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RESEARCH REPORT

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Paradoxical somatic information processing for interoception and anxiety in alexithymia

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Abstract

The concept of alexithymia has garnered much attention in an attempt to understand the psychological mechanisms underlying the experience of feeling an emotion. In this study, we aimed to understand how the interoceptive processing in an emotional context relates to problems of alexithymia in recognizing self-emotions. Therefore, we prepared experimental conditions to induce emotional awareness based on interoceptive information. As such, we asked participants to be aware of interoception under an anxiety-generating situation anticipating pain, having them evaluate their subjective anxiety levels in this context. High alexithymia participants showed attenuated functional connectivity within their 'interoception network', particularly between the insula and the somatosensory areas when they focused on interoception. In contrast, they had enhanced functional connectivity between these regions when they focused on their anxiety about pain. Although access to somatic information is supposed to be more strongly activated while attending to interoception in the context of primary sensory processing, high alexithymia individuals were biased as this process was activated when they felt emotions, suggesting they recognize primitive and unprocessed bodily sensations as emotions. The paradoxical somatic information processing may reflect their brain function pathology for feeling emotions and their difficulty with context-dependent emotional control.

KEYWORDS
alexithymia, emotion, insula, interoception, somatic information

List of abbreviations: ACC, anterior cingulate cortex; BA, Brodmann area; BOLD, blood-oxygen-level-dependent signals; ES, electric shock; FC, functional connectivity; FIR, finite impulse response; fMRI, functional magnetic resonance imaging; MAS, Manifest Anxiety Scale; MPFC, medial prefrontal cortex; MSPQ, Modified Somatic Perception Questionnaire; pIns/S1, posterior insula/primary sensory cortex; ROI, region of interest; SADS, Social Anxiety Disorder Scale; SIBIQ, Structured Interview for Beth Israel hospital Questionnaire; TAS-20, Toronto Alexithymia Scale; VAS, Visual Analogue Scale.

1 | INTRODUCTION

'Alexithymia' is a common personality trait among patients with psychosomatic disorders. It was originally described as 'relative constriction in emotional functioning, poverty of fantasy life, and inability to find appropriate words to describe their emotions' (Sifneos, 1973). Sifneos observed many patients who experienced difficulty for finding words to explain their feelings and seemed to have 'emotional agnosia' because they did not appear to understand the 'feeling'. He defined this trait as alexithymia. Several studies have revealed that individuals with high alexithymia are more vulnerable to physical illness (Tolmunen et al., 2010), because they are not good at controlling their emotion-related arousal levels and undergoing stressful conditions that last a long time, as compared with those with low alexithymia (Porcelli & Taylor, 2018). Nowadays, the concept of alexithymia is widely recognized and is attracting much attention, even in the fields of cognitive neuroscience, to better understand the neural mechanisms of subjective feeling of emotions (Moriguchi & Komaki, 2013; Taylor & Bagby, 2004; Wingbermuhle et al., 2012).

Although the detailed mechanisms underlying how feelings of bodily responses turn into emotions remain unresolved, evidence points to how tightly the bodily sensations and emotions are connected. For example, the bodily sensations associated with emotions are shared by people across cultures (Nummenmaa et al., 2014), and many studies have reported physiological responses characteristic of basic emotions (Ekman et al., 1983; Levenson et al., 1990; Rainville et al., 2006). Because high alexithymia individuals are impaired in their feeling and describing of sensations in emotional situations using appropriate words, they can potentially serve as an informative model to consider the relationship between emotional awareness and bodily sensation. The perception of afferent information arising from anywhere and everywhere within the body has been termed 'interoception' (Cameron, 2001; Sherrington, 1906), and numerous researchers have tackled the relationship between interoception and emotion in an attempt to disentangle the psychological and neural mechanisms underlying feeling emotions (Critchley et al., 2004; Terasawa, Fukushima, & Umeda, 2013; Terasawa, Shibata, et al., 2013).

If interoception serves as the foundation of feeling emotions, we are able to assume an altered interoceptive processing or altered association between interoception and emotion in individuals with high levels of alexithymia. This may manifest as, for example, a lower interoceptive accuracy or a certain disconnection between interoception and emotion. Although several previous studies have investigated whether high alexithymia is associated with high or low interoceptive ability, results remain controversial. Whereas some studies that used an experimental task with heartbeat perception pointed to lower interoceptive accuracy in high alexithymia individuals (Herbert et al., 2011; Shah et al., 2016), other studies have pointed to an increased or decreased attention to interoception using self-report questionnaires such as the Body Perception Questionnaire (Brewer et al., 2016; Ernst et al., 2014; Longarzo et al., 2015; Muir et al., 2017; Porges, 1993). One element to consider is that subjective measurements require self-reflection of one's own mind, which is the very core problem of alexithymia, and a questionnaire for alexithymia should be affected by individuals' concomitant problem of impaired self-awareness. Thus, it will be beneficial to identify the common neural underpinnings of both interoception and emotional experience and assess the association between alexithymia and neural activation in those brain regions, which may compensate for challenges linked to subjective measurements in alexithymia.

To deepen our understanding of alexithymia, several neuroimaging studies were conducted to explore the neural underpinnings of alexithymia. Most studies asked participants to evaluate the emotional values of stimuli such as facial expressions and emotional pictures and then examined how the participants' alexithymia levels modulated neural activation during the task (Berthoz et al., 2002; Jongen et al., 2014; Kano et al., 2007; Moriguchi et al., 2006; Suslow et al., 2016). In addition, some studies stimulated somatosensory sensations, such as painful stimuli (Bird et al., 2010; Moriguchi et al., 2007). A review of the neuroimaging studies on alexithymia points to the characteristics of neural responses in high alexithymia as decreased neural responses to emotional stimuli in emotion-related regions, such as the medial prefrontal cortex (MPFC), anterior cingulate cortex (ACC), insula and amygdala and increased responses to somatosensory stimuli in somatosensory or sensorimotor areas, including the insula (see the review by Moriguchi & Komaki, 2013). Interestingly, these brain regions are also well known areas as the regions underlying interoception (Schulz, 2016), indicating that interoceptive processing should be an important element in alexithymia, which should reflect the alterations in neural levels.

To the best of our knowledge, there are only a few neuroimaging studies, however, that examined the association between alexithymia and interoception (Ernst et al., 2014; Wiebking & Northoff, 2015). In a functional neuroimaging study (Wiebking & Northoff, 2015), neural activation during the heartbeat counting task negatively correlated with alexithymia scores in supragenual ACC (BA24/32) activity, while the insula activity was

enhanced in participants with high alexithymia scores. A magnetic resonance spectroscopy study (Ernst et al., 2014) suggests that glutamate-mediated excitatory transmission nested in the insula underlies enhanced interoceptive sensibility in high alexithymia. The results from these studies imply that interoceptive as well as somatosensory or sensorimotor processing is enhanced in high alexithymia, as reflected in their increased insula activation. Although there are a few neuroimaging studies focusing on alexithymia in the context of neural responses to emotional stimuli or interoception individually, no study has addressed how alexithymia modulates the neural processing of interoception in the context of emotional experience and the awareness thereof, such as in the context of interoception when feeling emotions. This approach will allow us to consider whether biased interoception underlies poor emotional experience in high alexithymia. Furthermore, the results will advance our understanding of the mechanisms underlying the construction of emotions.

In this study, we developed a task to examine interoception-related neural activity under an emotional situation that induces anxiety. When participants were made to feel anxious in light of an upcoming electric shock, they were requested to orient their attention to interoceptive or exteroceptive information while waiting for the shock. This procedure allowed us to examine the interoceptive or exteroceptive information processing under anxious situations and how the attention to interoception modulates anxious feelings. It would be appropriate to choose anxiety as an emotion to investigate interoceptive processing under an emotional situation, as previous studies have suggested the tight connection between levels of anxiety and interoception (Domschke et al., 2010; Melzig et al., 2008).

We sought to understand how interoceptive processing in an emotional context relates to problems of alexithymia in recognizing self-emotions. In order to assess changes in activity levels according to the degree of alexithymia, brain activity was measured by functional magnetic resonance imaging (fMRI) (1) while participants attended to interoception and (2) while participants were emotionally aware of experimentally induced anticipatory anxiety. First, we investigated local neural activation in interoception-related areas such as the insula. In addition to local activities, we investigated functional connectivity (FC) that involve emotion and interoception regions, as some previous studies reported that alexithymia was associated with decreased or increased FC of the insula (Sutherland et al., 2013) and sensorimotor cortex (Ho et al., 2016; Liemburg et al., 2012). Through this study, we aimed to see the neural activity and FC in the areas related to interoception and their association with the degree of alexithymia, while participants attended to interoception and anxious state.

2 | METHODS

2.1 | Participants

Thirty-three right-handed undergraduate and graduate students (13 males, 20 females; mean $\pm$ *SD* age $= 22 \pm 1.6$ years) participated in and completed a semi-structured interview and questionnaires. Eighteen of them (11 male, 7 female) also participated in and completed an fMRI experiment by their own volition. The final sample size for fMRI experiment was decided based on consideration of prior, conceptually related work (i.e., Ernst et al., 2014), and data were not analysed until data collection was completed. No participants had any ongoing psychiatric disorders nor were they taking any medications. The study was performed with the approval of the National Centre of Neurology and Psychiatry Research Ethics Committee (No. 2011-035), which complied with the Helsinki Declaration of 1975, as revised in 2008. Before participating in the study, all individuals read and signed a written informed consent form explaining (i) the purpose and procedure of the study and (ii) that they were able to withdraw from the study at any time.

2.2 | Procedures

2.2.1 | Semi-structured interview

To assess alexithymia traits, we employed the Japanese version of Structured Interview for Beth Israel hospital Questionnaire (SIBIQ; Arimura et al., 2002). The SIBIQ is based on the Beth Israel hospital psychosomatic questionnaire (Sriram et al., 1988) and has been used in a couple of neuroimaging studies to objectively assess individual alexithymia tendencies (Moriguchi et al., 2006, 2007, 2009). In this interview, participants were asked to recall their personal painful or pleasant memories and express the feelings they experienced at the events. In addition, they reported how they handled the problems. They were also asked to imagine a person who they thought they were close to and share their feelings about that person. Two experienced raters, one of whom was the interviewer, independently evaluated the dialogue from the aspects of emotional awareness, ability to describe their own or other's emotions and luxuriance of imagination. Ten scoring items were closely associated with the evaluation of alexithymia.

Such items include, 'Subject has difficulty to tell the interviewer about his/her feelings' and 'Subject tends to refer to the facts about the events and describe them precisely, rather than to refer to his/her feelings for the events'. Two independent raters rated the participant on each item by seven steps, after which the total score of the 10 items was regarded as the participant's level of alexithymia. Consistency between the two raters was assessed by a mixed-model intraclass correlation coefficient (ICC(2,1)). On the basis of the SIBIQ score, we divided the subjects into two groups: Participants whose SIBIQ score was in the upper and lower half were classified as being in the high and low alexithymia group, respectively.

2.2.2 | Questionnaires

We used four questionnaires to assess the individual inclination of emotional processing, including the Social Anxiety Disorder Scale (SADS; Kaiya, 2009), Manifest Anxiety Scale (MAS; Abe, 1968; Taylor, 1953), Modified Somatic Perception Questionnaire (MSPQ; Main, 1983) and NEO Five-Factor Inventory (Mccrae & Costa, 1991; Shimonaka et al., 1999). We also used the Japanese version of the 20-item Toronto Alexithymia Scale (TAS-20; Bagby et al., 1994; Komaki et al., 2003) to compare the self-rated questionnaire with the aforementioned semi-structured interview.

2.2.3 | fMRI experiment

Eighteen participants (10 males, 8 females; mean ± *SD* age = 22 ± 1.9 years) agreed to proceed to an fMRI experiment after completing the questionnaires and interview. To assess the neural correlates for attending to their own bodily and emotional states, we prepared two conditions, an interoceptive condition and exteroceptive condition, to accentuate the neural correlates of attending to a bodily state (interoceptive condition) by contrasting the interoceptive with the exteroceptive condition. Because participants were instructed before the experiment that there may be a risk of receiving an electric shock (ES) on their wrist in each trial, they were exposed as such to an anticipatory anxious feeling. We asked them to evaluate their own anxiety levels in each trial. ESs were delivered by STM100C (BIOPAC systems, Inc.), and the maximum amplitude of the stimulus was set for each participant using adjusting method prior to scans. The experimenter presented some stimuli with STM100C to each participant and set the level of stimulation at allowable maximum point.

At the beginning of each trial (Figure 1), a cue for the interoceptive or exteroceptive condition was presented for 2 s on a monitor placed in the MRI scanner. 'Heartbeat' and 'Scan sounds' were presented as a cue for the interoceptive and exteroceptive condition, respectively. Subsequently, the sentence 'Press L or R' was presented, to which participants were requested to respond by pressing one of two buttons, left or right, on an MRI-compatible mouse controller, which was connected to the control computer and recorded the responses. They

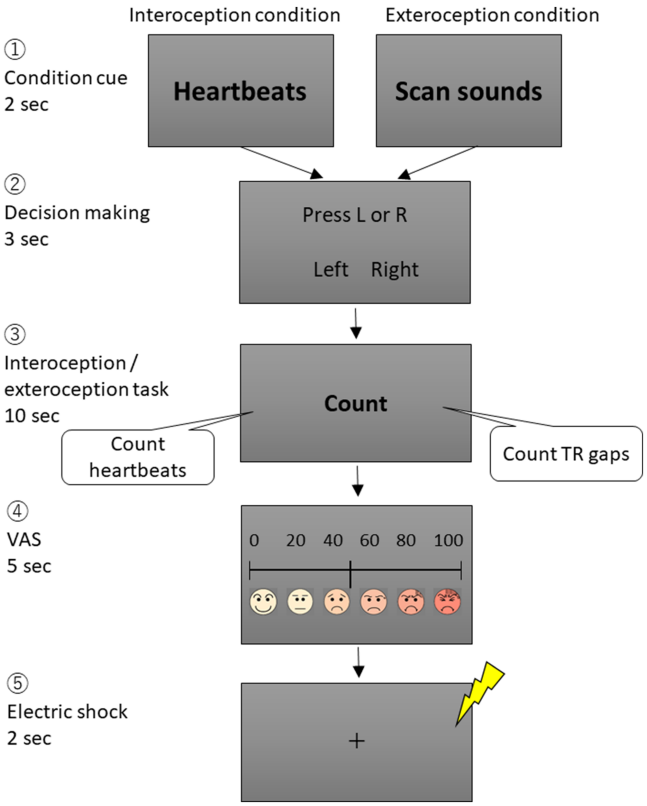

FIGURE 1 Functional magnetic resonance imaging (fMRI) task design. (1) At the beginning of each trial, a cue for the interoceptive or exteroceptive condition was presented for 2 s. 'Heartbeats' was presented as a cue for the interoceptive condition, and 'Scan sounds' was presented for the exteroceptive condition. (2) 'Press L or R' was presented, to which participants were requested to respond by pressing one of two buttons, left or right, on an MRI-compatible mouse controller. (3) 'Count' was presented for 10 s as an attending period. In the interoceptive (Heartbeats) condition, participants were asked to attend to their own heartbeats and count them during this period. In the exteroceptive (Scan sounds) condition, they were asked to attend to MRI scanner sounds and count the sound iterations (more specifically the gaps of the sounds). (4) A Visual Analogue Scale (VAS) was presented for 5 s, and participants were required to evaluate the level of anticipatory anxiety about receiving an electric shock (ES). (5) In the end of a trial, an ES was delivered to the participant pseudorandomly (25% of trials for each condition)

were instructed that they would receive an ES at the end of each trial, which was dependent on their choice in some way, so that the participants could not understand how their decision was linked to the subsequent incidence (i.e., electrical shock). Next, the word 'Count' was presented for 10 s as an attending period. In the interoceptive (heartbeat) condition, participants were asked to attend to their heartbeats and count them during this period. Conversely, they were asked to attend to repetitive sounds from the MRI scanner and count the sounds (one for each repetition time) in the exteroceptive (Sound) condition. Thereafter, a Visual Analogue Scale (VAS) was presented for 5 s, and the participants were required to evaluate their level of anticipatory anxiety with regard to receiving an ES. This evaluation of their own anxiety with VAS should reflect their 'emotional awareness' and could vary depending on the preceding attending strategy (that is, interoceptive or exteroceptive). Responses ranged from 0 to 100. At the end of a trial, an ES was delivered to the participant pseudorandomly, although participants believed that the ES depended on the 'Left or Right' choice that they had already made. Because an ES was delivered in 25% of trials for each condition, participants actually felt strong anticipatory anxiety during this period. Thirty-two trials (16 trials for each condition) were divided into two runs. A run consisted of 8 interoceptive and 8 exteroceptive trials, with 16 trials in total. Two out of 8 trials in each condition were associated with ES. We set two types of runs with different sequential orders of the 16 trials (run A and B), in both of which interoceptive and exteroceptive trials appeared randomly, with no ES delivered successively. All the participants went through two runs (once for each run A and B), and the order of the two runs (A → B or B → A) was counterbalanced across the participants.

2.2.4 | Anticipatory anxiety about the ES

The anticipatory anxiety about the ES was evaluated by the VAS in each trial. We expected that three factors would affect the VAS scores: (1) experimental conditions (interoception vs. exteroception), (2) alexithymia levels (high vs. low) and (3) run order (first vs. second), thereby constituting a three-way analysis of variance (ANOVA) model. Because previous studies reported that the orientation to bodily sensation would modulate anxiety levels (Domschke et al., 2010), we first assessed whether the VAS scores in the two conditions (interoception/exteroception) were different. Second, as alexithymia levels are considered to be associated with anxiety, we divided the subjects into two groups based on the SIBIQ scores and compared the VAS scores between high and low alexithymia groups. We took into account a 'learning effect' linked to the increased number of runs over time, as the anticipatory anxiety was expected to be altered by the accumulating experience of pain. Thus, we estimated the interactive effects of runs on the other two factors.

2.3 | fMRI data analysis

2.3.1 | Data acquisition

For fMRI scanning, we used a 3T Siemens Verio scanner with an 8-channel head coil for data acquisition. Scanning was carried out as two experimental functional runs and a high-resolution T1-weighted structural scan (3D MPRAGE with 1-mm isotropic resolution). Each functional run consisted of 240 whole-brain T2* weighted single-shot gradient-echo planar imaging (EPI) images, which produced blood-oxygen-level-dependent signals (BOLD), collected in an oblique axial orientation (TR 3s, TE 30 ms, FA 90 degrees, voxel size 3.5 × 3.5 × 3 mm, 44 slices [descending], slice gap 1 mm). The structural scan was co-registered to the participant's mean EPI image.

2.3.2 | Data processing

Individual data were preprocessed and analysed using SPM8 software (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). Functional time-series images from each participant were spatially corrected for head movement, and temporally corrected for slice timing, spatially normalized to the Montreal Neurological Institute template and smoothed with a three-dimensional Gaussian filter (8-mm full width half maximum, FWHM). In addition, a high-pass temporal filter with a cut-off of 128 s was applied to remove low-frequency drift in the signals.

2.3.3 | fMRI data analyses for the attending period

We used a finite impulse response (FIR) model to identify the neural correlates of processing interoceptive and exteroceptive information during the trials in an experimental manner. We did not exploit any canonical haemodynamic responses for this analysis, because we did not have any a priori hypothesis with regard to the detailed haemodynamic curves during this relatively long-lasting psychological task trial. As shown in Figure 2, a trial lasted 20 s, followed by a 10-s period of eye movement fixation. We set eight 3-s bins, and BOLD

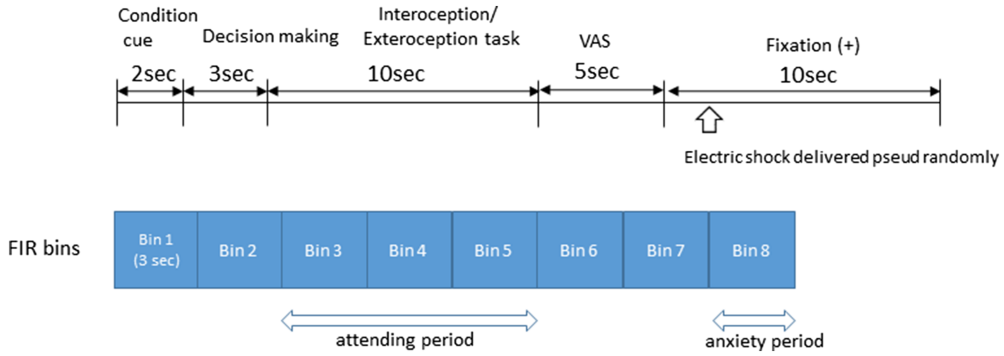

FIGURE 2 The inter-trial interval (ITI) was 30 s. We set eight 3-s bins to cover the haemodynamic changes due to each trial (20 s). The third, fourth and fifth bins were considered reflective of the haemodynamic changes with participants paying attention to the interoception or exteroception. The eighth bin was considered reflective of haemodynamic changes with anxiety caused by the anticipation of an electric shock. Blood-oxygen-level-dependent signals (BOLD) signals were also compared between the two task conditions

signals averaged across the third, fourth and fifth bins (corresponding to the putative time to reflect their attending process), which were compared between the interoceptive and exteroceptive conditions. Contrasted individual BOLD signal maps were subsequently fed into second-level group analyses for the attending period, taking into account the random effects. The statistical threshold was set to $p < 0.05$, with a false discovery rate (FDR) correction by cluster-level extent.

2.3.4 | fMRI data analyses for the anxiety period

We defined the eighth bin, which was associated with the ES period, as an anxiety period. Because the eclectic shock was delivered in 25% of this period, participants were assumed to be anxious, which should be reflected in the signal changes during this bin, regardless of whether they have received the shock or not. We compared the BOLD signals of this bin between interoceptive and exteroceptive conditions to assess the effects of the direction of attention on anxiety. Similar to the attending period, contrasted individual activation maps were subsequently fed into second-level group analyses, and the statistical threshold was set to $p < 0.05$, with an FDR correction by cluster-level extent.

2.3.5 | FC analyses

We further assessed whether the individual alexithymia levels would be associated with FC that connects a brain region with other remote regions, during each both the attending and anxiety period. Firstly, we created 6-mm-radius sphere regions of interest (ROIs) around the peaks of regions that we had identified as being significantly greater BOLD signals while attending to interoception rather than exteroception. The ROIs for the anxiety period were defined in a similar fashion, by comparing BOLD signals in the anxiety period between interoceptive and exteroceptive conditions. Spherical ROIs were then created. Next, we set such ROIs as the 'seed' regions for FC analyses. Time-series BOLD signals at the seed region were incorporated into voxel-by-voxel correlation analyses with BOLD signals across the whole brain using generalized linear model (GLM). This whole-brain GLM analysis exploits voxel-by-voxel regression of a voxel's signals on the seed signal, with head motions and hypothetical stimulus-locked transient haemodynamic responses to the events as confounding covariates. The signals that were used in the GLM analyses had been filtered with a bandpass filter (0.008–0.16 Hz), which had been optimized through a spectral analysis to capture effective event-related FC in this GLM. FC during the attending period and FC during the anxiety period in each was contrasted between the interoceptive and exteroceptive condition, thereby producing individual contrast maps. Such contrasted maps of connectivity were entered into second-level correlation analyses with individual alexithymia scores measured by SIBIQ. We used the CONN FC toolbox (http://www.nitrc.org/projects/conn/) for FC analyses. The statistical threshold was set to $p < 0.05$, with an FDR correction by cluster-level extent.

3 | RESULTS

3.1 | Psychological assessments: Semi-structured interview for alexithymia (SIBIQ) and questionnaires

Table 1 shows the means and standard deviations for the semi-structured interview (SIBIQ) and questionnaires,

TABLE 1 Descriptive and correlational analyses of semi-structured interview (SIBIQ) and questionnaires

		All participants ($n = 33$)			MRI participants ($n = 18$)			All vs. MRI participants		
				Correlation with SIBIQ			Correlation with SIBIQ			
		Mean	*SD*	*r*	Mean	*SD*	*r*	*t* value	*p* value	
Alexithymia trait (SIBIQ)		39.72	11.40		41.44	11.21		0.97	0.34	n.s.
Social Anxiety Disorder Scale	Fear	10.30	5.95		10.44	5.76		0.15	0.88	n.s.
	Avoidance	7.21	5.57		7.11	6.21		0.11	0.91	n.s.
	Somatic symptoms	8.55	6.25		9.06	6.47		0.51	0.62	n.s.
	Daily life interference	2.12	5.45		3.33	6.86		1.42	0.17	n.s.
	Total	28.18	19.46	−0.41*	29.94	21.75	−0.40	0.56	0.58	n.s.
TAS-20	Difficulty identifying feeling	10.76	6.44		11.11	5.22		0.34	0.74	n.s.
	Difficulty describing feelings	10.61	3.59		11.61	3.16		1.83	0.08	n.s.
	Externally oriented thinking	10.12	3.02		10.33	3.40		0.44	0.67	n.s.
	Total TAS	31.48	8.98	−0.04	33.06	7.88	0.19	1.10	0.28	n.s.
MAS		18.43	7.11	−0.47**	18.94	6.58	−0.29	0.48	0.64	n.s.
MSPQ		10.03	6.10	−0.26	10.11	5.75	−0.10	0.08	0.94	n.s.
BDI		7.15	4.75	−0.28	7.89	4.42	−0.14	0.98	0.34	n.s.
NEO-FFI	Neuroticism	23.42	7.62	0.20	25.06	8.26	0.00	1.37	0.18	n.s.
	Extraversion	28.27	6.39	−0.19	26.61	6.41	−0.37	1.68	0.10	n.s.
	Openness	32.52	6.20	0.37*	33.17	5.98	0.57**	0.66	0.52	n.s.
	Agreeableness	29.76	6.40	0.13	28.22	5.67	0.02	1.54	0.13	n.s.
	Conscientiousness	27.64	6.64	−0.54**	26.61	7.91	−0.64**	0.97	0.34	n.s.

Abbreviations: MAS, Manifest Anxiety Scale; MRI, magnetic resonance imaging; MSPQ, Modified Somatic Perception Questionnaire; SIBIQ, Structured Interview for Beth Israel hospital Questionnaire; TAS, Toronto Alexithymia Scale.
*$p < 0.05$. **$p < 0.01$.

and the correlations among them, in all participants as well as MRI participants. No difference was observed in the scores between all participants and MRI participants; subsequently, the following results, in this section, were reported for all participants.

Two independent experienced raters assessed participants' alexithymia traits based on their responses in the SIBIQ. The ICC(2,1) indicated that the ratings by the two different raters had good consistency ($\rho = 0.68$, $df = 29$, $p < 0.01$).

As previously reported (Marchesi et al., 2014), our study also showed that self-reported questionnaires for alexithymia were positively correlated with negative affect. Total and difficulty in identifying emotion (DIF) scores in the TAS-20 were positively correlated with anxiety levels as assessed by MAS ($r\,(31) = 0.42$, $p = 0.02$ and $r\,(31) = 0.40$, $p = 0.03$, respectively), and total scores in the TAS-20 tended to correlate with depression scores on the beck depression inventory (BDI) ($r\,(31) = 0.31$, $p = 0.08$). In addition, DIF and total scores in the TAS-20 were positively correlated with symptom scores in the SADS ($r\,(31) = 0.35$, $p = 0.05$ and $r\,(31) = 0.36$, $p = 0.04$, respectively). In contrast, alexithymia trait assessed by the SIBIQ was not positively but rather negatively correlated with negative affect, such as total scores in the SADS, general anxiety (MAS) and neuroticism (NEO-N) ($r\,(30) = -0.40$, $p = 0.02$, $r\,(30) = -0.47$, $p = 0.01$, $r\,(30) = -0.43$, $p = 0.02$, respectively). These results indicate that the TAS-20 may be strongly affected by negative affect such as anxiety and depression, which is not consistent with the original concept of alexithymia features. In contrast, the interview assessed those who express 'less expression of negative affect' as being alexithymic, which may fit well with the clinical features of individuals with alexithymia. Therefore, we used the SIBIQ score as reflective of participants' levels of alexithymia in

further analyses. Participants were divided into high and low alexithymia groups based on the SIBIQ score (high alexithymia: $N = 9$, mean = 50.11, $SD = 5.74$ and low alexithymia: $N = 9$, mean = 32.78, $SD = 8.08$).

3.2 | Effects of attending to interoception on anxiety levels

The anticipatory anxiety about the ES was evaluated by the VAS in each trial, and we performed a three-way ANOVA to examine the effects of the following three factors on the anxiety scores: (1) experimental conditions (interoception vs. exteroception), (2) alexithymia levels (high vs. low) and (3) runs (first vs. second). We found no main effect of attention to interoceptive/exteroceptive information ($F(1, 16) = 1.71$, $p = 0.21$), alexithymia levels ($F(1, 16) = 0.77$, $p = 0.39$) or runs ($F(1, 16) = 0.41$, $p = 0.53$) on VAS scores. However, the interaction of interoceptive/exteroceptive information and runs was significant at high alexithymia ($F(1, 16) = 5.54$, $p = 0.03$), and post-hoc tests revealed that high alexithymia showed enhanced anxiety in the interoception condition on the second run ($F(1, 32) = 6.13$, $p = 0.02$; Table 2). This result shows that the experience of pain in individuals with high alexithymia may enhance their anxiety about ES after they have been directed to focus on interoception.

3.3 | fMRI results

3.3.1 | Attending to interoception versus exteroception

We compared BOLD signals during the attending period to identify regions specifically activated in the interoceptive and exteroceptive conditions. We found a stronger activation in the interoceptive than in the exteroceptive condition in the left middle insula/frontal operculum, the critical region for interoception and the supplementary motor area ($p < 0.05$, FDR corrected by cluster-level extent; Table 3, Figure 3). In contrast, auditory areas (the bilateral posterior superior temporal gyri) were more activated in the exteroceptive condition (Table 3); 6-mm-radius sphere ROIs were created around the peaks of regions that were strongly activated in the interoceptive rather than in the exteroceptive condition, but the activation of ROIs was not correlated with SIBIQ scores.

3.3.2 | Feeling anticipatory anxiety in expectation of pain after interoceptive versus exteroceptive attention

We found that the assessment of their own anxiety after interoceptive attention resulted in stronger activation in the bilateral middle to posterior insular cortex compared with that after exteroceptive attention ($p < 0.05$, FDR corrected by cluster-level extent; Table 4, Figure 4), thereby indicating that interoceptive orientation may modulate the neural process linked to the self-awareness of an emotion. ROIs around the peaks were defined by the similar procedure, as reported in section of *Attending to interoception versus exteroception*. Activation of ROIs was not significantly correlated with SIBIQ scores, thereby suggesting that alexithymia is not linearly related to regional neural activation.

3.3.3 | Functional connectivity

We conducted FC analyses to investigate how the degree of alexithymia modulates connectivity between the neural underpinnings of interoception and other brain regions.

For the attending period, we created 6-mm-radius sphere ROIs centred on the peak of the regions with higher activation in the interoception than in the exteroception condition (left insula: $x = -56$, $y = 2$, $z = 12$, supplementary motor cortex: $x = 2$, $y = -8$, $z = 62$) and set these ROIs as the seeds in the FC analyses. Results revealed that individuals with higher alexithymia showed more negative or less positive FC values seeded at the left middle insula when they attended to interoceptive information; the SIBIQ scores

TABLE 2 VAS scores for anxiety

	1st run				2nd run			
	Interoception		Exteroception		Interoception		Exteroception	
High alexithymia	32.8	(4.8)	33.1	(4.9)	36.5	(3.8)	33.5	(4.4)
Low alexithymia	39.9	(6.1)	39.4	(6.0)	41.5	(7.2)	41.0	(7.0)

Note: The table shows means and standard errors in parentheses.
Abbreviation: VAS, Visual Analogue Scale.

TABLE 3 Neural correlates for attending interoception and exteroception ($p < 0.05$ FDR corrected by cluster-level extent)

Regions of activation	Number of voxels in cluster	L/R	BA	*t* value	MNI		
					x	*y*	*z*
Interoception > exteroception	Extent threshold: $k = 407$						
Frontal inferior operculum	407	L	44	5.24	−56	2	12
Middle insula		L	13	4.30	−38	2	10
Supplementary motor area	409	L/R	6	3.95	2	−8	62
Exteroception > interoception	Extent threshold: $k = 690$						
Superior temporal gyrus	1816	L	41	6.56	−40	−34	10
Superior temporal gyrus		L	22	3.36	−62	−44	13
Posterior insula		L	13	3.35	−43	−10	−3
Posterior insula	2163	R	13	6.40	52	−18	6
Superior temporal gyrus		R	41	6.37	52	−28	10
Superior temporal gyrus		R	22	5.67	60	−20	3
Middle occipital gyrus	4624	L	18	5.82	−24	−92	2
Middle occipital gyrus		L	18/19	5.48	−26	−92	−12
Cuneus, Lingual gyrus		R	17	5.22	28	−86	−6
Paracentral lobule	690	L/R	3/4/6	4.55	4	−30	68
Frontal inferior operculum	1619	R	9	4.54	44	14	26
Middle frontal gyrus		R	46	3.98	52	34	20
Middle frontal gyrus		R	47	3.72	38	30	4

Abbreviations: BA, Brodmann area; FDR, false discovery rate; MNI, Montreal Neurological Institute.

were negatively correlated with the FC from the left middle insula to left postcentral/middle frontal gyrus and somatosensory cortex (BA2, 3, 4, 6, 40), right pre/postcentral gyrus (BA2, 3, 4, 6) and middle/inferior temporal gyrus (BA37) ($p < 0.05$, FDR corrected; Table 5 and Figure 5).

For the anxiety period, we created 6-mm-radius sphere ROIs from activated regions in the interoception compared with the exteroception condition, which corresponded to the bilateral middle to posterior insula cortices extending to the primary sensory cortex (peaking at $[x = -40,\ y = -2,\ z = 10]$ and $[x = 50,\ y = -18,\ z = 36]$). Results revealed that individuals with higher alexithymia exhibit more positive FC from the right posterior insula/primary sensory cortex (pIns/S1); the SIBIQ scores were positively correlated with the FC from the seed ROI to the right inferior/superior parietal cortex, which may represent bodily sensation (BA 7, 39, 40) ($p < 0.05$, FDR corrected; Table 6 and Figure 6). We did not observe any significant correlation between the SIBIQ score and FC from the left middle posterior insula.

The results of the FC analyses showed that alexithymia is associated with biased attention to bodily sensations and interoception.

4 | DISCUSSION

In this study, we focused on interoceptive processing and difficulties related to emotional functions in alexithymia by examining the relationship between alexithymia and neural activity while participants were instructed to attend to interoception in anxious situations. We observed activity levels in several brain regions that were consistent with previous studies on emotion and interoception. Although we did not find a linear relationship between the regional activity in these regions and the alexithymia levels as evaluated by the structured interview, we found that FC from these regions to somatosensory areas varied according to the alexithymia levels.

4.1 | Alexithymia and brain activity while attending to interoception

As mentioned in the result section, enhanced activation in the left middle insular cortex and the medial frontal cortex (supplementary motor area) was observed while attending to interoception. Because previous studies reported the involvement of these regions in interoception related to cardiac and respiratory activity

(e.g., Critchley et al., 2004; Liotti et al., 2001; Terasawa, Fukushima, & Umeda, 2013), we confirmed that the participants in this study made an effort to feel their heartbeats while attending to interoception in response to specific instructions. In contrast, enhanced activation in the auditory areas (the bilateral posterior superior temporal gyri) was observed while attending to sounds in the scanner in the exteroception condition (reviewed in Alho et al., 2014). These results clearly show that participants were engaged in the cognitive task in the scanner, as instructed, for both tasks.

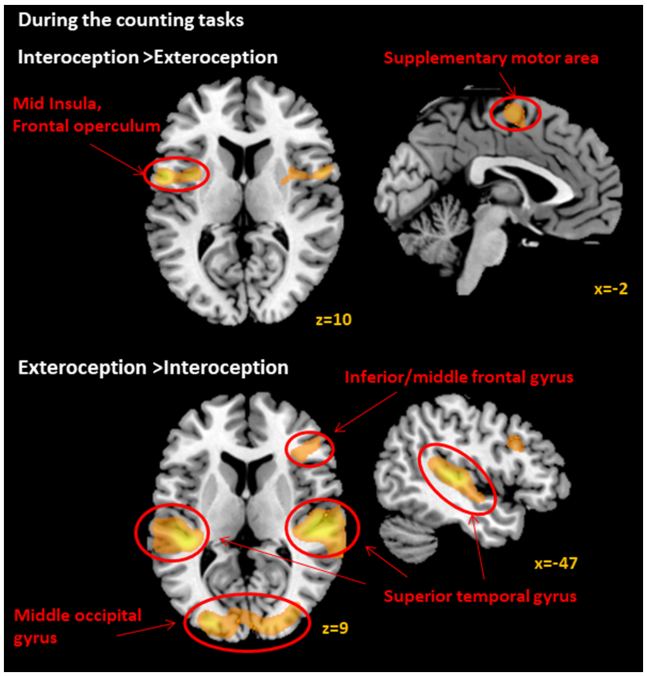

FIGURE 3 Activated regions during the attending period ($p < 0.05$ false discovery rate [FDR] corrected, cluster-level extent). Upper figure: Regions strongly activated in the interoception condition compared with the exteroception condition. Lower figure: Regions strongly activated in the exteroception condition

The absence of a linear relationship between the alexithymia level and regional neural activation, however, may suggest that enhanced or attenuated interoception is not the fundamental factor related to alexithymia, at least as in the non-clinical group in this study. These results imply that they could attend and detect interoceptive information when they were explicitly instructed to direct their attention to their own interoception. This fact may be linked to the conflicting findings of previous studies on the relationship between alexithymia and interoception, as some studies showed positive associations between them, whereas other studies showed negative associations between them (e.g., Ernst et al., 2014; Herbert et al., 2011; Longarzo et al., 2015; Shah et al., 2016). This inconsistency may result from the subtle differences in the task settings used to evaluate the levels of alexithymia and interoception, rather than from the fundamental dysfunction of interoception itself in alexithymia.

We obtained interesting findings that demonstrated that the FC from the insula and its adjacent area to other regions were significantly modulated by alexithymia

TABLE 4 Neural correlates for evaluating anxiety level in the interoception and the exteroception conditions ($p < 0.05$ FDR corrected by cluster-level extent)

Regions of activation		Number of voxels in cluster	L/R	BA	*t* value	MNI		
						x	*y*	*z*
Interoception > exteroception	Extent threshold: $k = 817$							
	Insula	1,358	L	13	4.43	−40	−2	10
	Precentral and postcentral gyrus		L	6/40/43	3.30	−56	−16	16
	Superior temporal gyrus, Supramarginal gyrus		L	41/42	3.66	−66	−22	36
	Precentral and postcentral gyrus (primary sensory cortex)	817	R	3/4	4.02	50	−18	36
	Insula		R	13	3.76	46	−20	16
	Superior temporal gyrus and supramarginal gyrus		R	41/43	3.69	36	−22	12
Exteroception > interoception								
	N.A.							

Abbreviations: BA, Brodmann area; FDR, false discovery rate; MNI, Montreal Neurological Institute.

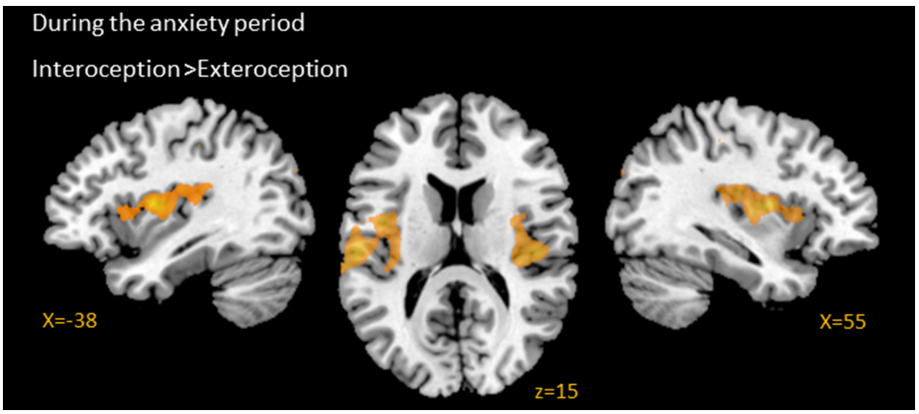

FIGURE 4 Activated regions during the anxiety period ($p < 0.05$ false discovery rate [FDR] corrected, cluster-level extent). Bilateral dorsal middle to posterior insular cortex was activated in the interoception condition compared with the exteroception condition ($p < 0.05$ FDR corrected, cluster-level extent)

TABLE 5 Functional connectivity that correlated with alexithymia level (SIBIQ) while attending interoception ($p < 0.05$ FDR corrected)

						MNI		
		Number of voxels in cluster	**L/R**	**BA**	***t* value**	**x**	**y**	**z**
Seed region: MPFC (2, −8, 62)		Extent threshold: $k = 439$						
Positive correlation								
	Cerebellum posterior lobe	439	R	-	6.15	14	−82	−28
	Cerebellum posterior lobe		R	-	4.07	34	−76	−32
	Cerebellum posterior lobe		R	-	3.58	24	−74	−34
Negative correlation								
	N.A.							
Seed region: left insula (−56, 2, 12)		Extent threshold: $k = 487$						
Positive correlation								
	N.A.							
Negative correlation								
	Middle frontal gyrus	620	R	4/6	8.78	30	−10	48
	Postcentral gyrus		R	2/3	5.75	30	−24	44
	Supplementary motor area		R	6	4.67	14	−22	52
	Precentral gyrus	1949	L	2/3	6.26	−48	−28	60
	Postcentral gyrus		L	2/40	5.63	−46	−30	48
	Supramarginal gyrus		L	40	5.03	−50	−28	32
	Inferior temporal gyrus	487	R	37	5.24	52	−58	−4
	Middle temporal gyrus		R	19	4.67	34	−60	20
	Inferior temporal gyrus		R	37	4.48	42	−60	−2

Abbreviations: BA, Brodmann area; FDR, false discovery rate; MNI, Montreal Neurological Institute; MPFC, medial prefrontal cortex; SIBIQ, Structured Interview for Beth Israel hospital Questionnaire.

during the attending and anxiety periods in the interoception condition. In the attending period, the FC from the left insula to three regions, (1) the left postcentral/middle frontal gyrus and somatosensory cortex (BA2, 3, 4, 6, 40), (2) the right pre/postcentral gyrus (BA2, 3, 4, 6) and (3) the middle/inferior temporal gyrus (BA37), were negatively correlated with the SIBIQ score. In other words, high alexithymia participants presented weaker connections between the insula, a core region for interoception and the somatosensory areas when they were

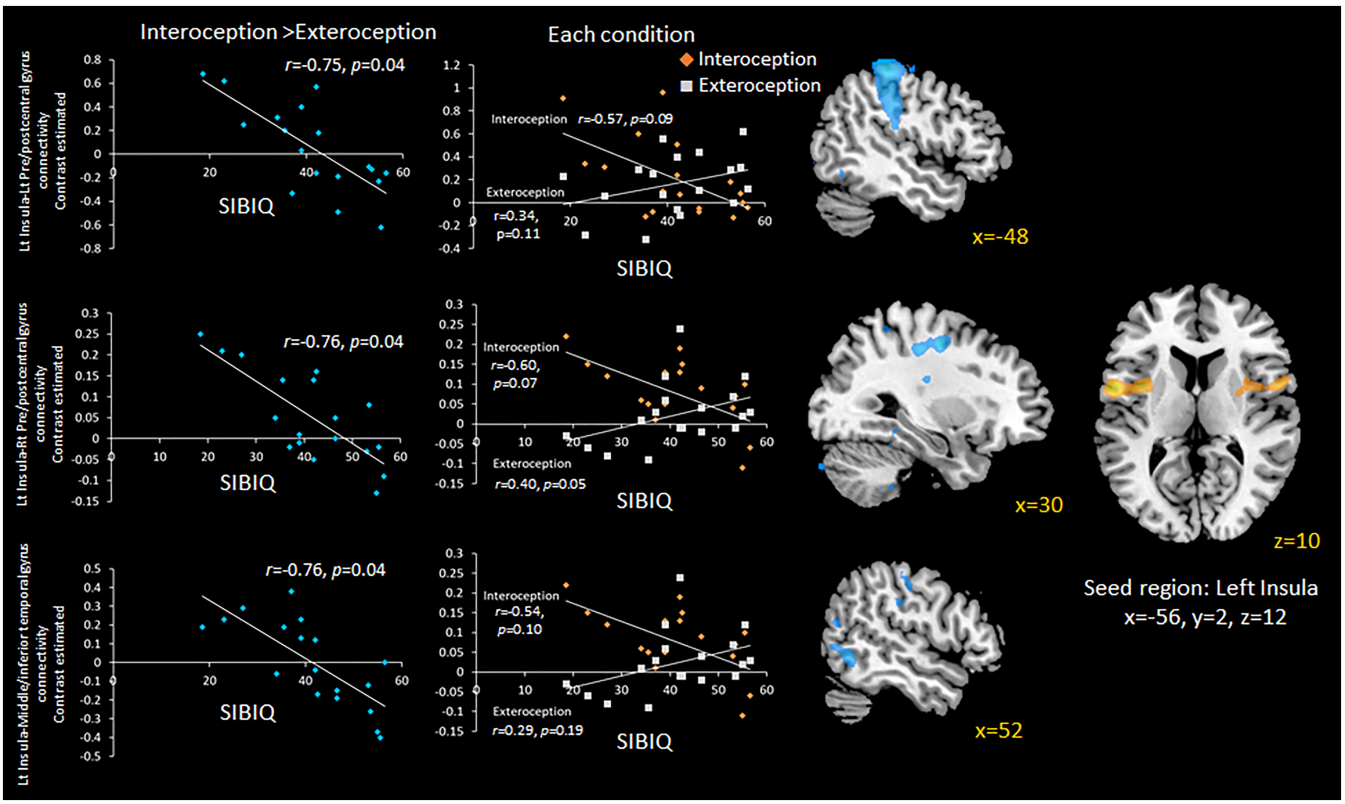

FIGURE 5 Regions whose functional connectivity (FC) with the left middle to posterior insula cortex (seed region) were negatively correlated with alexithymia levels measured by Structured Interview for Beth Israel hospital Questionnaire (SIBIQ) ($p < 0.05$ false discovery rate [FDR] corrected) during the attending period

TABLE 6 Functional connectivity that correlated with alexithymia level (SIBIQ) while feeling anxiety in the interoception condition ($p < 0.05$ FDR corrected)

					MNI		
	Number of voxels in cluster	**L/R**	**BA**	***t* value**	***x***	***y***	***z***
Seed region: right pIns/S1 (50, −18, 36)	Extent threshold: $k = 490$						
Positive correlation							
Superior parietal lobule	490	R	7	6.39	34	−68	64
Angular gyrus		R	40	6.00	44	−60	54
Inferior parietal lobule		R	7, 39, 40	4.23	56	−44	52
Negative correlation							
N.A.							

Abbreviations: BA, Brodmann area; FDR, false discovery rate; pIns/S1, posterior insula/primary sensory cortex; MNI, Montreal Neurological Institute; SIBIQ, Structured Interview for Beth Israel hospital Questionnaire.

attending to interoception. These areas constitute the 'interoceptive neural network' (Smith & Lane, 2015), in which whole-body somatotopy is represented in the mid/anterior insula and somatosensory areas, integrating such pieces of information to generate a whole bodily representation through the network. In this regard, the present findings suggest that alexithymia is considered the disruption of communication within the regions in the 'interoceptive neural network'. The insula is not the only region that detects cardiac interoception, as the somatosensory area plays an important role in this function.

A 'dual pathway hypothesis' has been proposed for feeling heartbeats, one of which is the insula-ACC

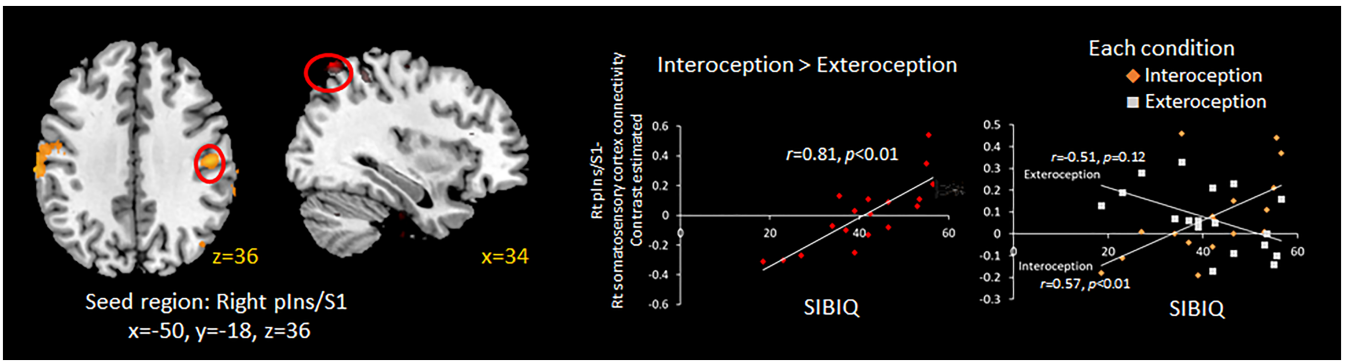

FIGURE 6 Functional connectivity (FC) between the right posterior insula/primary sensory cortex (pIns/S1) (seed region) and the right somatosensory cortex was positively correlated with alexithymia levels measured by Structured Interview for Beth Israel hospital Questionnaire (SIBIQ) ($p < 0.05$ FDR corrected) during the anxiety period

centred pathway for visceral sensation, and the other of which is somatosensory pathway for sensation from body surface (Khalsa et al., 2009). Our study's results suggest that people with high alexithymia have a problem integrating information from both pathways, that is, the visceral (interoception) and surface bodily sensations underlying cardiac interoception. The challenge linked to integrating whole-body sensations via such different channels may have a deleterious impact on the conception of bodily responses associated with emotions. Difficulties with integrating bodily sensations in those with higher levels of alexithymia may lead to emotional awareness detached from bodily sensation, thereby resulting in compromised body-related emotional responses.

4.2 | Alexithymia and brain activity while attending to anxiety

In anxiety periods of the interoception condition, we obtained larger BOLD signals in the bilateral middle to posterior insular cortex and the primary sensory cortex as compared with in the exteroception condition. Some previous studies reported that bilateral insular activity was enhanced in the context of anticipatory anxiety evoked by ESs, aversive images or sounds (e.g., Carlson et al., 2011; Simmons et al., 2011). A neuroimaging study (Drabant et al., 2011) showed that anxiety linked to ESs on the wrist enhanced activation in the right insula and parietal cortex, which is consistent with the regions we observed to be activated in our study (i.e., the insula and somatosensory areas). In our study, attention paid to interoceptive information was considered to enhance anticipatory anxiety at least at an implicit level.

Although we did not observe a linear relation between alexithymia levels and regional activation in the bilateral insular cortices, the FC between the right pIns/S1 and right somatosensory cortex (BA 7) was *positively* correlated with alexithymia while participants were anxious. Our study's results may demonstrate that individuals with high alexithymia tend to feel anxiety that is tightly related to a sensation on a certain part of the body when they are facing pain-related anxiety. This notion is consistent with the levels of emotional awareness (LEAS) hypothesis proposed by Lane and Schwartz (1987), which highlights the hierarchical structure of emotion from lower levels (bodily sensations) to higher levels (blended complex emotions). An emotional state directly connected with a somatic sensation such as pain is considered subject to lower LEAS. The positive correlation between alexithymia and somatosensory oriented FC suggests that the psychosomatic problems in alexithymia stem from lower LEAS.

The result of the *positive* correlation between alexithymia and FC during the anxiety period appears contradictory with the result of the *negative* correlation during the attending period. However, it may represent the difference in bodily related information processing between interoception and emotional awareness. Although a dominance of somatic processing in high alexithymia was observed in previous studies (Ihme et al., 2014; Liemburg et al., 2012), our study's result shows that the somatic dominance in alexithymia plays a role only in its emotional awareness process but not in the interoceptive process. In a trial, participants attended to interoception and emotion successively, and this setting enabled us to compare the neural underpinnings for interoception and emotion. We asked participants to attend to interoception under conditions of anticipatory anxiety related to upcoming pain, after which participants evaluated their subjective anxiety level in this context. This procedure served to induce emotional awareness based on interoceptive awareness. In the

attending to interoception period, high alexithymia participants showed attenuated FC within their 'interoception network', especially between the insula and the somatosensory areas. On the other hand, they presented enhanced FC between these regions in the anxiety period. Although access to somatic information in primary sensory processing is supposed to be more strongly activated in the attending period, high alexithymia individuals activated this process in the anxiety period, which should have incurred higher cognitive and emotion related processing. Information processing and integration of somatic sensations should have developed interoception; however, they robustly invoke those functions for constructing emotional awareness rather than interoception. This 'paradoxical' somatic information processing in alexithymia may represent their brain function pathology linked to feeling emotions. Individuals with alexithymia recognize primitive and unprocessed bodily sensations as emotions, as our results showed, such that their emotional expressions are too tightly associated with such bodily sensations, thereby enabling a reasonable explanation of their difficulty with context-dependent emotional control.

4.3 | Subjective anxiety and alexithymia

Participants with high alexithymia presented increased subjective anxiety as measured by the VAS in the second run, which appears to be connected with a somatic dominant process as shown in the FC analyses. We consider that this inclination could represent 'somatic amplification', which is known to be a major feature of psychosomatic disorders and alexithymia. Somatic amplification modulates somatic sensations as intense, noxious and disturbing (Barsky, 1992). This tendency may be enhanced by excessive biased attention paid to local bodily sensations (Moriguchi & Komaki, 2013) and a dysregulated reappraisal system linked to the impact of pain-related stimuli. As mentioned above, high alexithymia was associated with greater activation in somatosensory areas while individuals paid attention to bodily sensations (Ihme et al., 2014; Kano et al., 2007; Liemburg et al., 2012; Moriguchi et al., 2007). Together, these previous findings and our findings suggest that high alexithymia individuals are predisposed to attend to physical pain or bodily sensations rather than emotions, even in emotionally arousing situations. We suppose that both the increased vigilance and weakened habituation to the somatic sensations may be reflected in somatic amplification, especially in a context closely associated with physical pain based on past experience.

4.4 | Structured interview and questionnaire as a measurement for alexithymia

In this study, we used the SIBIQ and TAS-20 to measure alexithymia. Some studies reported positive correlations between self-reported alexithymia scales, such as the TAS-20, and negative affects such as anxiety (De Gucht et al., 2004; Marchesi et al., 2014). We also observed positive correlations between the TAS-20 and the MAS and SADS, whereby 'high alexithymia individuals' defined by the TAS-20 had a higher sensitivity to negative affect, which appears to differ somewhat from the original concept of alexithymia. Individuals with a higher TAS-20 score showed both higher DIF and neuroticism scores and were considered excessively sensitive to how accurately they can express emotions (Ueno et al., 2014). Thus, those who scored high on the TAS-20 may include those who are not very alexithymic in the original definition. This phenomenon challenges the validity of self-report measurements of alexithymia. Self-report questionnaires for alexithymia were also used in previous studies focusing on the relationship between interoception and alexithymia, such that the results from the previous studies, including neuroimaging studies, were affected by negative affect or emotional instability, the very traits that the questionnaires focus on. Though some studies reported higher insular activity in the higher alexithymia group, results may be enhanced by the sample in which a negative affect such as anxiety is dominant because the high anxiety group is repeatedly reported to show enhanced insular activation in emotional situations. We assume that our research may provide a description of the features of interoception and emotion in high alexithymia individuals, irrespective of such a confounding factor associated with self-report questionnaires.

4.5 | Limitations

First, it is difficult to quantify participants' attentional control (i.e., interoception vs. exteroception) objectively, other than via brain activations that allow us to see participants' spontaneous ways of controlling attention. In future studies, it will be important to assess the triadic relationship between the quality of attentional control, alexithymia and neural responses when participants are attending to interoceptive information. Second, the participants in this study were healthy volunteers, meaning that results cannot directly reflect mechanisms underlying psychosomatic problems found in patient populations. A clinical population remains to be studied in the future to better understand how problems in emotion recognition develop into

psychosomatic and physical disorders. Third, we could not record the exact value of the ES thresholds for perceiving pain in individuals; thus, the association between the thresholds and alexithymia level was not able to be discussed in this study. Fourth, it remains unclear how our results in high alexithymic individuals reflect overall emotion processing or are specific to anxiety. Finally, an experimental condition that does not include ES would be useful for understanding the relationship between somatic amplification and interoception. This condition would enable us to compare the neural activation between anxious and non-anxious states, and it will be beneficial to see how anxious feelings modulate interoceptive processing, and vice versa. Future studies should consider this issue in order to develop a better understanding of the features of their emotional processing.

5 | CONCLUSION

In this study, we assess neural activation while attending to interoception and emotion and then considered the association between alexithymia and neural activation and FC. We sought to understand how interoceptive processing in an emotional context relates to problems of alexithymia in recognizing self-emotions. We did not find a linear relationship between alexithymia and the activity levels of the insula, MPFC or somatosensory cortex. However, high alexithymia participants showed attenuated FC within the 'interoception network', especially between the insula and the somatosensory areas when they focused on interoception. On the other hand, they had enhanced FC between these regions in the anxiety period. These findings may point to a dysfunctional 'the interoception neural network' and inappropriate somatic information processing for constructing emotional awareness. Individuals with high alexithymia are predisposed to attend to physical pain or bodily sensations rather than emotions, which may result in the dissociation between their somatic sensations and subjective emotions.

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CONFLICT OF INTEREST

We have no conflicts of interest to declare in this study.

AUTHOR CONTRIBUTIONS

Yuri Terasawa performed the conceptualization, methodology, formal analysis, writing—original draft & editing and funding acquisition. Kentaro Oba performed the methodology, investigation and writing—review & editing. Yuki Motomura and Hiroki Murakami performed the methodology and investigation. Ruri Katsunuma performed the investigation. Yoshiya Moriguchi performed the conceptualization, methodology, writing—review & editing and supervision.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/ejn.15528.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to ethical restrictions.

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