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Self-referential processing in individuals with nonsuicidal self-injury: An fMRI study

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ABSTRACT

Nonsuicidal self-injury (NSSI) is associated with considerable deficits in managing negative self-directed internal experiences. The present study explores the neurophysiological correlates of self-referential processing in individuals with NSSI. A total of 26 individuals with NSSI (≥5 episodes of NSSI behavior in the past year, without suicide attempts) and 35 age-, sex-, education-, and intelligence quotient (IQ)-matched controls participated in this study. Participants underwent fMRI scanning as they performed a personal relevance rating task, which required them to evaluate the personal relevance of emotional words. As predicted, we found that individuals engaging in NSSI tended to rate negative adjectives as more relevant and positive adjectives as less relevant. An analysis of functional neuroimaging data showed that the NSSI group had increased activity relative to the control group in the inferior parietal lobe, inferior temporal gyrus, calcarine, insula, and thalamus in response to positive adjectives. The NSSI group also demonstrated greater activation in the calcarine and reduced activation in the inferior frontal gyrus in response to negative self-referential stimuli compared with the control group. In addition, increased right inferior parietal lobe activity during positive self-referential processing was correlated with reduced suicidal ideation in the NSSI group. Our study provides neural evidence for self-referential processing bias in individuals with NSSI and highlights the need for further research to clarify the pathophysiological features that are specific to NSSI.

1. Introduction

Nonsuicidal self-injury (NSSI) is defined as the direct, deliberate destruction of one's body tissue in the absence of the intent to die (Nock, 2009). NSSI behavior is closely related to individuals' unpleasant internal experiences (Klonsky, 2007, 2009; Taylor et al., 2018). According to empirical evidence, the vast majority of people who self-injured reported that they engage in NSSI to fulfill automatic/intrapersonal and social/interpersonal functions (Klonsky and Glenn, 2009; Klonsky et al., 2015; Zetterqvist et al., 2013). Of these functions, a recent meta-analysis reported that intrapersonal functions of NSSI, aimed at removing or distracting from aversive self-awareness (Armey and Crowther, 2008; Klonsky, 2007), are more prominent (66–81%) than interpersonal functions of NSSI (33–56%) (Taylor et al., 2018).

Indeed, negative self-evaluation per se is a significant risk factor for NSSI (Kim, 2017; Klonsky and Muehlenkamp, 2007), and increasing evidence has also demonstrated that negative self-image may predict NSSI behavior. For example, individuals who engage in NSSI exhibit a high level of self-criticism (Gilbert et al., 2010; Zelkowitz and Cole, 2019), negative feelings about the self (Forrester et al., 2017; Lloyd-Richardson et al., 2007), self-hatred (Klonsky, 2007; Nock et al., 2009), and low self-esteem (Cawood and Huprich, 2011; Lundh et al., 2007). A longitudinal analysis also revealed that self-esteem and self-efficacy significantly predict the occurrence of NSSI (Tatnell et al., 2014). Even the themes of rumination shown in individuals with NSSI relate to self-blame (Gong et al., 2019; Hoff and Muehlenkamp, 2009), and these repetitive and distorted thoughts may exacerbate their negative affectivity and negative self-image, even leading to increased susceptibility to anxiety and depressive disorder (Claes et al., 2014; Marshall et al., 2013).

Individuals who describe themselves in negative terms automatically consider negative information to be relevant to them without any deliberation (Grimm et al., 2009). Their negative, self-deprecating ideas are a form of self-referential processing. Self-referential processing refers to the cognitive process in which individuals evaluate the relevance of the information to the self and integrate it into their own experience

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(Northoff and Bermpohl, 2004; van der Meer et al., 2010). Several years of neuroimaging research have documented that the medial prefrontal cortex (MPFC), posterior cingulate cortex (PCC), and inferior parietal lobe (Fossati et al., 2003; Herbert et al., 2011; Northoff and Bermpohl, 2004) are recruited during self-referential processing in nonclinical populations. A meta-analysis also revealed that anterior paralimbic regions, e.g., the insula, temporal pole, and inferior frontal cortex, were functionally involved in the representation and processing of self-relevant information (van der Meer et al., 2010). The authors showed that self-referential processing, inevitably related to sensory and higher-order processing, recruits a wide range of cortical regions responsible for bottom-up and top-down modulations. In particular, self-referential processing of negative words induces increased activity in the inferior parietal lobe and insula of the general population (Fossati et al., 2003), and in people with depression, both positive and negative self-referential processing may increase brain activity (Wagner et al., 2015). This increase in neural activity may reflect the increased amount of cognitive effort required to process certain self-referential stimuli.

However, little is currently known regarding the neural basis of self-referential processing in individuals with NSSI. As mentioned above, existing NSSI research has only focused on self-criticism or self-esteem; only one study has examined the processing of self-relevant information in NSSI, and even this has been conducted on depressed adolescents (Quevedo et al., 2016). Given that young adults who continue NSSI behaviors can suffer severe mental health problems, more studies examining psychological and neural processing in adults who engage with NSSI are needed (Groschwitz et al., 2015). Therefore, we aimed to investigate the neural mechanisms of self-referential processing in young adults who engage in self-injury without suicidal intention.

In this study, we hypothesized that young adults who engage in NSSI, compared with the controls, would evaluate negative stimuli as more relevant to themselves and consider positive stimuli to be less relevant. Given that previous literature suggested limbic and cingulate areas as candidate regions for disrupted self-referential processing in depressed adolescents who harm themselves (Quevedo et al., 2016), we also expected to find altered neural activity during self-related processing in adults who engage in NSSI, perhaps reflecting the underlying psychopathology of NSSI.

2. Methods

2.1. Participants

Ninety-seven participants (34 in the NSSI group and 40 in the control group) were recruited from social networking sites and online forums (e.g., online communities, online NSSI forums, and Twitter). Among them, 13 participants were excluded from the analysis due to technical problems (4 NSSIs and 2 controls), withdrawal of intention to participate (3 NSSIs and 2 controls), and head motion (1 NSSI and 1 control) (Supplement 1). In total, 61 participants between 19 and 30 years of age were analyzed in the present study. Among them, 26 individuals (20 females, mean age 23.2 ± 2.9 years) had more than five episodes of NSSI in the previous 12 months and no suicide attempts during the same period. Their most recent NSSI episodes occurred within 3 weeks of evaluation. Additionally, 35 age-, sex-, and education-matched controls who had no history of NSSI (25 females, mean age 22.7 ± 2.8 years) participated in this study.

The exclusion criteria for all participants were as follows: 1) aged under 19 years, 2) lifetime history of psychotic and neurological disorders, 3) use of any psychotropic medication or participation in any psychotherapy during the last month, 4) any family history of psychotic disorders (up to second-degree relatives), and 5) an estimated Wechsler Adult Intelligence Scale (WAIS) IQ < 80 (based on the Korean version of the Wechsler Adult Intelligence Scale) (Choe et al., 2014; Hwang et al., 2012). All participants passed safety screening for functional magnetic resonance imaging (fMRI) scans (e.g., claustrophobia, ferrous metals in the body).

Each participant was evaluated via phone screening and was scheduled to undergo the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 Clinical Version (SCID-5-CV) (First et al., 2016) by two well-trained bachelor-level clinical raters (GN and HM) and a licensed psychologist (JH). The final decision concerning diagnosis was made according to the agreement between the two raters, and all procedures were supervised by the licensed psychologist. We also conducted a brief interview to obtain information on NSSI histories, such as the age of onset and frequency. As a result, 11 participants with NSSI appeared to have comorbid mental disorders (major depressive disorder, $n = 8$; major depressive disorder and anxiety disorder, $n = 1$; obsessive–compulsive disorder, $n = 1$; and eating disorder, $n = 1$).

The controls had no current or lifetime history of mental disorder as determined by the Structured Clinical Interview for Non-Patient Edition (SCID-NP)(First et al., 2001). Written informed consent was obtained from all participants, and the University Institutional Review Board approved the procedure (IRB No. 1041078–201806-BRSB-110–01).

2.2. Materials and methods

2.2.1. Self-report questionnaires

2.2.1.1. Inventory of statements about self-injury (ISAS). The ISAS scale was used to evaluate the frequency and functions of NSSI (Klonsky and Glenn, 2009). The ISAS consists of 2 sections; each section measures lifetime NSSI frequency and functions. In this study, we modified section 1 such that it probes the frequency of NSSI behaviors in the last three weeks. The ISAS has good internal consistency and test–retest reliability (Glenn and Klonsky, 2011). Korean version of the ISAS validated by Kim et al. (2019) was used to assess the frequency and versatility of NSSI behaviors.

2.2.1.2. Beck depression inventory-II (BDI-II). To measure the level of depression of the participants, the Beck Depression Inventory-II was used (Beck et al., 1996). The BDI-II, which can measure emotional, cognitive, and somatic symptoms of depression in the last two weeks, consists of 21 items rated on a 4-point Likert scale ranging from 0 to 3. A higher score on this questionnaire indicates severe depression. The internal consistency reliability of the Korean version of the BDI-II was 0.89, and the test–retest reliability was 0.90 (Kim et al., 2015b). In our study, Cronbach's alpha of the BDI-II was 0.94.

2.2.1.3. Beck anxiety inventory (BAI). The BAI was used to assess participants' anxiety levels (Beck et al., 1988). The BAI consists of 21 items rated on a 4-point Likert scale ranging from 0 to 3. A higher total score on this questionnaire indicates higher anxiety. The internal consistency reliability of the Korean version of the BAI was 0.90, and the test–retest reliability was 0.84 (Kim et al., 2015a). Cronbach's alpha in our study was 0.93.

2.2.1.4. Scale for suicide ideation (SSI). The SSI (Beck et al., 1979) is a reliable and valid interview-based assessment of suicidal ideation. In this study, we used the self-rating form of the Korean version of the SSI (Shin et al., 1990). The scale consists of 19 items rated on a 3-point Likert scale ranging from 0 to 2. Higher scores on the SSI indicate higher degrees of suicidal intent. In our study, Cronbach's alpha of the SSI was 0.91.

2.2.2. Personal relevance rating fMRI task

Neural activation during the self-referential process was examined using a modified personal relevance rating task (PRRT) (Siegle et al., 2007). The PRRT is a task used to evaluate individuals' responses to emotional adjectives by requiring participants to press a button when the adjectives are presented to indicate their relationship with themselves as either 'not relevant,' 'somewhat relevant,' or 'relevant.' Two types of stimuli, participant-generated and normed emotional adjectives, were used in this task. In terms of the participant-generated stimuli, participants selected 10 positive and 10 negative adjectives from the list of emotional words (20 positive and 20 negative) before the experiment. Normed stimuli (10 positive, 10 negative, and 20 neutral words) were used equally for all participants. Hence, 20 positive, 20 negative, and 20 neutral words were used in the analysis. These words were selected from a list of emotional Korean words (Park and Min, 2005). All of the word stimuli were controlled by word length and emotional intensity (Supplement 2). One trial consisted of a fixation cue (1 sec) followed by an emotional word (positive, negative, or neutral; 2 sec), followed by a mask (row of Xs; 10.8 sec). Participants were asked to rate the personal relevance of the emotional words by pressing a button while the masked prime stimuli, a row of Xs, were presented. E-prime 3.0 was used to display a sequence of stimuli and record participants' response times and accuracy.

2.3. Procedure

Upon arrival at the magnetic resonance imaging (MRI) unit, each participant completed the safety form to reaffirm the safety of undergoing an MRI scan and answered the questionnaire to create individualized adjectives for the PRRT. After completing self-report questionnaires, participants entered the MR scanner and performed the PRRT. At the end of all the procedures, each participant was debriefed regarding the aims of the study.

2.4. Neuroimaging data acquisition

Brain imaging data were acquired by a 3 T Siemens MAGNETOM trio (Siemens, Germany) with a 32-channel head coil. Functional T2-weighted echo-planar images (EPIs) were obtained parallel to the anterior and posterior commissure (AC-PC) line in the following sequence: repetition time (TR) = 2,000 ms, echo time (TE) = 26 ms, flip angle (FA) = 80 deg, field of view (FoV) = 210 × 210 mm, and voxel size = 2.5 × 2.5 × 3.4 mm. The acquired volume covered the whole brain (37 slices, 3.4 mm slice thickness with no gap).

For functional image analysis, T1-weighted structural images were obtained in the following sequence: TR = 2,400 ms, TE = 2.19 ms, FA = 8 deg, FoV = 272 × 272 mm, voxel size = 0.8 × 0.8 × 0.8 mm, 224 slices, 0.85 mm slice thickness with no gap).

2.5. Data analysis

The independent *t*-test and chi-squared test were used to examine group differences in demographic and clinical characteristics, and multivariate analysis of variance (MANOVA) was used for the analysis of the behavioral PRRT performance. The fMRI images were preprocessed and analyzed using Statistical Parametric Mapping (SPM) 12 (Functional Imaging Laboratories, London, UK). For preprocessing, slice timing was corrected with a reference slice (middle slice), and head movements were entered as multiple regressors. Participants with excessive head movement (>1.5 mm rotation or > 3.0 mm translation) were excluded from the analysis. Then, the functional data were aligned to the structural images and normalized using the Montreal Neurological Institute (MNI) East Asian template. Normalized images from echo-planar imaging (EPI) sequences were smoothed using a 6 × 6 × 6 full-width half-maximum (FWHM) Gaussian kernel. In the first-level analysis, the following two contrasts were set: (1) positive > neutral and (2) negative > neutral (Supplement 3; Additional positive vs. negative contrasts analysis result shown in Supplement 4). For the second-level analysis, a two-sample *t*-test was performed to assess between-group differences via a general linear model with the use of SPM12. Depression and anxiety levels measured by the BDI-II and BAI were included in second-level analyses as covariates of no interest. Significant activations were reported with a threshold of $_{\text{uncorrected}}P < .001$ and a cluster extent threshold of $k \geq 20$ voxels to minimize the chance of Type I errors and to enhance the statistical power of the fMRI analysis (Eklund et al., 2016; Poldrack, 2011; Roiser et al., 2016). This threshold was more stringent than the $_{\text{uncorrected}}P < .005$, $k \geq 20$, equivalent to a false discovery rate (FDR) of 0.05 (Lieberman and Cunningham, 2009). Brain region labeling was performed with automated anatomical labeling (aal). When significant group differences were found, we performed a *Spearman's rho* correlation analysis to examine the association between the participants' brain activity (beta values) and clinical measurements and between the participants' brain activity and behavioral performance in each group separately. The beta values were extracted using the MarsBaR toolbox (https://marsbar.sourceforge.net). To prevent Type I errors, Bonferroni's correction was applied, and $P < 0.0056$ was regarded as significant [$P = 0.05/9$]. The data obtained were analyzed using SPSS 25 for Windows (IBM Corp, Armonk, NY, USA).

3. Results

3.1. Demographic and clinical characteristics

A total of 61 individuals (mean age, 22.90 ± 2.83; 45 females) participated in this study (Table 1). For these individuals, the mean number of years of education was 14.57 years (*SD* = 1.78, range 12–19), and the mean estimated WAIS IQ was 109.98 (*SD* = 9.22, range 90.40–128.84). The groups were not significantly different in age, sex, education level, estimated IQ, or handedness (all *Ps* > 0.05). The ISAS data of the NSSI group are also shown in Table 1 and Supplement 5.

Group differences were reported for the BDI-II, BAI and SSI ($t_{(34.52)}$ = 7.96, $P < .001$; $t_{(28.29)}$ = 5.53, $P < .001$; $t_{(30.87)}$ = 5.84, $P < .001$,

Table 1
Demographic and clinical characteristics of participants in the NSSI group and control group.

	Group		$t/(\chi^2)$	*P*
	NSSI (*N* = 26)	Control (*N* = 35)		
Age (years)	23.15 (2.94)	22.71 (2.77)	0.60	0.553
Sex (male/female)	6/20	10/25	(0.23)	0.629
Education (years)	14.58 (2.06)	14.57 (1.58)	0.01	0.991
Estimated WAIS IQ	109.26 (9.38)	110.51 (9.19)	−0.52	0.604
Handedness (L:R:A)	1:24:1	2:28:5	(2.02)	0.364
NSSI frequency (last 3 weeks)	104.81 (133.73)	N/A		
≤ 50 times	*N* = 11			
51–100 times	*N* = 5			
100–200 times	*N* = 7			
> 200 times	*N* = 3			
Duration of NSSI behavior (months)	117.50 (73.46)	N/A		
NSSI versatility	4.12 (2.18)	N/A		
BDI-II score	23.25 (10.07)	6.09 (5.10)	7.96	<0.001
BAI score	12.92 (9.29)	2.51 (2.76)	5.53	<0.001
SSI score	12.23 (7.04)	3.70 (2.79)	5.84	<0.001
PRRT response score (1 = not relevant, 2 = somewhat relevant, 3 = relevant)				
Positive	1.91 (0.58)	2.55 (0.40)	25.85	<0.001
Neutral	1.98 (0.38)	1.69 (0.29)	11.48	0.001
Negative	2.35 (0.56)	1.56 (0.39)	42.69	<0.001
PRRT reaction time (ms)				
Positive	1306.53 (528.08)	1133.68 (545.14)	1.54	0.220
Neutral	1455.95 (523.14)	1262.34 (578.73)	1.81	0.184
Negative	1193.80 (400.07)	1139.95 (472.92)	0.22	0.641

Mean (SD); NSSI, nonsuicidal self-injury; L, left; R, right; A, ambidextrous; N/A, not applicable; NSSI versatility, total number of different NSSI methods used; BDI-II, Beck Depression Inventory-II; BAI, Beck Anxiety Inventory; SSI, Scale for Suicide Ideation; PRRT, Personal Relevant Rating Task.

respectively).

3.2. Behavioral results

Regarding the results of the participants' PRRT performance, significant group differences were found in the participants' responses to the positive and negative word lists [Wilks' lambda = 0.54, $F_{(3,57)}$ = 16.37, P <.001, η_p^2 =.46; Supplement 6]. The members of the NSSI group rated negative and neutral adjectives as more relevant to themselves than the controls did [negative: $F_{(1,59)}$ = 42.69, P <.001, η_p^2 =.42; neutral: $F_{(1,59)}$ = 11.48, P =.001, η_p^2 =.16]. Regarding positive adjectives, however, the control group considered positive adjectives to be more self-relevant [$F_{(1,59)}$ = 25.85, P <.001, η_p^2 =.30]. Notably, we found no significant differences in response time [Wilks' lambda = 0.93, $F_{(3,57)}$ = 1.46, P =.236, η_p^2 =.07; Table 1].

3.3. Neuroimaging results

3.3.1. Whole-brain analysis between the NSSI group and the control group during self-referential processing

We performed a whole-brain analysis to identify group differences in brain regions associated with self-referential processing. During positive self-referential processing, individuals with NSSI showed increased activation in the bilateral inferior parietal lobe, right inferior temporal gyrus, left calcarine, left insula, and right thalamus compared with the controls (Table 2 and Fig. 1). In contrast, the control group showed greater activation in the bilateral inferior frontal gyrus than the NSSI group during the processing of negative adjectives (Table 2 and Fig. 2). Additionally, calcarine activity was significantly enhanced in individuals with NSSI compared with the controls in both positive and negative self-referential processing. Brain images were created with SPM12 and a template from MRIcron.

3.3.2. Correlation analysis between neuroimaging data and clinical and behavioral measurements

Suicidal ideation scores were negatively correlated with increased blood oxygen level-dependent (BOLD) signals during self-referential processing by individuals with NSSI (right inferior parietal lobe: *Spearman's rho* = -0.63, P =.001; left inferior parietal lobe: *Spearman's rho* = -0.43, P =.028; left insula: *Spearman's rho* = -0.44, P =.023; right thalamus: *Spearman's rho* = -0.48, P =.014; left calcarine: *Spearman's rho* = -0.40, P =.041). After Bonferroni's correction, only the correlation between the right inferior parietal lobe and suicidal ideation remained significant (Fig. 3). No significant correlations of brain activations were found with either the PRRT response patterns (i.e., participants' response or reaction times) or NSSI severity (i.e., frequency, duration, and versatility of NSSI) (all Ps > 0.05). The results remained the same when Pearson's correlation was applied to the same variables.

Table 2
Peak coordinates of significant group differences in brain activation in response to positive and negative adjectives on whole-brain analysis.

Max location	MNI peak coordinates (x, y, z)	*k*	Peak *Z*
Positive > Neutral contrast			
NSSI > Control			
Parietal lobe			
R Inferior parietal lobe	32–40 50	61	4.12
L Inferior parietal lobe	−26–44 50	101	3.99
Temporal lobe			
R Inferior temporal gyrus	46–20 −28	26	4.09
Occipital lobe			
L Calcarine	−6–80 10	45	3.63
Sub-lobar			
L Insula	−30 4–12	81	3.92
R Thalamus	24–30 10	21	3.85
Control > NSSI			
No significant clusters found			
Negative > Neutral contrast			
NSSI > Control			
Occipital lobe			
L Calcarine	−8–80 12	25	3.42
Control > NSSI			
Frontal lobe			
L Inferior frontal gyrus	−34 22 10	35	3.94
R Inferior frontal gyrus	24 0 38	25	3.56

$_{uncorrected}P$ <.001; depression and anxiety entered as covariates; NSSI, nonsuicidal self-injury; *k*, cluster size; L/R, left/right hemisphere.

4. Discussion

The present study sought to explore self-referential processing and its neural bases in medication-free individuals who engaged in NSSI behaviors. As expected, individuals engaging in NSSI behaviors considered more negative and fewer positive self-referential adjectives to be relevant. We also found increased brain activity in the temporoparietal and subcortical areas in individuals with NSSI compared with that in controls during positive self-referential processing after controlling for the effects of depression and anxiety. Increased calcarine activation in those with NSSI was also observed specifically for negative self-referential processing. However, the controls, relative to individuals with NSSI, yielded increased inferior frontal gyrus activity in response to negative self-referential processing. Additionally, right inferior parietal lobe activity, which showed significantly stronger activation in the NSSI group during positive self-referential processing, was found to be negatively correlated with suicidal ideation. To our knowledge, this study is the first to demonstrate aberrant self-referential processing and altered neural functioning in young adults who engage in NSSI.

First, our behavioral results indicate that individuals with NSSI exhibit deficiencies in normative self-referential processing. Consistent with our hypothesis, individuals engaging in NSSI are more likely to rate negative adjectives as more relevant to themselves and positive adjectives as less relevant to themselves compared with the controls. Considerable evidence indicates that biased self-referential processing is closely related to dysfunctional coping strategies (Hsu et al., 2020; Mennin and Fresco, 2013). In particular, negative self-referential processing facilitates cognitive and emotion regulation deficits and, in turn, leads to maladaptive behavioral responses to unwanted emotional stimuli (Frewen et al., 2020; Mennin and Fresco, 2013; Renna et al., 2017). These findings, therefore, warrant further investigation into the contribution of negative self-referential processing to the onset and maintenance of NSSI. Interestingly, the individuals with NSSI in this study were more likely to perceive the neutral stimuli as self-referential stimuli. In fact, in psychological research, whether neutral stimuli are actually perceived as neutral by people with psychiatric disorders is an important issue (Leppänen et al., 2004). Previous literature has already provided empirical evidence that individuals with mental disorders may give meaning to and show biased processing of neutral stimuli (Filkowski and Haas, 2017; Ruhe et al., 2019). Therefore, future research is necessary to examine the tendency of self-focused cognitive processes of individuals with NSSI to respond to neutral or ambiguous stimuli.

On the neural level, we found distinct alterations in the brain function of people with NSSI in response to self-referential information. In previous fMRI studies on nonclinical samples and a *meta*-analysis of these studies, the inferior parietal lobe (Burrows et al., 2016; Northoff et al., 2006), inferior temporal gyrus (Herold et al., 2016), insula, and thalamus have been shown to be involved in the retrieval of self-related information (Burrows et al., 2016; Denny et al., 2012; Herold et al., 2016; Northoff et al., 2006). Regarding these regions, we found that individuals who engaged in NSSI showed greater activation during self-referential processing of positive trait words in the bilateral inferior parietal lobe, inferior temporal gyrus, insula, thalamus, and calcarine. Positive self-referential information is more likely to be experienced as mood-incongruent in individuals suffering from affective distress

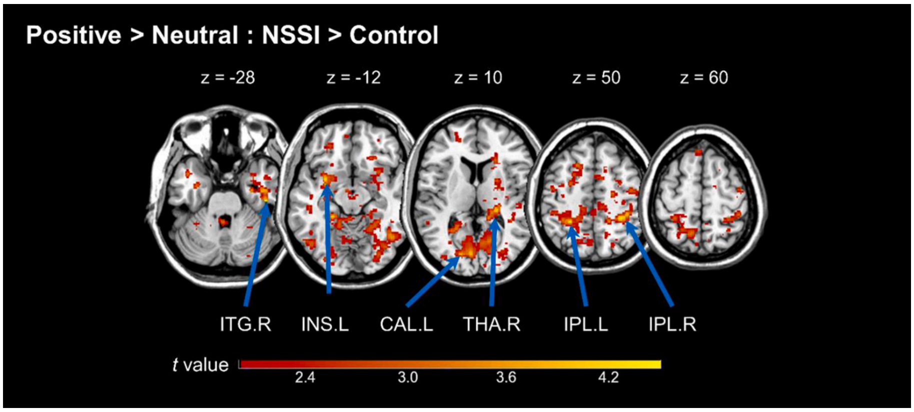

Fig. 1. Brain regions showing significant group differences in the positive > neutral contrast. A two-sample *t* test was performed using depression and anxiety as covariates of no interest. SPM activation maps overlaid on a template from MRIcron. Compared with the controls, the NSSI group exhibited an increased response (in warm colors) during positive self-referential processing (positive versus neutral word condition) in the right inferior temporal gyrus, left insula, left calcarine, right thalamus, and bilateral inferior parietal lobe. NSSI, nonsuicidal self-injury; ITG, inferior temporal gyrus; INS, insula; CAL, calcarine; THA, thalamus; IPL, inferior parietal lobe; L, left; R, right; $_{\text{uncorrected}}P < .001$; minimum cluster size of 20.

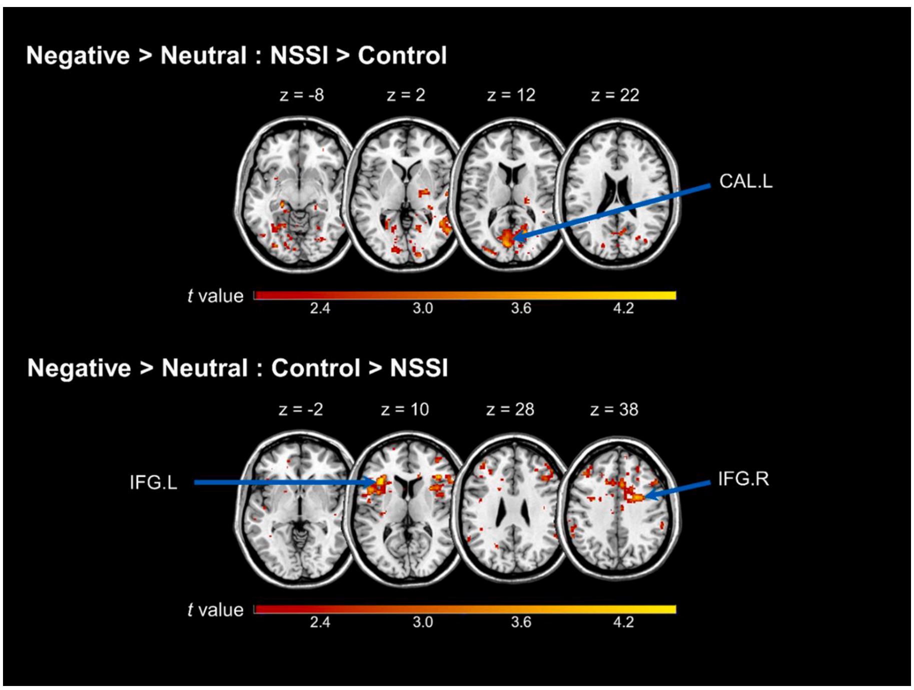

Fig. 2. Brain regions showing significant group differences in the negative > neutral contrast. A two-sample *t* test was performed using depression and anxiety as covariates of no interest. SPM activation maps overlaid on a template from MRIcron. During negative self-referential processing (negative versus neutral word condition), the NSSI group showed greater activation (in warm colors) in the left calcarine, while the control group showed increased bilateral inferior frontal gyrus activation. NSSI, nonsuicidal self-injury; CAL, calcarine; IFG, inferior frontal gyrus; L, left; R, right; $_{\text{uncorrected}}P < .001$; minimum cluster size of 20.

(Wagner et al., 2015). A previous depression study demonstrated that depressed individuals who self-harm experienced greater physiological reactivity when they thought about themselves from unfamiliar perspectives (Quevedo et al., 2016). Thus, our findings of increased neural activity during self-referential processing in people with NSSI could be construed in light of several studies (Hu et al., 2016; Lemogne et al., 2009) tentatively reporting that the increased neural reactivity to stimuli represents an increased amount of effort needed for individuals to process the task. However, the clinical implications of the increased neural reaction to positive self-referential processing in individuals with NSSI need further scrutiny.

In this regard, intriguingly, we also found that enhanced inferior parietal lobe activity while individuals attempted to attend to and integrate positive emotional stimuli was associated with lower levels of suicidal ideation in individuals with NSSI. The inferior parietal lobe is commonly activated during the regulation of both positive and negative emotions in healthy adults (Seo et al., 2014). As previously mentioned, NSSI behaviors alleviate acute aversive innate experiences or prevent suicidal thoughts (Klonsky et al., 2011). Prior literature has also demonstrated that NSSI is a coping strategy for handling suicidal thoughts and behaviors in a maladaptive but effective way (Kraus et al., 2020; Paul et al., 2015; Whitlock and Knox, 2007). As this study did not directly compare the anti-suicidal function of NSSI behavior and neural alterations, further studies are needed to clarify the role of the inferior parietal lobe in relation to 'nonsuicidality' in individuals with NSSI.

We also observed that individuals engaging in NSSI exhibited poor inferior frontal gyrus recruitment during negative self-referential processing. Our finding is partly consistent with previous research in which decreased inferior frontal gyrus activity to the valence of emotional stimuli was found in individuals with NSSI (Plener et al., 2012). In general, enhanced activity in the inferior frontal gyrus in healthy controls was observed in a study that evaluated participants' responses to unpleasant stimuli (Blakemore et al., 2016). The inferior frontal gyrus guides inhibition, attention reorientation, and coping with emotional distraction, controlling the impact of emotional distractors and the subjective feeling of being distracted (Aron et al., 2014; Hampshire et al., 2010; Sagaspe et al., 2011). A previous neuroimaging study also suggested the specialized roles of the left inferior frontal gyrus (controlling the impact of emotional distraction on cognitive performance) and the right inferior frontal gyrus (controlling the subjective feeling of being distracted) in emotional control (Dolcos et al., 2006). Therefore, failure to recruit the bilateral inferior frontal gyrus in response to

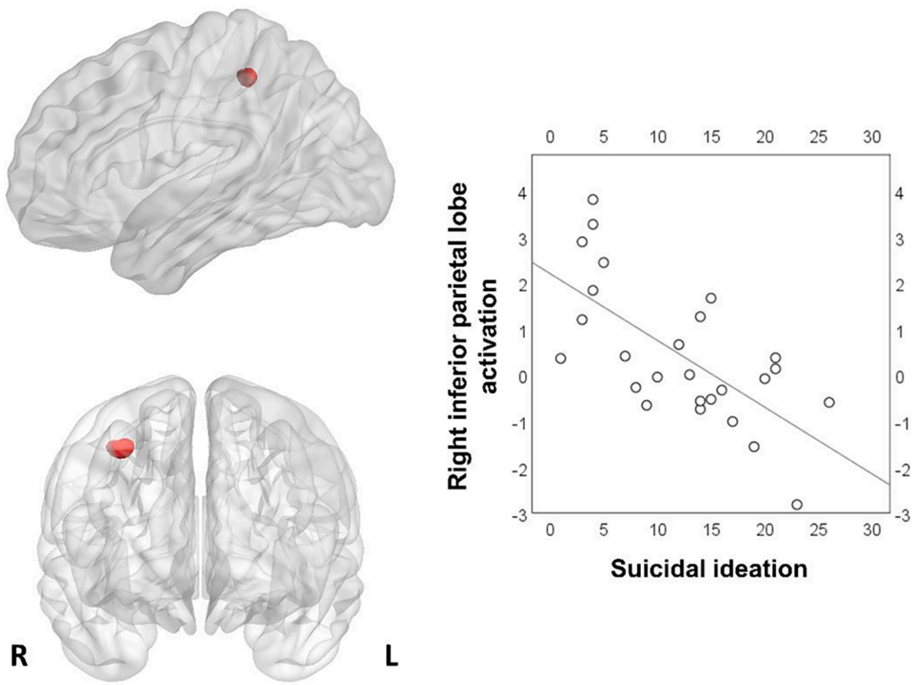

Fig. 3. Scatter plot of right inferior parietal lobe activation and suicidal ideation in participants in the NSSI group. A negative correlation was found in the right inferior parietal lobe activation during the positive self-referential processing and suicidal ideation scores in the NSSI group (*Spearman's rho* = -.63, *P* = .001; significant with Bonferroni's correction).NSSI, nonsuicidal self-injury; L, left; R, right

negatively valenced self-relevant information may reflect a phenotype of people with NSSI in which they use dysfunctional coping responses to internal or external stimuli threatening their self-worth.

Finally, we found increases in calcarine activation in people with NSSI during both positive and negative self-referential processing. The calcarine is repeatedly reported to be involved in self-reflection processes (Fuentes-Claramonte et al., 2019; Fuentes-Claramonte et al., 2020; Van der Cruijsen et al., 2019; Zhu et al., 2012). Similar to our finding, Wagner et al. (2015) showed that both processes could induce increased occipital lobe activity in depressed individuals. Many clinical studies have noted increased activation and/or connectivity across the occipital regions as one of the neural underpinnings of altered self-referential processing, for example, those of borderline personality disorder (Ueltzhoffer et al., 2019), social anxiety disorder (Goldin et al., 2009), and MDD with NSSI (Yan et al., 2022). An adolescent study also replicated the hyperactivity of the occipital regions, including the calcarine gyrus, during sad, introspective, self-referential processing (Vilgis et al., 2020). Therefore, given that similar patterns have been observed across various clinical conditions, further studies are needed to delineate the contribution of occipital cortex activity to the nature of self-referential processing regarding not only the NSSI pathology but also the transdiagnostic perspectives.

As we used a rigorous approach for recruitment and analyses, we were able to control the effect of medication, depression, and anxiety on self-referential processing in individuals who engage in NSSI. In addition, as we recruited the general population who engaged in NSSI through social media, the comorbidity of individuals with NSSI was relatively low compared with previous clinical research (Fischer et al., 2014; Selby et al., 2012). Thus, the current result may allow us to comprehend the nature of NSSI independent of the potential effect of depression or anxiety. However, despite this notable strength, the limitations of the current study also need to be noted. First, this work has a restriction in that we did not acquire the valence of emotion experienced by the participants in response to stimuli. Although the current stimuli were selected from a validated database of emotional Korean words and were controlled for valence, arousal, and word length, further work regarding each participant's subjective experience with the trait adjectives is required to confirm our findings. Second, the small sample size and the lack of a control group consisting of patients with psychiatric disorders should be considered when interpreting the results. Therefore, further research with larger and more diverse samples will be necessary to replicate and extend the present findings. Last, the individuals with NSSI in this study rated neutral words as more self-relevant to themselves. Given this, a more appropriate alternative as a baseline control condition instead of the use of neutral words as a control condition should be considered in future research.

5. Conclusions

In conclusion, this study provides the first evidence of the altered recruitment of subcortical, temporoparietal, and occipital areas related to self-referential processing bias in individuals engaging in NSSI. Understanding the neural basis that could account for the nature of self-injuries without suicidal intent will further elucidate the nosology of self-harm as well as the underlying pathophysiology of NSSI. Further studies with a larger sample and a variety of emotional valences may advance the role of aberrant brain function in NSSI pathology.

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CRediT authorship contribution statement

Gieun Nam: Conceptualization, Formal analysis, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Hyeri Moon:** Data curation, Investigation, Methodology. **Jang-Han Lee:** Resources, Supervision. **Ji-Won Hur:** Conceptualization, Formal analysis, Methodology, Visualization, Writing – original draft, Writing – review &

editing, Funding acquisition, Project administration.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2022.103058.

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