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The Relationship Between Brain Activation for Taking Others' Perspective and Interoceptive Abilities in Autism Spectrum Disorder: An fMRI Study

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Objectives: In this functional magnetic resonance imaging study, we aimed to investigate the differences in brain activation between individuals with autism spectrum disorder (ASD) and typically developing (TD) individuals during perspective taking. We also examined the association between brain activation and empathic and interoceptive abilities.
Methods: During scanning, participants from the ASD (n=17) and TD (n=22) groups were shown pain stimuli and asked to rate the level of the observed pain from both self- and other-perspectives. Empathic abilities, including perspective taking, were measured using an empathic questionnaire, and three dimensions of interoception were assessed: interoceptive accuracy, interoceptive sensibility, and interoceptive trait prediction errors.
Results: During self-perspective taking, the ASD group exhibited greater activation in the left precuneus than the TD group. During other-perspective taking, relative hyperactivation extended to areas including the right precuneus, right superior frontal gyrus, left caudate nucleus, and left amygdala. Brain activation levels in the right superior frontal gyrus while taking other-perspective were negatively correlated with interoceptive accuracy, and those in the left caudate were negatively correlated with perspective taking ability in the ASD group.
Conclusion: Individuals with ASD show atypical brain activation during perspective taking. Notably, their brain regions associated with stress reactions and escape responses are overactivated when taking other-perspective. This overactivity is related to poor interoceptive accuracy, suggesting that individuals with ASD may experience difficulties with the self-other distinction or atypical embodiment when considering another person's perspective.

Keywords: Autism spectrum disorder; Brain; Functional magnetic resonance imaging; Perspective taking; Empathy; Interoception; Embodiment.

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INTRODUCTION

Autism spectrum disorder (ASD) is a lifelong disorder characterized by core features of impairments in social interaction and communication, and restricted or repetitive patterns of behavior, interests, and activities [1]. In the 1970s, the prevalence of ASD was estimated to be 0.04%. However, recent reports from the United States, Europe, and other countries have reported an increase in the prevalence of ASD. According to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), the prevalence of ASD in Korea is 2.20% [2]. This highlights the growing need for research aimed at uncovering the fundamental pathophysiology of ASD and applying it to treatment. The primary difficulties experienced by individuals with ASD are often related to social cognition, including mind reading, emotion recognition, and empathy, with one area of increasing interest being perspective taking. Perspective taking is the ability to adopt and understand another person's viewpoint or perspective, allowing one to see the world from that person's viewpoint, think from their position, or feel their emotions [3]. Successful perspective taking indicates the ability to flexibly switch between a first-person perspective for understanding one's own mental state and a third-person perspective for recognizing the mental states of others.

Recently, Healy and Grossman [4] have argued that perspective taking can be divided into cognitive and affective aspects. Cognitive perspective taking involves inferring another person's thoughts and beliefs from their perspective, whereas affective perspective taking involves inferring another person's emotions and feelings. These two types of perspective taking do not correspond to the concepts of cognitive and affective empathy but rather involve considerably different mechanisms. For example, affective perspective taking, by definition, is more closely related to cognitive empathy than affective empathy. Definitions of affective empathy vary among researchers. However, there is a growing consensus that merely feeling empathic distress due to the contagion of another person's emotions or pain does not constitute true affective empathy. Instead, it has been argued that eliciting empathic concern and genuine feelings of compassion are essential [5]. Hence, empathic distress, affective perspective taking, and compassionate empathy can manifest in distinct ways. Although difficulties in cognitive empathy in ASD have been consistently reported, findings regarding affective empathy remain inconclusive. This may be due to the traditional inclusion of both personal distress and empathic concern in affective empathy, leading to discrepancies in research findings. A recent meta-analysis reported that individuals with ASD show comparable or excessive empathic distress compared to typically developing (TD) individuals, yet exhibit lower empathic concern [6].

A representative example of neuroimaging research related to perspective taking involves the use of a functional magnetic resonance imaging (fMRI) task that presents visual stimuli designed to evoke thoughts of physical pain, asking participants to evaluate the pain from either a self- or other-perspectives. Jackson et al. [7] observed activation in key areas of pain-related processing, such as the anterior insula, anterior cingulate cortex (ACC), and middle cingulate cortex (MCC), in response to visual pain stimuli, regardless of the perspective. However, when adopting a self-perspective, greater activation was observed in the thalamus and somatosensory cortex than when other-perspective was adopted, with reverse contrast revealing greater activation in the temporoparietal junction and precuneus. The authors suggested that differences in brain activation depending on perspective contribute to maintaining a self–other distinction, thus enabling appropriate empathic responses. Decety et al. [8] revealed that individuals with psychopathy show typical neural responses when evaluating pain from a self-perspective but display atypical brain activation and effective connectivity from another perspective. Considering the psychological and behavioral characteristics of ASD, it is surprising that there is a lack of research investigating pain-related perspective taking and consequent brain activation in this population.

Interoception is defined as a sense of the physiological condition of all internal tissues in the body [9]. It plays a crucial role in monitoring the internal milieu in real-time and conveying the state of our body to the central nervous system, thereby generating "feeling" [10]. This sense of internal physiological condition is not only pivotal in emotional processing but may also play a significant role in social processing. Accurately understanding the interoceptive cause of one's own behavior can aid in the interoceptive inference for predicting others' behavior [11]. Importantly, the major neural correlates associated with interoception include the insula and ACC, which are also involved in pain-related processing from both the self- and other-perspectives. This indicates a close relationship between the two processes. Research on the general population has shown that interoception is related to the emotional aspects of perspective taking and linked to the capacity for empathy toward others [11-13]. These findings highlight the need to further investigate the association between interoception and emotional and social processing in individuals with ASD [14]. However, the relationship between interoception and perspective taking in patients with ASD remains largely unexplored.

A commonly used method for investigating interoception is the heartbeat detection task, which allows a subjective experience to be measured objectively. Researchers have proposed distinguishing interoception into three distinct dimensions [15]: 1) interoceptive accuracy, which is the performance of objective behavioral tests of heartbeat detection, 2) interoceptive sensibility, the self-evaluated assessment of subjective interoception gauged using interviews or questionnaires, and 3) interoceptive awareness, which is the metacognitive awareness of interoceptive accuracy, as exemplified by the confidence-accuracy correspondence. Although numerous studies have investigated interoception in individuals with ASD, the diversity of assessment methods and subjects has led to mixed results.

Therefore, in the current study utilizing fMRI, we sought to explore the following: when visual pain stimuli are presented and both self- and other-perspective taking are implemented, will individuals with ASD show differences in brain responses compared to TD individuals? If differences in brain responses between the two groups are observed, will the activity in these brain regions correlate with empathic abilities, including perspective taking? Will there be a correlation between the interoceptive abilities of individuals with ASD and activation levels in the aforementioned brain regions? If so, how can the relationship between perspective taking and interoception in ASD be explained?

METHODS

Participants

All participants were recruited from a university hospital's department of psychiatry, psychiatric clinics, online community advertisements, and outreach at several schools and colleges. The inclusion criteria for the ASD group were as follows: 1) diagnosis of ASD based on the DSM-5 criteria by two child and adolescent psychiatrists, and confirmation by a qualified clinical psychologist through administration of the Autism Diagnostic Observation Schedule, 2nd edition (ADOS-2) [16], and 2) absence of major mental illnesses such as schizophrenia or bipolar disorder, as verified by the Mini-International Neuropsychiatric Interview (MINI) 5.5.0 [17] or MINI-for children and adolescents (MINI-KID) 6.0 [18]. The inclusion criteria for the TD group were as follows: 1) absence of a psychiatric history, and 2) no mental illness conditions being identified using MINI 5.5.0 or MINI-KID 6.0. None of the participants had any structural brain abnormalities or neurological disorders. Participants under 16 years of age were assessed for intelligence quotient (IQ) using the fourth edition of the Korean Wechsler Intelligence Scale for Children [19], while participants aged 16 and above were assessed using the fourth edition of the Korean Wechsler Adult Intelligence Scale [20]. All participants were required to achieve an IQ score above 70. Handedness was assessed using the Edinburgh Handedness Inventory [21]. Written informed consent was obtained from all participants. The study was approved by the Bioethics Committee at Chungbuk National University Hospital (IRB No. 2022-04-021) and conducted in accordance with the Declaration of Helsinki.

Initially, 27 participants with ASD and 24 TD participants were recruited. Of these, four with ASD were excluded due to IQ scores below 70, and one with ASD was excluded for refusing magnetic resonance imaging (MRI) scans. Additionally, two participants with ASD were excluded due to errors in the magnetic resonance (MR) parameter settings, and three participants with ASD and two TD participants were excluded due to severe motion artifacts. Consequently, data were analyzed for 17 participants with ASD and 22 TD participants.

Empathic abilities

Empathic abilities were assessed using the Interpersonal Reactivity Index (IRI) [22], a self-reported questionnaire designed to evaluate empathy in a multidimensional manner. The IRI comprises four subscales, each consisting of 7 items, for a total of 28 items. The perspective taking subscale measures the ability to understand from others' viewpoints; the fantasy subscale assesses the extent of immersion in the characters of movies or novels; the empathic concern subscale evaluates the level of concern for others in adverse situations; and the personal distress subscale measures the discomfort felt when observing others in pain. Each item is rated on a Likert scale ranging from 0 (does not describe me at all) to 4 (describes me very well). The Korean version, translated by Kang et al. [23], was used in this study.

Interoceptive abilities

Interoceptive accuracy

We measured interoceptive accuracy using a heartbeat detection task. During the task, participants were asked to sit comfortably with their eyes closed and count the heartbeats they felt in their chest, with instructions to avoid any contact with their chest or actions that could manually measure their pulse. The actual heart rate of the participants was monitored using a portable electrocardiography-measuring device, RefitPatch U9 (Solmitech, Daejeon, South Korea), placed on the left side of the chest. The task consisted of 12 trials with time windows of 25, 30, 35, 40, 45, and 50 seconds, each occurring twice in a randomized order. After each trial, participants reported the number of heartbeats felt, and the interoceptive accuracy for each trial was calculated using the following formula [24]:

$$\text{Interoceptive Accuracy} = 1 - \frac{|\text{nbeats}_{real} - \text{nbeats}_{reported}|}{\text{nbeats}_{real}}.$$

The final interoceptive accuracy score was derived from the average of the 12 trials.

Interoceptive sensibility

We used the awareness section of the Body Perception Questionnaire-Short Form (BPQ-SF-Awareness) [25]. This subscale consists of 26 items that rate subjective sensitivity to various bodily sensations on a Likert scale ranging from 1 (never) to 5 (always), with the total score reflecting the temperamental tendency to focus on internal sensations.

Interoceptive trait prediction error

Interoceptive trait prediction error (ITPE) represents the discrepancy between objective interoceptive accuracy and subjective interoceptive sensibility and quantifies 'interoceptive surprise.' We calculated the ITPE following the methodology of Garfinkel et al. [26], which involved z-transforming both the interoceptive accuracy and BPQ-SF-Awareness scores and subsequently subtracting the former from the latter. A positive ITPE value indicated a tendency to overestimate interoceptive abilities, whereas a negative ITPE value indicated an underestimation. Values close to zero indicate a higher level of interoceptive awareness.

fMRI

Task design

From the Visually-Induced Pain Empathy Repository database, as referenced in Paulus et al. [27], we selected 20 images as pain stimuli that appeared to be sufficiently painful. These images depicted various types of pain, such as pricking, cutting, and mechanical pressure, capturing painful situations occurring in everyday life and consisting of human limbs and objects that cause pain. In addition, we chose 20 neutral images that resembled the circumstances of the pain stimuli without any pain components to serve as no-pain stimuli.

At the start of each block, a 4-second instruction was provided, guiding participants to assess the level of pain on a scale from 1 (not painful at all) to 4 (very painful). In the self-perspective taking in painful situations (SP) block, participants were instructed to imagine themselves in the situations in the pictures and rate the pain they would feel. In the other-perspective taking in painful situations (OP) block, participants were instructed to imagine the situations in the pictures happening to another person and to rate the level of pain they believed the person would feel. For each stimulus presented, the participants were instructed to respond by pressing the keypad buttons held in both hands. Each block consisted of four pain stimuli displayed for 4 seconds, followed by a 16-second resting period. During the resting state, participants were instructed to gaze at a cross displayed at the center of a black screen. This study included five SP and OP blocks each. Additionally, we designed five self-perspective taking blocks and five other-perspective taking blocks for the no-pain stimuli (SN and ON respectively), following the same protocol as for the pain-stimuli blocks. Twenty blocks were presented in randomized order. Stimuli were presented using E-Prime 2.0 (Psychology Software Tools, Sharpsburg, PA, USA). Fig. 1 shows an example of an fMRI task.

MRI acquisition

Scanning was conducted at Ochang Center of the Korea Basic Science Institute using a 3.0 Tesla Achieva MRI scanner (Philips Medical Systems, Best, The Netherlands). During

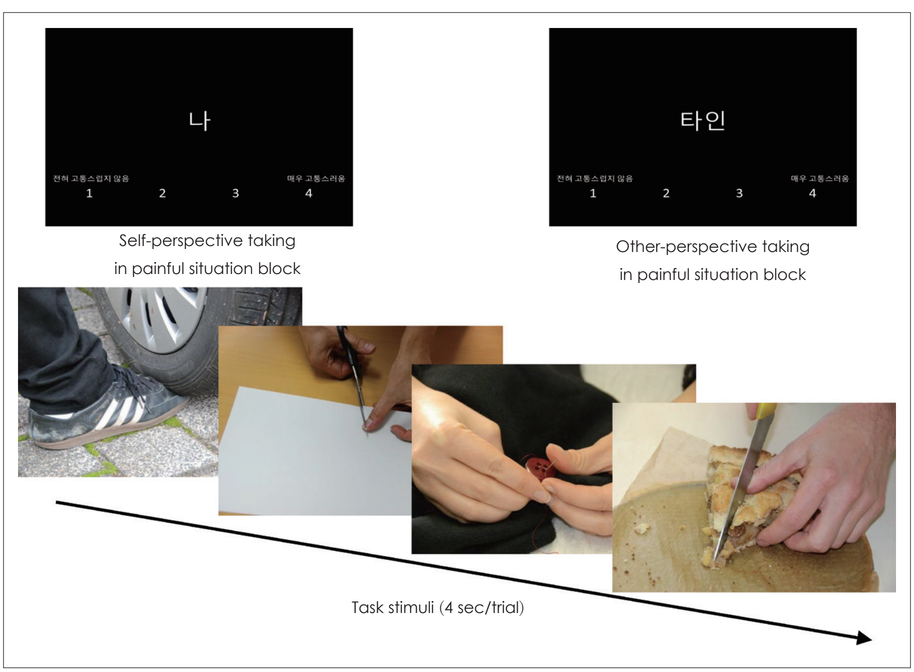

Fig. 1. Example of fMRI task. During the scanning, participants were shown pictures composed of human limbs and objects. In the SP block, they were instructed to imagine themselves in the situations in the pictures and to rate the pain they would feel. In the OP block, they were instructed to imagine the situations in the pictures happening to another person and to rate the level of pain they believed that person would feel. The instructions at the start of each block were presented in Korean. OP, other-perspective taking in painful situations; SP, self-perspective taking in painful situations.

fMRI scanning, a blood-oxygen-level-dependent technique with an echo planar imaging (EPI) sequence was applied. Each image slice had a thickness of 3.5 mm, and there was no gap between the slices. The MR parameters were as follows: repetition time (TR)=2000 ms, echo time (TE)=30 ms, flip angle=90 degrees, field of view=220×220×122 mm, matrix=64×64, and 36 slices. T1-weighted anatomical gradient echo scans were obtained after fMRI. The MR parameters for these images were as follows: TR=6.4–6.8 ms, TE=3.0–3.2 ms, flip angle=12 degrees, field of view=220×220×188 mm, matrix=220×220, and 180 slices.

Image processing and analysis

fMRI images were processed using SPM12 (Wellcome Department of Imaging Neuroscience, London, UK) in MATLAB R2023a (MathWorks Inc., Natick, MA, USA). The EPI images were realigned for motion correction, and participants whose images exhibited translations exceeding 3 mm or rotations greater than 3° were excluded from further analyses. The images were then coregistered with the participants' T1-weighted MR images and segmented. Subsequently, they were normalized to the standard Montreal Neurological Institute (MNI) space using deformation fields and smoothed with an 8 mm full-width at half-maximum isotropic Gaussian Kernel.

We focused on investigating the differences between the ASD and TD groups in terms of self-perspective and other-perspective adoption. Accordingly, two contrasts were examined in this study: self-perspective taking in painful situations versus resting states (SP-R) and other-perspective taking in painful situations versus resting states (OP-R). For each participant's data, statistics were computed at the first level using a general linear model. Images derived from the first-level analysis were then included in the second-level analyses. Within both the ASD and TD groups, one-sample t-tests were conducted for SP-R and OP-R contrasts. These analyses were thresholded at an uncorrected $p<0.00005$ for magnitude, with a cluster threshold of 100 voxels and an uncorrected $p<0.05$. Two-sample t-tests were performed for each group to investigate between-group differences. These analyses were thresholded at an uncorrected $p<0.001$ for magnitude, with a cluster threshold of 100 voxels and an uncorrected $p<0.05$. Additionally, brain regions that showed family-wise error corrected $p<0.05$ at the cluster level in the results of the one-sample and two-sample t-tests were identified. Given our focus on brain regions activated during task performance as opposed to the resting state, there may be increased nonspecific brain activation compared with a design incorporating a control task. Therefore, the threshold for the one-sample t-test was set higher because nonspecific brain activation could be more pronounced in the one-sample t-test than in the two-sample t-test. The brain regions that were significantly activated in the analyses were labeled using automated anatomical labelling atlas 3 [28], a toolbox for SPM.

Brain regions demonstrating between-group differences were designated as regions of interest (ROIs). Using the SPM toolbox MarsBaR [29], parameter estimates (percent signal change) were extracted from within an 8 mm radius of each ROI. These values were then used to investigate correlations with other variables.

Statistical analyses

Continuous variables were compared between the ASD and TD groups using independent t-tests or Mann–Whitney U tests, depending on normality, which was assessed using the Shapiro–Wilk test. Categorical variables were compared using Fisher's exact test. Correlation analyses were conducted to investigate the relationships between the parameter estimates of the ROIs and variables such as interoceptive and empathic abilities. Pearson's correlation analysis was applied to variables that met the normality assumption, whereas Spearman's correlation analysis was used for variables that did not. Statistical significance was defined as $p<0.05$. Statistical analyses were performed using the CRAN R statistical package, version 4.2.0. (https://www.r-project.org).

RESULTS

Participant characteristics

Table 1 shows the demographics and other characteristics of the participants. No significant differences were found between the ASD and TD groups in age, sex, IQ score, or handedness. Regarding the empathic abilities measured through IRI across four dimensions, it was observed that in the ASD group, the scores for perspective taking and empathic concern were significantly lower compared to the TD group, with mean scores of 13.53±5.51 vs. 19.86±4.86 (U[37]=60.5, $p<0.001$) and 14.18±4.54 vs. 17.81±4.84 (t[37]=-2.41, p=0.021), respectively. However, the score for personal distress was higher in the ASD group (18.06±4.75) than the TD group (11.18±4.73; t[37]=4.49, $p<0.001$). Regarding interoceptive abilities, no significant differences were noted between the two groups in terms of interoceptive accuracy, interoceptive sensibility, and ITPE. Yet, there was a marginal difference in the interoceptive accuracy between the ASD group (0.45±0.28) and TD group (0.61±0.17; t[37]=-1.97, p=0.061). Module 4 of the ADOS-2 was used to confirm ASD diagnosis, as all participants in the ASD group were verbally fluent adolescents or adults. Administration of the ADOS-2 revealed that the

Table 1. Demographics and other characteristics of the ASD and TD groups

	ASD group (n=17)	TD group (n=22)	t/U	p
Age	20.24±2.92	22.27±3.57	t=-1.95	0.058
Male‡	16 (94.11)	17 (77.27)		0.206
IQ	105.92±22.97	102.39±14.68	U=201	0.702
Handedness‡				0.528
Right handed	13	20		
Ambidextrous	2	1		
Left handed	2	1		
IRI				
Perspective taking	13.53±5.51	19.86±4.86	U=60.5	<0.001†
Fantasy	15.64±4.82	18.14±4.76	t=-1.61	0.117
Empathic concern	14.18±4.54	17.81±4.84	t=-2.41	0.021*
Personal distress	18.06±4.75	11.18±4.73	t=4.49	<0.001†
Interoceptive abilities				
Interoceptive accuracy	0.45±0.28	0.61±0.17	t=-1.97	0.061
Interoceptive sensibility	69.53±19.92	67.90±28.44	t=0.21	0.836
ITPE	0.40±1.12	-0.31±1.28	t=1.86	0.071
ADOS-2				
Social affect	8.88±2.06	NA		
RRB	1.06±0.34	NA		
Total	9.94±2.10	NA		

Data are presented as mean±standard deviation unless otherwise indicated. *$p<0.05$; †$p<0.001$; ‡comparison by Fisher's exact test. ADOS-2, Autism Diagnostic Observation Schedule, 2nd edition; ASD, autism spectrum disorder; IQ, intelligence quotient; IRI, Interpersonal Reactivity Index; ITPE, interoceptive trait prediction error; NA, not assessed; RRB, restricted and repetitive behavior; t, t-value by Student t-test; TD, typically developing; U, U-value by Mann-Whitney's U test

score for social affect was 8.88±2.06, the score for restricted and repetitive behaviors (RRB) was 1.06±0.34, and the total score was 9.94±2.10.

Behavioral data on fMRI task performances

In the ASD group, reaction times for the SP, SN, OP, and ON were 1457±497 msec, 1214±346 msec, 1499±530 msec, and 1274±413 msec, respectively. In the TD group, reaction times were 1466±373 msec, 1291±299 msec, 1426±409 msec, and 1292±236 msec, respectively, showing no significant differences between the two groups. Pain ratings in the ASD group for the SP, SN, OP, and ON conditions were 3.42±0.48, 1.32±0.48, 3.30±0.58, and 1.29±0.43, respectively. In the TD group, they were 3.47±0.45, 1.12±0.25, 3.50±0.45, and 1.12±0.24, respectively, with no significant differences between the two groups.

fMRI results

Within-group analyses

In the SP-R and OP-R contrasts, the common brain regions were significantly activated in both groups. First, both the ASD and TD groups activated core regions associated with pain-related processing, including the anterior and middle cingulate cortices and the insula, except for the TD group in the OP-R contrast. Second, areas within the dorsolateral prefrontal cortex (DLPFC), including the middle frontal gyrus and triangular and opercular parts of the inferior frontal gyrus, also showed significant activation. These regions are responsible for higher cognitive functions such as judgment and evaluation. Third, several regions related to visual processing, such as the lingual gyrus, fusiform gyrus, calcarine fissure, and the surrounding cortex, were activated. For more details on the within-group analyses, refer to Supplementary Tables 1-4.

Between-group analyses

In the SP-R contrast, the ASD group exhibited greater left precuneus activation than did the TD group. In the OP-R contrast, the ASD group showed relative hyperactivation not only in the left precuneus but also in the right precuneus, left parahippocampal gyrus, left inferior temporal gyrus, left amygdala, right superior temporal gyrus, right superior frontal gyrus, and left caudate nucleus (Table 2 and Fig. 2). There were no brain regions in which the TD group showed greater activation than the ASD group in both the SP-R and OP-R contrasts.

Table 2. Significant activity observed in between-group comparisons for contrasts of interest

Side	Region	Peak				Cluster	
		MNI x, y, z (mm)			Max (t)	Extent (voxels)	p
ASD > TD							
SP-R							
Left	Precuneus	-4	-70	52	5.27	309	0.008*
Left	Precuneus	-14	-56	62	3.57		
OP-R							
Left	Parahippocampal gyrus	-16	-6	-24	5.53	199	0.025
Left	Inferior temporal gyrus	-36	6	-36	4.41		
Left	Amygdala	-24	-8	-14	3.73		
Left	Precuneus	-4	-64	52	5.11	824	<0.001*
Left	Precuneus	-12	-50	16	4.85		
Right	Precuneus	10	-52	42	4.56		
Right	Superior temporal gyrus	52	-22	10	4.70	201	0.024
Right	Superior frontal gyrus, dorsolateral	22	-8	58	4.66	401	0.003*
Right	Superior frontal gyrus, dorsolateral	30	-4	56	4.25		
Left	Caudate nucleus	-8	12	2	4.18	180	0.032
Left	Caudate nucleus	-12	22	10	4.15		
Left	Caudate nucleus	-4	2	12	3.57		
TD > ASD							
SP-R	(No active region was found)						
OP-R	(No active region was found)						

The region labeling is written according to the form provided by AAL3 toolbox in SPM12. Peak thresholded at uncorrected $p<0.001$. Cluster thresholded at 100 voxels and uncorrected $p<0.05$. *family-wise error corrected $p<0.05$. AAL3, automated anatomical labelling atlas 3; ASD, autism spectrum disorder; MNI, Montreal Neurological Institute; OP-R, other-perspective taking in painful situations versus resting states; SP-R, self-perspective taking in painful situations versus resting states; TD, typically developing

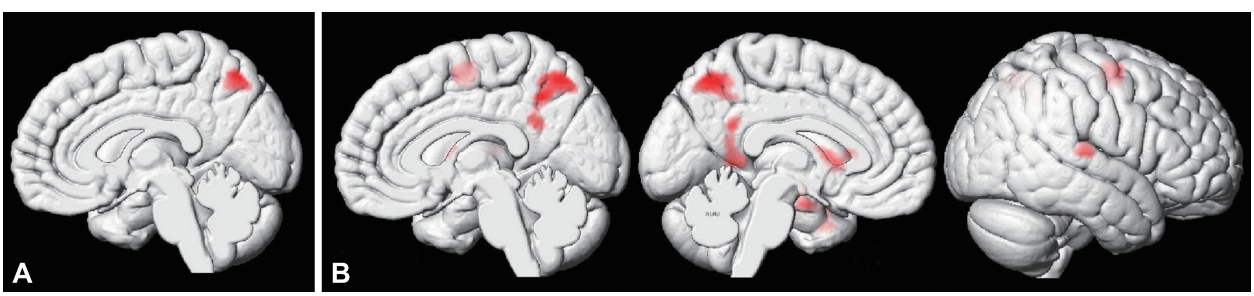

Fig. 2. Group differences in brain activities for each contrast of interest. A: The regions where the ASD group showed greater activity than the TD group under the SP-R contrast. B: The regions where the ASD group showed greater activity than the TD group under the OP-R contrast. There was no region where TD group exhibited greater activity than the ASD group in both SP-R and OP-R contrasts. Peak thresholded at uncorrected $p<0.001$. Cluster thresholded at 100 voxels and uncorrected $p<0.05$. ASD, autism spectrum disorder; OP-R, other-perspective taking in painful situations versus resting states; SP-R, self-perspective taking in painful situations versus resting states; TD, typically developing.

Correlations between interoceptive abilities, empathic abilities, and neural activities in the ASD group

We investigated the correlation between neural activity in the ROIs and interoceptive and empathic abilities. Neural activity in the SP-R contrast showed no correlation with interoceptive or empathic abilities.

However, the neural activity in the OP-R contrast exhibited several significant correlations. The overall results of the correlation analysis are shown in Fig. 3. Regarding interoceptive abilities, interoceptive accuracy showed a negative correlation with the activation level in the right superior frontal gyrus (30, -4, 45; MNI coordinates) ($r[15]=-0.66$, $p=0.004$), whereas ITPE exhibited a positive correlation with the activation level in the same brain region ($r[15]=0.60$, $p=0.012$) (Fig. 4). Regarding empathic abilities, the IRI-personal distress score showed a positive correlation with the activation level of the left amygdala (-24, -8, -14; MNI coordinates) ($r[15]=0.49$, $p=0.046$). The IRI-perspective taking score was negatively correlated with the activation level of the left caudate nucleus ($r[15]=-0.51$, $p=0.036$). Additionally, the IRI-

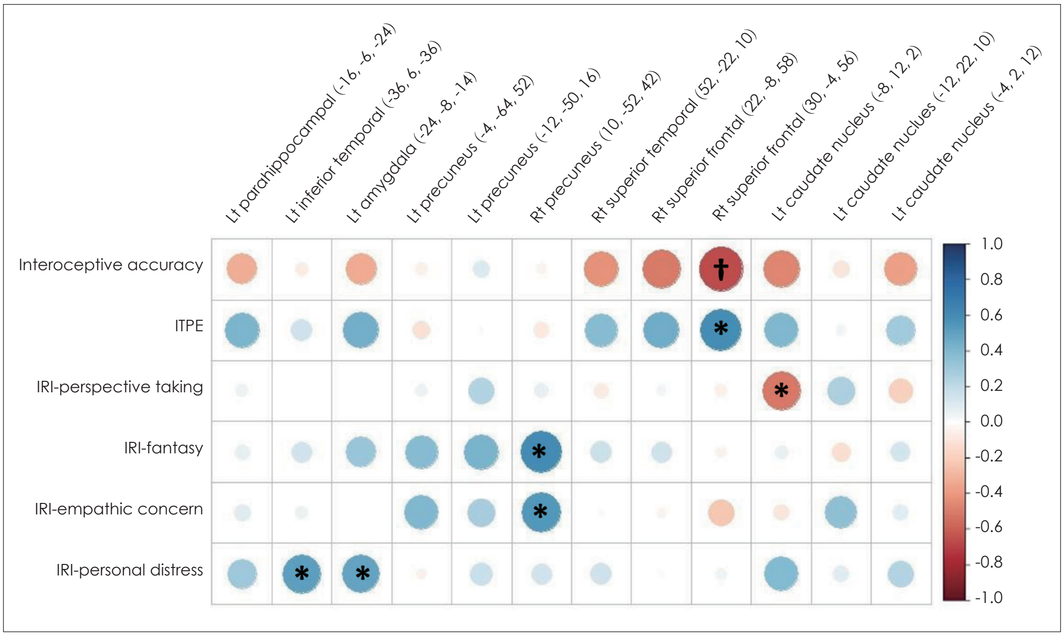

Fig. 3. Correlations between brain activities in the regions where the ASD group showed more activations than the TD group for the OP-R contrast and interoceptive and empathic abilities in the ASD group. $^{*}p<0.05$; $^{\dagger}p<0.01$. ASD, autism spectrum disorder; IRI, Interpersonal Reactivity Index; ITPE, interoceptive trait prediction error; Lt, left; OP-R, other-perspective taking in painful situations versus resting states; Rt, right; TD, typically developing.

fantasy score and the IRI-empathic concern score were positively correlated with the activation level of the right precuneus (10, -52, 42; MNI coordinates) (r[15]=0.60, p=0.010; r[15]= 0.548, p=0.022, respectively).

DISCUSSION

The current study investigated brain activation in ASD and TD groups when evaluating painful situations from both self- and other-perspectives. We also explored how brain activation was related to empathic and interoceptive abilities. Empathic abilities assessed using the IRI showed varying patterns of group differences across dimensions. Specifically, the IRI-perspective taking and IRI-empathic concern scores were lower in the ASD group than in the TD group, while the IRI-personal distress score was higher. Regarding interoceptive abilities, there were no significant differences between the two groups across the three dimensions, although a trend toward lower interoceptive accuracy was observed in the ASD group than in the TD group. Compared to the TD group, the ASD group showed hyperactivation in the precuneus during both SP and OP. Moreover, during other-perspective taking, the ASD group showed further hyperactivation in the right superior frontal cortex (dorsolateral), left caudate nucleus, parahippocampal gyrus, inferior temporal gyrus, amygdala, and superior temporal gyrus compared with the TD group. In the ASD group, during other-perspective taking, the activity level in the right superior frontal gyrus showed a negative correlation with interoceptive accuracy and a positive correlation with ITPE, whereas the activity level in the left caudate nucleus showed a negative correlation with the IRI-perspective taking score, and the activity level in the left amygdala showed a positive correlation with the IRI-personal distress score.

In this study, the IRI-perspective taking and IRI-empathic concern scores were lower in the ASD group than in the TD group, whereas the IRI-personal distress score was higher in the ASD group than in the TD group. These findings align precisely with the results of a meta-analysis published by Song et al. [6], and similar results have been reported in other studies [30-32]. Perspective taking refers to understanding the viewpoint of "another person", and empathic concern denotes worry for "another person" in distress, whereas personal distress refers to the stress "oneself" feels upon seeing another person in a difficult situation. Thus, perspective taking and empathic concern are other-oriented and enable empathic interaction, whereas personal distress is self-oriented and can lead to social withdrawal due to overwhelming emotions if felt excessively. For empathy to lead to prosocial behavior, one must experience a manageable level of emotional contagion while also understanding the situation or emotions of others. The results of this study suggest that individuals with ASD may feel emotional stimuli more intensely, but may not be able to develop this into compassion

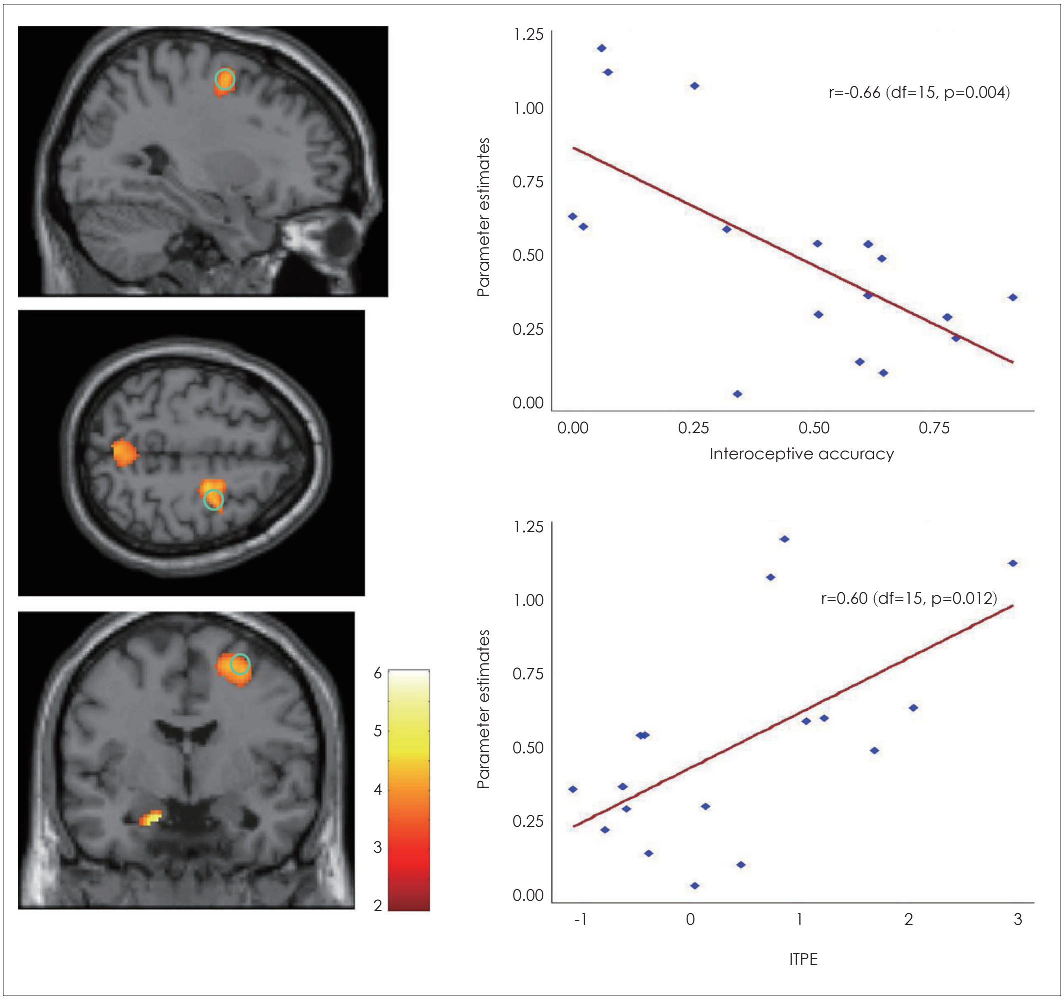

Fig. 4. Interoceptive abilities and brain activity in the region where the ASD group showed more activation than the TD group for OP-R contrast. Interoceptive accuracy was negatively correlated with activity in the right superior frontal gyrus (30, -4, 56; MNI coordinates), while ITPE was positively correlated. ASD, autism spectrum disorder; ITPE, interoceptive trait prediction error; MNI, Montreal Neurological Institute; OP-R, other-perspective taking in painful situations versus resting states; TD, typically developing.

aimed at helping others in distress.

Interoceptive accuracy, interoceptive sensibility, and ITPE showed no significant differences between the groups. However, a trend toward lower interoceptive accuracy was observed in the ASD group than in the TD group. The findings of studies investigating interoceptive ability in individuals with ASD are inconsistent [26,33,34]. Some reports indicate reduced interoceptive accuracy in children with ASD, whereas adults with ASD may not differ from TD individuals [35]. Some researchers have argued that interoceptive impairments are more closely related to the alexithymia accompanying ASD than to the ASD itself [36]. A recent meta-analysis reported decreased objective interoceptive accuracy and increased subjective interoceptive confidence [37]. It is possible that the marginal difference in interoceptive accuracy between the two groups was due to the small sample size, which led to insufficient statistical power. Future research should investigate the interoceptive differences in individuals with ASD according to age or alexithymia.

The results of within-group analyses indicated that both the ASD and TD groups activated key regions of pain-related processing, including the insula, ACC, and MCC, while performing tasks. These core regions are commonly activated when experiencing pain and observing pain in others [38]. This suggests that the task used in this study elicited appropriate neural responses to pain stimuli. Furthermore, both groups commonly activated the DLPFC, which is associated with higher cognitive functions, such as judgment and evaluation. This finding supports the idea that participants perform pain ratings conscientiously while engaging in the task. Since we used the resting state as a control condition to calculate task-related brain activity, within-group analyses may reveal nonspecific brain activation (e.g., brain activity related to visual processing). However, in between-group comparisons, brain activity during the resting state may be negated. Therefore, we focused on the results of the between-group analysis.

The ASD group showed greater activation of the precuneus than the TD group in both the SP-R and OP-R contrasts. This structure is part of the "core module" associated with perspective taking [4] and is linked to self-referential thinking and episodic memory as a component of the default mode network system (DMN) [39]. Observing a painful situation and rating the pain based on a self- or other-perspective requires recalling similar personal experiences (i.e., episodic memory) and assessing how painful it was (i.e., self-referential thinking). Thus, hyperactivation of the precuneus suggests that individuals with ASD may have atypical self-referential processing based on past experiences. Interestingly, the range of hyperactivated precuneus areas in the ASD group extended from left to right in the OP-R contrast compared to the SP-R contrast. This suggests that other-perspective taking may be more atypical in the ASD group than in the TD group. Cheng et al. [40] reported in a large-scale fMRI study that individuals with ASD show reduced functional connectivity in key systems, including the precuneus, which could be associated with impaired theory of mind processing. Therefore, the altered neural response of the precuneus observed in the ASD group may represent compensatory hyperactivation. The activation level of the right precuneus, which was only hyperactivated in the OP-R contrast in the ASD group, showed positive correlations with the IRI-fantasy and IRI-empathic concern scores. This provides evidence that the ASD group may have excessively recruited the right precuneus to compensate for their lower perspective taking abilities.

The ASD group exhibited greater activation of the right superior frontal gyrus than the TD group in the OP-R contrast, which corresponds to the caudal portion of the dorsal premotor cortex (PMdc). This area, which primarily receives inputs from the somatosensory cortex and is directly connected to the primary motor cortex and spinal cord [41], is involved in coding limb movements during motor planning [42]. Notably, all pain-related images used in the fMRI task included human limbs. Thus, it can be inferred that the ASD group demonstrated an exaggerated brain response associated with motor planning of limb movement in response to vicarious pain experiences compared to the TD group. An important point to highlight is that this overactivation of the PMdc was observed only in the OP-R contrast and not in the SP-R contrast. This suggests that a strong escape response—a motor response to move away from the painful stimulus—was elicited in the ASD group as if they were feeling the pain themselves, even when attempting to assess it from another person's perspective. Significantly higher activity levels in the right superior frontal gyrus of the ASD group were associated with lower interoceptive accuracy. Palmer and Tsakiris [43] argued that interoceptive processing plays a role in stabilizing the model of oneself, enabling us to easily attribute mental states to ourselves or others while maintaining a clear distinction between "self" and "other." This hypothesis implies that low interoceptive accuracy may blur the boundary between the self and others, complicating the discernment of whether emotional stimuli originate internally or externally. Applying this model to the results of our study, the ASD group, which showed a tendency toward lower interoceptive accuracy than the TD group, may have an unclear self–other distinction. The lower the interoceptive accuracy, the more pronounced is the merging of self and other, as reflected in the strong escape response manifested by hyperactivation of the PMdc, even when evaluating pain from another perspective. The positive correlation between the activation levels of the right superior frontal gyrus and ITPE can be understood in a similar manner. An increase in ITPE could indicate a deepening discrepancy between subjective interoceptive sensibility and objective interoceptive accuracy. Thus, higher ITPE predicts anxiety, making predictions about interoception more inaccurate [44]. The relationship between increased ITPE and anxiety has been confirmed in individuals with ASD [26]. Therefore, participants with ASD with higher ITPE in this study may exhibit larger escape responses, as shown by the hyperactivation of the PMdc, due to increased anxiety from inaccurate internal perception predictions. Although evidence remains sparse, interventions based on emotional awareness and mindfulness for individuals with ASD are considered promising [45,46]. We speculate from the results of this study that improving interoceptive difficulties might contribute to enhancing perspective taking, which is central to the theory of mind in individuals with ASD. Further research on the relationship between interoception and perspective taking is needed.

Another explanation for the aforementioned results could be that when compared to the SP-R contrast, the ASD group experienced greater embodiment than the TD group in the OP-R contrast. The mechanism of embodiment occurs through sensorimotor simulation [47,48], rendering the PMdc a representative neural correlate of the embodiment mechanism. Hence, it can be argued that the ASD group experienced excessive distress due to excessive embodiment while evaluating pain from another's perspective, which manifested as escape behavior, represented by hyperactivation of the PMdc. According to Erle et al. [49], visuo-spatial perspective taking (VPT) is classified into levels 1 and 2. The Level 1 VPT is the ability to understand that another person can see things differently from one's own viewpoint, whereas the Level 2 VPT is the ability to judge what a visual scene looks like from another's viewpoint. Level 2 VPT requires the perspective-taker to mentally simulate the movements or rotations of their body toward physical objects, necessitating a more extensive embodiment process than Level 1 VPT. Importantly, efficient Level 2 VPT and high interoceptive accuracy may be closely related because both processes are inherently embodied. Individuals who can accurately perceive their internal state may better distinguish between their visual perspectives and those of others [50]. Erle et al. [49] showed that interoceptive accuracy was positively correlated with the ability to perform Level 2 VPT in the general population. However, in the present study, the ASD group showed a negative correlation between the degree of brain activation related to embodiment and interoceptive accuracy. This suggests that lower interoceptive accuracy could lead to more pronounced blurring of the self–other boundary, resulting in excessive or atypical embodiment.

In the OP-R contrast, the ASD group exhibited higher neural activity in the left caudate nucleus than did the TD group. This brain region is not only involved in planning the execution of movement but also plays a crucial role in the active avoidance of aversive stimuli [51]. Thus, similar to the previously mentioned case of PMdc, this finding implies that an excessive escape response occurred. The occurrence of such an escape response from another perspective, rather than a self-perspective, indicates that other-perspective taking could be stressful for the ASD group, whether due to blurring of the self–other boundary as a result of a lack of interoceptive accuracy or for other reasons. Neural activity in the left caudate was nucleus negatively correlated with the IRI-perspective taking score. Since causality was not investigated in this study, it is challenging to clarify definitively; however, it is possible that participants with ASD who struggle with perspective taking might exhibit stronger brain activation related to avoidance responses when taking the other-perspective on pain due to stress, and vice versa.

Numerous studies have consistently reported amygdala hyperactivation in stress or anxiety [52-54]. The result of the ASD group showing greater activation of the left amygdala in the OP-R contrast than the TD group suggests that participants with ASD may have found taking other-perspectives of pain to be more emotionally arousing and may perceive these as more threatening or stressful. This corresponds with an earlier claim that participants with ASD may have encountered challenges in prediction and exhibited an excessive escape response in the OP-R contrast. Furthermore, the activity level of the left amygdala in the ASD group positively correlated with the IRI-personal distress score. This provides neurobiological evidence that the finding of a significantly higher IRI-personal distress score in the ASD group than in the TD group applies equally to the context of acquiring a perspective on others' pain. Additionally, compared with the TD group, the ASD group showed greater activation of the left parahippocampal gyrus and left inferior temporal gyrus (corresponding to the temporal pole) in the OP-R contrast, which are areas associated with autobiographical memory [7,55]. This suggests that participants with ASD may have employed more self-oriented episodic memories to evaluate the pain of others.

This study had several limitations. First, we did not use brain activation in response to pain-free stimuli as the control condition in our analysis. This decision was based on our observation that brain responses to no-pain stimuli showed only minimal differences from responses to pain stimuli. This likely occurred because the components of the no-pain stimuli were almost identical to those of the pain stimuli, leading to pain-related processing even in response to no-pain stimuli. However, as shown in the within-group analysis results, relevant brain responses to pain stimuli clearly occurred in both the SP-R and OP-R contrasts. Thus, these two contrasts proved reliable for our analysis. Second, the sample size was small. This may have resulted in a lack of statistical power, potentially leading to missed discoveries of the existing differences or effects. Third, the participants' ages ranged from 15 to 28 years, but we did not account for the impact of developmental stage on our analysis. Fourth, most participants were male. These limitations restrict the generalizability of the findings. Nevertheless, this study has important implications for understanding ASD. We discovered a significant connection between empathic abilities, interoceptive abilities, and brain activation related to perspective taking, which is a crucial component of empathy.

CONCLUSION

Our results provide new insights at both the behavioral and brain levels into the link between difficulties in perspective taking, a core feature exhibited by individuals with ASD, and interoception. When assessing pain from both self- and other-perspectives, individuals with ASD show hyperactivation of the precuneus, which is related to self-referential processing. Further, more atypical neural activity occurs during other-perspective taking compared with self-perspective taking. That is, they show overactivated brain regions, including the right superior frontal gyrus, left caudate nucleus, and left amygdala. Notably, activity levels in the right superior frontal gyrus during other-perspective taking tend to be negatively correlated with interoceptive accuracy in patients with ASD. This suggests that difficulties in interoception could blur the distinction between self and others or elicit atypical embodiment, causing the brain of an individual with ASD to trigger intense stress reactions and excessive escape responses. Our findings highlight the need to investigate the impact of interoception-related interventions such as mindfulness on improving the core symptoms of ASD. Future studies should delve into the connections between interoception, core symptoms of ASD, and their neural underpinnings to accumulate more evidence.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.5765/jkacap.240008.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

Conflicts of Interest

Jung-Woo Son, a contributing editor of the *Journal of the Korean Academy of Child and Adolescent Psychiatry*, was not involved in the editorial evaluation or decision to publish this article. All remaining authors have declared no conflicts of interest.

Author Contributions

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