signals directly above the activated cerebral areas, were analyzed. The MEG data were sampled at 1000 Hz with an online bandpass filter of 0.1–200 Hz. The head position relative to the MEG sensor location was measured by the magnetic signal produced by current leads to four head position indicators (HPIs) at forehead (left and right) and bilateral mastoids. The three fiducial points based on a Cartesian coordinate system were determined using a 3D digitizer.

Table 1
Demographic and clinical data of each patient with panic disorder.

NO.	Age	Gender	Disease Duration (Year)	HAM-A	Current Treatment	Current Comorbidity	STAI score	
							State	Trait
1	48	F	5	16	AD,BZD	Agoraphobia	27	68
2	58	F	8	11	AD,BZD	Persistent depressive disorder	38	42
3	55	M	2	8	AD,BZD	Persistent depressive disorder	41	42
4	41	M	1	17	AD,BZD	–	30	40
5	44	M	3	8	AD	–	28	41
6	56	M	1	12	AD,BZD	Agoraphobia	41	29
7	59	F	3	12	AD,BZD	–	34	38
8	57	M	11	13	AD,BZD	Agoraphobia	36	44
9	53	F	13	13	AD,BZD	Hypochondriasis	44	44
10	38	M	1	8	AD	–	40	42
11	57	F	6	14	AD,BZD	Agoraphobia	50	43
12	45	F	1	27	AD,BZD	Agoraphobia, Persistent depressive disorder	47	48
13	35	F	1	10	AD,BZD	–	48	44
14	46	F	8	20	AD,BZD	–	49	48
15	47	F	16	7	AD,BZD	–	41	47
16	51	M	7	14	AD,BZD	Agoraphobia	50	56
17	28	M	1	19	AD	Persistent depressive disorder	60	55
18	42	F	6	11	AD,BZD	Hypochondriasis	34	37

HAM-A = Hamilton scale for anxiety, AD = antidepressants, BZD = benzodiazepines, STAI = State-Trait Anxiety Inventory.

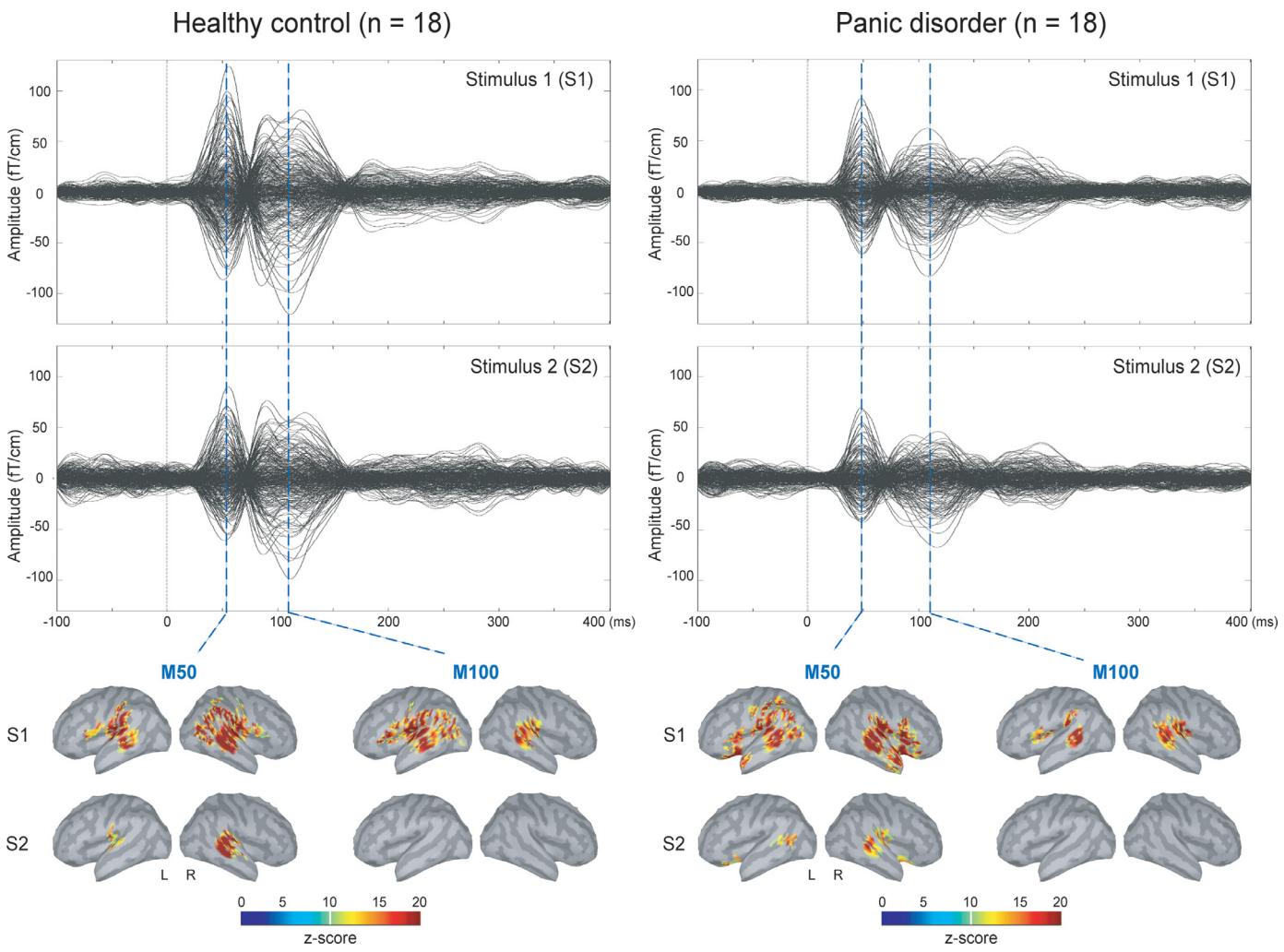

Fig. 1. Upper panel: Grand-averaged auditory evoked sensor-waveforms to S1 and S2 in each group. Lower panel: Cortical activation of minimum norm estimate (MNE) regarding the M50 and M100 components are mapped onto ICMB152 brain template. The cortical surfaces have been smoothed for better visualization (dark gray = sulci, light gray = gyri). *L* = left hemisphere, *R* = right hemisphere.

At least 100 trials of both S1 and S2 were collected. All the MEG data were pre-processed with the Maxfilter software based on the temporal extension of the signal space separation algorithm to reduce artifacts originating inside and/or outside the MEG device (Taulu et al., 2004).

2.4. Magnetic source imaging

The AEFs were filtered offline with a bandpass of 1–30 Hz, with a 100-ms baseline correction. The spatiotemporal dynamics of the neuromagnetic responses were performed using cortically constrained, depth-weighted MNE (Hamalainen and Ilmoniemi, 1994), implemented in the Brainstorm software (Tadel et al., 2011). The representation of folded cortical surfaces was used to resolve the forward problem by applying an overlapping sphere model (Huang et al., 1999). The individual source map, consisting of ~15,000 elementary dipoles over the cortex, was rescaled to the ICMB152 brain template using Brainstorm registration methods with default settings.

The time-resolved magnitude of each dipole was normalized to its fluctuations over baseline, yielding a z-score map. Absolute z scores of M50 and M100 were extracted from S1 and S2 for subsequent analyses.

2.5. ROI selection and SG ratio

Previous studies have shown that the bilateral superior temporal gyri are the primary neural generators of P50/M50 (Edgar et al., 2003; Thoma et al., 2003) and N100/M100 (Smith et al., 2010; Wang et al., 2014) components during auditory SG processes. Furthermore, recent SG research has also revealed the involvement of frontal lobes, including the inferior frontal gyri (Weiland et al., 2008; Ehlis et al., 2009; Boutros et al., 2013). Hence, based on previous knowledge and our grand-averaged MNE source maps of S1 in healthy controls and patients with PD, the following four clusters of 40 vertices corresponding to 5–7 cm^2 were manually scouted as regions of interest (ROIs) on the Desikan-Killiany template: (1) the right superior temporal gyrus (RSTG), (2) the left superior temporal gyrus (LSTG), (3) the right inferior frontal gyrus (RIFG), and (4) the left inferior frontal gyrus (LIFG). Although STG and IFG cover a relatively wide area of cortical surfaces, the maximal activation cluster of each ROI in response to S1 was used as the center of the scout for both M50 and M100 from each participant. This method allowed us to extract the largest neural amplitudes of M50 and M100 to calculate SG ratios in each ROI.

Peak amplitudes of M50 and M100 were defined within the time window between 30 and 80 (Boutros and Belger, 1999; Patterson et al., 2008) and 70–160 ms (Naatanen and Picton, 1987; Lijffijt et al., 2009) after the onset of the stimulus, respectively. The M50 and M100 SG ratios from each ROI were calculated as S2/S1.

2.6. Statistical analysis

All the data were presented as mean ± standard deviation (SD). In each identified ROI, the M50 and M100 strength differences between S1 and S2 were compared by paired *t*-test in each group. The differences in the M50 and M100 SG ratios between the control and PD groups were compared using independent sample *t*-tests. Based on the ROIs with significant between-group findings, Pearson's correlation coefficients were used to further analyze the relationship between SG ratios and clinical severity measures among patients with PD, such as PDSS, BSQ, STAI, and SGI. A p value < 0.05 was considered to be statistically significant.

3. Results

3.1. MEG data

Two subjects from the control group were excluded due to substantial artifacts and technical problems. Therefore, a total of 18 healthy controls and 18 patients with PD were included in the final analyses.

In Fig. 1, the upper panel shows the grand-averaged sensor waveforms of AEFs to S1 and S2 in the control and PD groups. The lower panel of the figure exhibits MNE maps of M50 and M100 components in each group.

In both the control and PD groups, the M50 activation strength of S2 was significantly lower than that of S1 in the RSTG (control: S1 = 10.34 ± 5.91, S2 = 6.63 ± 3.93, $t = 5.82$, $p < 0.001$; PD: S1 = 8.32 ± 5.69, S2 = 4.76 ± 3.18, $t = 4.28$, $p = 0.001$), LSTG (control: S1 = 8.97 ± 5.96, S2 = 4.58 ± 3.01, $t = 4.83$, $p < 0.001$; PD: S1 = 8.22 ± 5.40, S2 = 4.09 ± 2.64, $t = 5.30$, $p < 0.001$), RIFG (control: S1 = 4.49 ± 1.80, S2 = 2.58 ± 1.43, $t = 7.06$, $p < 0.001$; PD: S1 = 4.16 ± 2.60, S2 = 3.25 ± 2.36, $t = 3.00$, $p = 0.008$), and LIFG (control: S1 = 4.37 ± 2.12, S2 = 2.37 ± 1.02, $t = 5.91$, $p < 0.001$; PD: S1 = 4.24 ± 2.40, S2 = 2.43 ± 1.54, $t = 5.81$, $p < 0.001$). The activation pattern was similar for the M100 component in the RSTG (control: S1 = 13.97 ± 9.14, S2 = 6.58 ± 4.62, $t = 6.66$, $p < 0.001$; PD: S1 = 8.74 ± 5.94, S2 = 4.91 ± 3.16, $t = 4.59$, $p < 0.001$), LSTG (control: S1 = 13.36 ± 10.45, S2 = 5.21 ± 2.29, $t = 3.32$, $p = 0.002$; PD: S1 = 8.08 ± 5.07, S2 = 4.27 ± 2.62, $t = 4.43$, $p < 0.001$), RIFG (control: S1 = 6.93 ± 3.84, S2 = 3.32 ± 2.03, $t = 5.94$, $p < 0.001$; PD: S1 = 5.39 ± 3.09, S2 = 3.88 ± 1.93, $t = 2.47$, $p = 0.024$), and LIFG (control: S1 = 5.43 ± 3.16, S2 = 3.04 ± 1.71, $t = 5.57$, $p < 0.001$; PD: S1 = 4.69 ± 1.99, S2 = 2.75 ± 1.48, $t = 6.44$, $p < 0.001$). These results suggested that the gating effects were robust in both groups.

We further compared the SG ratios between the two groups at the source level (Fig. 2). In the RSTG, patients with PD demonstrated a larger M100 SG ratio than the healthy subjects ($t = 2.31$, $p = 0.027$). It was particularly important to note that in the RIFG, the PD group exhibited significantly higher ratios of M50 ($t = 3.39$, $p = 0.002$) and M100 ($t = 2.48$, $p = 0.018$) than the control group.

3.2. Relationship between MEG data and clinical characteristics

As there were significant between-group differences in the RSTG and RIFG, we further investigated whether the SG ratios of these ROIs would be associated with the data of clinical assessments. Among patients with PD, a significant correlation was observed between the RIFG M50 SG ratio and the BSQ score ($r = 0.63$, $p = 0.003$), suggesting that a more severity of body sensation symptoms was accompanied with poor SG function (Fig. 3A). Moreover, the RIFG M50 SG showed a significant correlation with the distractibility score of SGI ($r = 0.43$, $p = 0.038$), suggesting that patients with more distractibility were accompanied by poor SG function (Fig. 3B).

4. Discussion

This study compared the SG function at the cortical level between patients with PD and healthy controls. The results showed significant between-group differences in SG ratios, particularly in the right frontal cortex. In addition, the SG ratios of the right frontal cortex positively correlated with the clinical symptoms of patients with PD.

To the best of our knowledge, this is the first study to elucidate the neural correlates of SG function in patients with PD and in comparison with a healthy control group. Our results were consistent with a previous ERP study, which also applied paired-click stimulation and demonstrated deficits of P50 SG in PD (Ghisolfi et al., 2006). In a similar vein, some studies have indicated an increased N100 response to repetitive, non-target stimuli during oddball paradigms (Iwanami et al., 1997; Wise et al., 2009) or during passive listening tasks (Knott et al., 1991). The enlargement of N100 responses or the lack of habituation to repetitive stimuli suggested a reduced ability to filter out irrelevant information (Pfleiderer et al., 2010). In addition, previous studies by examining sensorimotor gating, also a pre-attentive mechanism to regulate motor outputs by filtering out irrelevant sensory inputs, have demonstrated an abnormality of prepulse inhibition (PPI) in both medicated and non-medicated patients with PD compared with healthy controls (Ludewig et al., 2002; Ludewig et al., 2005). These findings, to some extent, corresponded to several clinical observations that patients with PD exhibited over-inclusion or distractible to the environmental stimuli, especially in the high sensory-load surroundings (Street et al., 1989). These maladaptive information processes at the pre-attentive stage might further lead to the inappropriate allocation of later-stage attentional processes.

The present study, extending the previous knowledge, has revealed that the right STG and IFG were the neural correlates associated with SG deficits in PD. In terms of STG, previous magnetic resonance imaging (MRI) studies using voxel-based morphometry (VBM) analyses have indicated a reduction in gray matter in bilateral temporal lobes in patients with PD compared to that in healthy controls (Sobanski et al., 2010). Another line of evidence supporting the relationship between the cortical thickness of STG and the SG ratio was provided by schizophrenia research, showing that a deficient SG ratio correlated with a thinner right-hemispheric cortex in schizophrenic patients (Thoma et al., 2004). Although we did not analyze gray matter volume, the aforementioned findings have suggested a possible association between neuroanatomy and neurophysiology underlying the SG measures. Regarding the IFG, there is ample evidence supporting the role of this brain region in the pathophysiology of PD. For example, VBM analyses of MRI data have indicated that patients with PD demonstrated gray matter reduction in the right IFG (Yoo et al., 2005; Lai and Wu, 2015) and bilateral pars triangularis (Kang et al., 2017). Taken together, our data suggest that STG and IFG, particularly the right hemisphere, play a role in the pathology of PD. Such inference was supported by a PET study, which showed that the decreased metabolism in both frontal and temporal lobes was modulated by the 12-week escitalopram intervention in patients with PD with treatment responders (Kang et al., 2012). A further investigation for analyzing the treatment effects on SG ratios in medication-naïve patients with PD is warranted.

In this study, it was worth noting that the M50 SG ratios of the RIFG correlated significantly with the BSQ scores. This result indicated that patients with PD with more deficient M50 SG displayed more disturbances in the interpretation of bodily sensations. A previous study investigating startle responses across three blocks also demonstrated a correlation between the percentage of habituation and the score of BSQ (Ludewig et al., 2005). The association between BSQ and pre-attentive SG or habituation suggested that patients with PD have defects in the early-stage information processing, which might further have adverse influences on the perception of somatic sensations. Another novel finding of the present study was the significant relationship between the

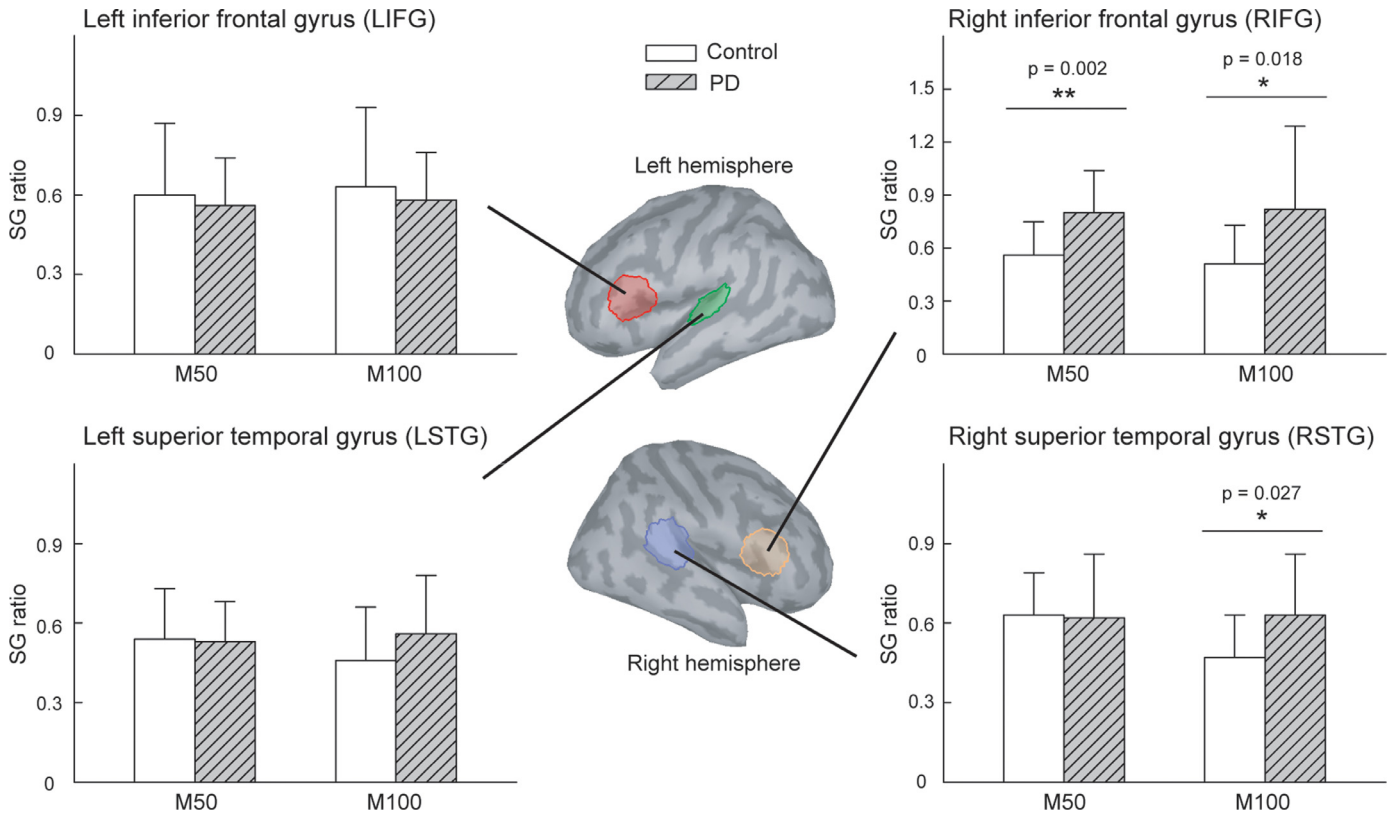

Fig. 2. Mean ± standard deviation (SD) of the M50 and M100 sensory gating (SG) ratios in the identified regions of interest (ROIs). Compared to the healthy controls, patients with panic disorder (PD) show significantly higher M50 SG ratios in the right inferior frontal gyrus, and higher M100 SG ratios in both right inferior frontal gyrus and superior temporal gyrus. The shaded areas cover each individual's ROI, which shows small variations among participants.

M50 SG ratio of RIFG and the behavioral ratings of distractibility, suggesting that patients with PD with more deficient SG ratios endorsed higher rates of reported distractibility. A previous research has reported that patients with PD were unable to focus their attention to the experimental instructions since they were not able to overcome the tendency for self-focused attention (Hayward et al., 2000). Previous electrophysiological studies that applied oddball discrimination tasks also confirmed that compared with healthy controls, patients with PD exhibited a declined P300 response, an ERP component that reflects attentional and working memory abilities (Turan et al., 2002; Wise et al., 2009; Howe et al., 2014). These findings implied that PD might have a maladaptive deployment of attention, secondary to the disturbances of pre-attentive information processing.

Some limitations should be considered when interpreting the results of this study. First, several patients showed the presence of comorbidities such as depression and agoraphobia. However, it should be noted that it was difficult to recruit patients with pure PD either from the clinical or from the community population. Nevertheless, our data that have provided information regarding the prevalence of comorbidities in patients with PD suggest that the current sample was representative of the general population. Second, 15 of the study patients were on treatment with benzodiazepines, which have been reported to reduce

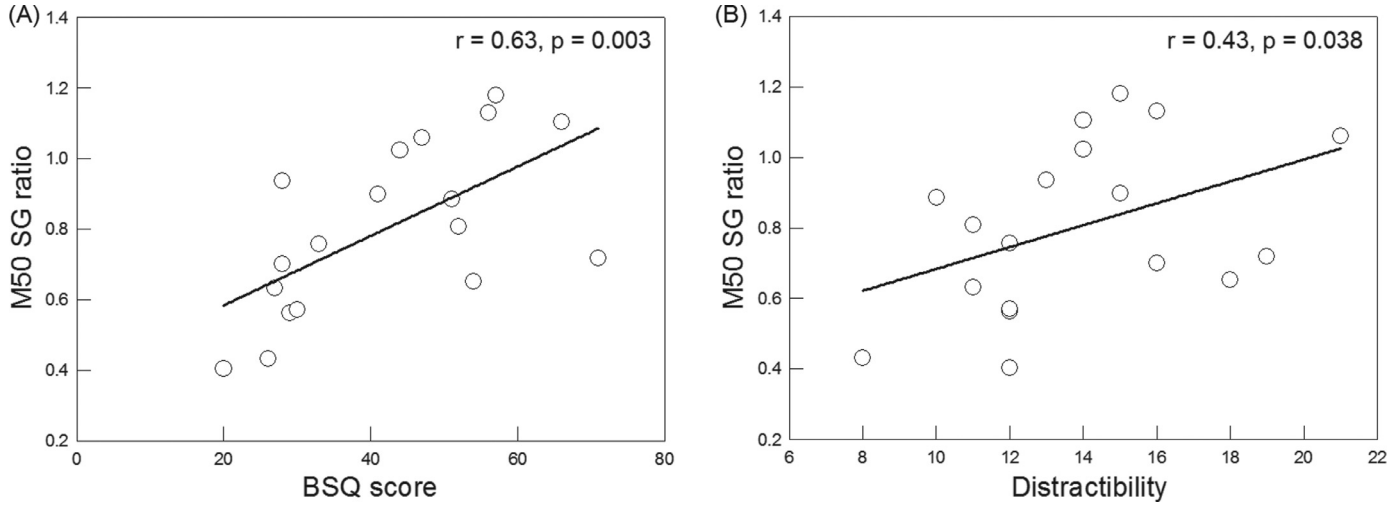

Fig. 3. Among the patients with panic disorder, the M50 sensory gating (SG) ratios of right inferior frontal gyrus are significantly associated with scores of Body Sensation Questionnaire (BSQ) and Distractibility scale of Sensory Gating Inventory (SGI).

the amplitudes of the N100 component to repetitive auditory stimuli (Rockstroh et al., 1991). Therefore, we reasoned that benzodiazepines might not contribute to the increased SG ratios in PD. However, we still could not rule out the effects of other treatments on the SG ratios. Finally, the sample size was relatively small, which might be one of the reasons that we could not detect a significant relationship between SG ratios and STAI scores.

In conclusion, the findings of the present study have made valuable contributions to the understanding of the neural correlates of SG deficits in patients with PD. Compared with healthy controls, patients with PD exhibited a deficient ability to filter out irrelevant sensory information, particularly in the right frontal cortex. Furthermore, SG deficits were associated with the cognitive misinterpretation of somatic sensations and distractibility.

CRediT authorship contribution statement

Chia-Hsiung Cheng: Conceptualization, Data curation, Methodology, Writing - original draft. **Pei-Ying S. Chan:** Methodology. **Shih-Chieh Hsu:** Investigation, Methodology. **Chia-Yih Liu:** Conceptualization, Investigation, Methodology, Writing - original draft.

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Conflicts of interest

The authors declare that they have no conflict of interest.

Ethics approval

The Institutional Review Board of Chang Gung Memorial Hospital (Linkou, Taiwan) approved this study.

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