Neural responses to affective and cognitive theory of mind in children and adolescents with autism spectrum disorder

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Neural responses to affective and cognitive theory of mind in children and adolescents with autism spectrum disorder

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<ABSTRACT>

Neural Responses to Affective and Cognitive Theory of Mind in Children and Adolescents with Autism Spectrum Disorder

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Objectives: Children and adolescents with Autism Spectrum Disorder (ASD) are characterized by the impairment of Theory of Mind (ToM) abilities. Recent evidence suggested that two aspects of ToM (cognitive ToM vs Affective ToM) is differentially impaired in individuals with ASD. In this study, we aimed to examine the neural correlates of cognitive and affective ToM processes in children and adolescents with ASD compared to typically developing controls (TDC).

Methods: 12 children and adolescents with a diagnosis of Autism Spectrum disorder (11 males, mean age 12.4) and age, IQ matched 12 healthy control subjects (12 males, mean age 11.7) participated in functional MRI study. The ToM task involved the attribution of cognitive and affective mental states to a cartoon character based on verbal and eye-gaze cues. The difference in brain activation between ASD and TDC subjects was examined contrasting affective and cognitive ToM conditions.

Results: In cognitive ToM tasks, ASD subjects recruited a region within the anterior prefrontal cortex (medial prefrontal cortex, anterior cingulate

cortex: mPFC/ACC) and superior temporal gyrus to a greater extent than TDC. In affective ToM tasks, they showed more activation in insula, middle frontal gyrus and precentral gyrus. Exploratory correlational analysis revealed that inverse relationship between autistic symptoms of social impairment and fMRI functional response for cognitive ToM task, and this result suggests that greater activation of the mPFC/ACC regions was associated with less symptom severity in ASD patients.

Conclusions: The present study demonstrated the neural bases of cognitive and affective ToM in ASD patients. From a clinical perspective, this data suggested that the recruitment of additional prefrontal resources can compensate for the successful performance in the ToM task at behavioral level in children and adolescents with ASD. This kind of research can be applied to the tailored implementation of treatment intervention for children and adolescents with ASD in the direction of strengthening the prefrontal function in the implementation of social skill training program for ASD patients.

Key words : theory of Mind, cognitive ToM, affective ToM, autism spectrum disorder, functional MRI

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I. INTRODUCTION

Children and adolescents with Autism Spectrum Disorder (ASD) are characterized by the impairment of Theory of Mind (ToM) abilities, which contribute to their characteristic impairment in social interaction and communication in this group of patients.[1]

Theory of Mind (ToM) refers to 'the process by which we make inferences about mental states to others.[2] The key regions recruited by ToM processes in the healthy brain comprises medial prefrontal cortex (mPFC), superior temporal sulcus (STS), the temporo-parietal junction (TPJ), the anterior temporal poles (TP) and precuneus.[3,4] In ASD patients, these ToM-related brain regions have been reported to show abnormal activation during ToM tasks in inferior frontal cortex (IFC), mPFC, STS, TP and anterior insula.[5,6,7]

However, the ToM is a broad concept encompassing various subcomponents, making it one that requires various different cognitive abilities.[8] Therefore, depending on which ToM task is used and which

aspect of ToM is focused on, each research on ToM of ASD patients reported somewhat different results.[9] To provide the explanation for these inconsistencies, recent studies have defined subcomponents of ToM, and one important differentiation is that of 'affective' ToM (inference about other people's emotional states and feelings) versus 'cognitive' ToM (inference regarding other people's thoughts and beliefs). These two aspects of ToM is reported to be mediated by overlapping but dissociated brain networks in healthy controls and a variety of psychiatric populations.[10-12]

Available evidence suggests that within the PFC, the orbitofrontal cortex (OFC: BA 11, 12, 47), vmPFC (BA 9, 32), and IFC (BA 44, 45, 47) are involved in affective TOM processing, and that the dorsolateral PFC and the dorsomedial PFC are uniquely involved in processing cognitive TOM.[9-11] The involvement of the vmPFC, OFC, and ILFC in the representation and regulation of socioemotional states and their dense connections with the amygdala makes these lesions suitable for synthesizing the diverse information needed for representing affective mental states.[10]

Although both emotional and cognitive components of ToM appear to trigger independent circuits within the larger mentalizing network, there seems to be interacting functions of the brain where affect and cognition can mutually affect each other. This is suggested by the reciprocally interconnected limbic-paralimbic and neocortical areas of the mentalizing network. The ACC is one candidate region where processing of this interaction between cognitive and affective representation takes place.[3]

Behavioral data suggested that 'cognitive' and 'affective' ToM is also differentially impaired in individuals with ASD, but the results are different in each studies.[9,13] These two aspects of ToM are reported to be differentially impaired in individuals with Asperger's syndrome.[13] Previous studies suggested that only affective ToM is impaired in adult individuals with ASD, but other study reported that only cognitive ToM is impaired, but affective ToM ability is preserved in adult ASD patients.[13]

With regard to neuroimaging studies, former studies with healthy population suggested that neural responses in the classic ToM network were detected in both cognitive and affective ToM conditions, but lesion studies showed only affective ToM recruited medial/ventromedial PFC (m PFC/ vm PFC).[9,14,15] Affective ToM processing is somewhat distinct from that related to cognitive ToM and depends in part on separate anatomical substrates. Furthur confirmation for partially different neural correlates in processing affective and cognitive ToM was recently provided by fMRI studies.[12] Other study reported that distinct brain regions have been implicated in distinct subcomponents of empathy[8]; affective components have been linked to the human mirror neuron system, as well as limbic structures and the insula.[11,16,17] In contrast, cognitive components seem to draw upon brain regions, such as mPFC, STS and TP. In studies investigating developmental trajectories of ToM subtypes, it seems to be that adolescents activated vmPFC more than did adults during affective ToM task.[18] However, few studies examined the neural circuitry underlying the cognitive and affective TOM separately in children and adolescents with ASD so far.

Under this background, we aimed to further examine the overlap and dissociation of neural bases of affective vs cognitive ToM, using functional magnetic resonance imaging (fMRI) in a group of children and adolescents with ASD, compared to typically developing control (TDC) subjects. Our key hypothesis were as follows based on the aforementioned results from other studies 1) Children and adolescents with ASD would show differences of activation in brain regions involved in ToM during the ToM tasks, relative to TDCs. 2) Cognitive and affective ToM might activate ToM- related structure in brain, but affective ToM may additionally recruit regions functionally related to integrate cognitive and affective information, such as mPFC, ACC, insula, and some subcortical paralimbic regions.

II. MATERIALS AND METHODS

1. Subject characteristics

15 high functioning subjects with ASD and 14 TDCs participated in fMRI study. 5 participants (3 ASDs, 2 TDCs) were excluded due to excessive motion during MRI scanning. Therefore, 12 children and adolescents with a diagnosis of Autism Spectrum disorder (11 males, mean age 12.4, SD=2.3) and age, IQ matched 12 TDCs (12 males, mean age 11.7, SD=2.1) were included in the final analysis. There were no group differences in full scale IQ as measured by the K-WISC-III (ASD: mean = 107.3, SD= 13.9, TDC: mean=113.7,

SD=12.8). All subjects were right-handed. Diagnosis was performed by a child and adolescent psychiatrist according to the standard Diagnostic and Statistical Manual of Psychiatric Disorders-IV. In addition to clinical diagnosis, we used the Autism Diagnostic Interview-Revised (ADI-R) and the Autism Diagnostic Observational Schedule (ADOS) in 9 participants to assess the current level of functioning for the ASD group. ASD subjects with comorbid Attention Deficit Hyperactivity Disorder (ADHD), depressive disorder, anxiety disorder were also included. Four out of 12 ASD participants were taking medication (1: Risperidone, Sertraline for Tic disorder, OCD, 2: Aripiprazole for Tic disorder, Escitalopram for depression, 3:Atomoxetine for ADHD, 4: Fluoxetine and Methylphenidate for depression, ADHD). Stimulants are discontinued 24 hour prior to the fMRI experiment, but other medications are continued. This study was approved by the Institutional Review Board of the Yonsei University College of Medicine and was carried out in compliance with the Declaration of Helsinki. All participants and their parents gave written informed assent or consent.

2. Behavioral task

A Korean modified version of the "Yoni" task introduced by Shamay-Tsoory et al.[19] was used as a behavioral task and it was adapted for the fMRI environment as an event-related paradigm. Yoni task is based on a task previously described by Baron-Cohen and involves the ability to judge mental states via analysis of verbal cues, eye gaze and facial expression, which are aspects of the sophisticated social mentalizing

processing.[2] An incomplete sentence about what image Yoni is referring to is presented, and the subject has to judge which of the four stimuli in the corners best fills the gap of the sentence. Only second order ToM items from the original Yoni task were chosen since previous study reported that second order ToM task evokes more activation in the ToM network than first order ToM task.[20] In this task, the four stimuli in the corners consist of faces and an inference regarding the interaction between Yoni's and the other stimuli's mental state is necessary. There are three main conditions in this task; 'cognitive' 'affective' 'physical' (serving as baseline control). In the cognitive (COG) ToM with the sentence, 'Yoni is thinking of the ….that……. wants', both the verbal and facial cues are neutral. In the affective (AFF) ToM condition with the sentence 'Yoni loves the …. that …… loves', both cues are affective. Physical (PHY) condition with the sentence 'Yoni has the same toys that …..has.' did not require the attribution of mental states to the characters. Each condition is consisted of 24 stimuli, so total of 72 questions in 1 run out of 2 runs. The item sets of all items subcategories are comparable with regard to sentence and visual complexity. The task has been validated before and has been shown to be positively correlated with verbal measures of ToM such as false belief stories.[9] The total task duration was 9 min 46 sec. All items were presented in randomized order for a maximum of 5.5 sec during which the subjects had to answer by tapping a four-button response box on both hands as fast as they could. Before experiment, all subjects received an introduction to the Yoni task with four explaining slides, and a training that resembled the test but with only 15 items (5 COG, 5 AFF, and 5

PHY) not included in the test.

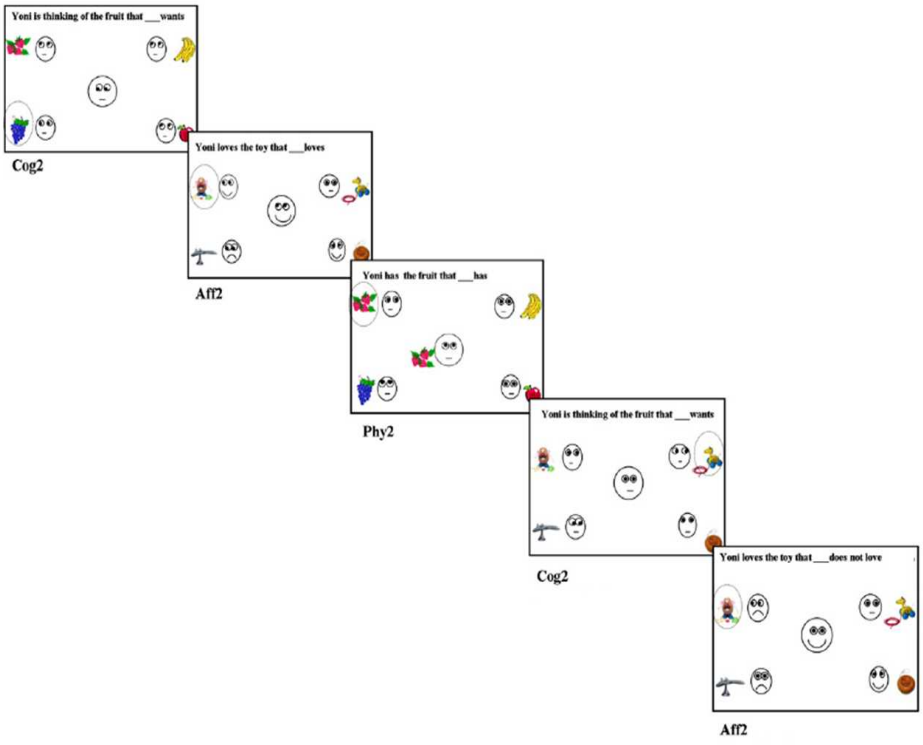

Fig 1. Examples of task stimulus of the Yoni ToM task modified from Shamay-Tsoory et al. (2007) for each condition; text were written in Korean, but translated in English in these examples.

3. Assessment of ToM abilities

Four aspects of ToM abilities were assessed using the Interpersonal Reactivity Index (IRI).[19] These scales assess both the cognitive and affective components of ToM separately, and were validated with other measures of empathy. This instrument consisits of four seven-item

subscales: Perspective Taking (PT), Fantasy Scale (FS), Empathic Concern (EC) and Personal Distress (PD). The perspective taking scale measures the reported tendency to spontaneously adopt the psychological point of view of others in everyday life. The fantasy scale measures the tendency to imaginatively transpose oneself into fictional situations. The PT and FS were found to be positively correlated with other validated measures of cognitive empathy. The empathic concern scale assesses the tendency to experience feelings of sympathy and compassion for others, personal distress scale taps the tendency to experience distress and discomfort in response of others' observed distress. These two scales measure an affective facet of empathy. To assess cognitive empathy we used the mean score of the PT and the FS subscales, whereas emotional empathy was assessed using the mean score of the EC and the PD subscales. The IRI has good internal consistency, with alpha coefficients ranging from 0.68 to 0.79.[19]

4. Behavioral analysis

Performance was rated for accuracy and reaction time (RT). Accuracy was scored on a binomial scale (1=correct, 0=incorrect). Accuracy scores and RT were subjected to separate 3 (Condition: cognitive, affective, physical) by 2 (Group: ASD, TC) ANOVA in SPSS.

5. MRI acquisition

Participants were scanned on a Philips Achieva 3.0T MR scanner

(Philips Medical Systems, Best, The Netherlands). E-Prime was used to present the task to the subjects during scanning. Functional MRI data comprised 293 volumes acquired with a T2-weighted single shot echo planar imaging (EPI) sequence, using a sense-8 head coil. Each participant was axially scanned using the following parameters: voxel size=2.75×2.75×4.0mm^3, matrix=80×80, repetition time (TR)=2000ms, echotime (TE)=30ms, field of view (FOV)=220mm. For the first 15 participants (8 TDC and 7 ASD), slices were acquired interleaved with a thickness=4mm (no gap), and a slice number=31. For the remaining 11 participants (6 TDC and 5 ASD), slices were acquired interleaved with a thickness=3.5mm, gap=0.5mm and a slice number=36, due to the system maintenance and software update of MR scanner.

6. Imaging data analysis

Data were preprocessed and analyzed using SPM8 (Wellcome Department of Imaging Neuroscience; http://www.fil.ion.ucl.ac.uk/spm/). Standard pre-processing was applied with slice time correction, realignment to the first volume to correct for interscan motion artifacts. After realignment, a mean EPI image was created, which was co-registered with the structural T1 image. Subsequently, images were spatially normalized to the standard stereotactic space defined by the Montreal Neurological Institute (MNI) template. Functional images were then smoothed with a 3D isotropic 6-mm full width/half-maximum (FWHM) Gaussian kernel. Low-frequency noise was removed by applying a high-pass filter (cut-off of 128s) to the f MRI time-series at each voxel.

The analysis of the BOLD difference between ASD and TDC groups was performed at a statistical threshold at uncorrected $p<0.001$ at the whole brain level, consisting of minimum of 35 neighboring voxels using SPM 8. The contrasts we performed were: Cognitive ToM (COG) > Physical Control (PHY), Affective ToM (AFF) > PHY, COG > AFF and AFF > COG. To further explore the relationship between brain function in regions showing the difference between the ASD and TDC groups and ToM abilities and clinical symptoms, correlation analyses were also conducted between BOLD signal estimates associated with the contrasts of interest and (i) IRI cognitive and affective empathy subscales across the two groups (ii) ADOS social subscale within the ASD group only. Coordinates are reported in MNI (Montreal Neurological Institute) space. Brain regions were identified with the Anatomical Automatic Labelling Toolbox for SPM.

III. RESULTS

1. Demographic and clinical characteristics of ASD and TDC

	ASD (n=12)	Control (n=14)	p
Age (SD)	12.4 (2.27)	11.7 (2.10)	0.41
IQ (SD)			
Verbal IQ	107.3 (13.8)	118.8 (12.7)	0.05*
Performance IQ	103.9 (15.4)	104.1(10.9)	0.98
Total IQ	107.3 (13.9)	113.9 (12.1)	0.25

ASD: Autism Spectrum Disorder, SD: standard deviation, IQ: intelligence quotient, *$p<0.05$: significant difference

2. In-scanner behavioral performance

For each participant, mean reaction time (RT) except missing trials and accuracy (percentage correct rates) were averaged across the two experimental runs. These results are presented in Table 2. Independent T-test showed that there are no significant difference in reaction time or in accuracy between ASD and TDC groups.

Table 2. Means and standard deviations for reaction time (RT) and percentage correct data for the Yoni task, presented by Condition and Group

	ASD (n=12)	TDC (n=12)	p
Mean RT (SD)			
Affective TOM	2797(453)	2729(438)	.63
Cognitive TOM	2881(480)	2897(455)	.91
Physical control	1726(403)	1792(395)	.60
Percent correct (SD)			
Affective TOM	84.2(13.2)	86.3(13.5)	.45
Cognitive TOM	79.3(17.4)	82.5(12.7)	.30
Physical control	89.3(14.9)	96.0(4.8)	.06

RT: reaction time; SD, standard deviation

3. Interpersonal Reactivity Index (IRI): cognitive and affective TOM subscales

The analysis of IRI subscales revealed that the ASD group showed trend for significantly lower scores on the empathic concern (EC) subscale compared to controls ($p<0.022$). There was no significant difference in any other subscales in IRI, and the two composite scores, cognitive TOM and Affective TOM did not show any significant difference between ASD and TDC groups (Table 3).

Table 3. The comparison of scores on the IRI subscales between ASD and TDC group

Perspective Taking (PT)	21.3 (4.3)	24.5 (4.3)	.085
Empathic Concern (EC)	21.8 (3.7)	25.5 (3.5)	.022
Personal Distress (PD)	20.3 (4.8)	19.7 (4.8)	.73
Fantasy (F)	22.1 (5.1)	25.0 (5.4)	.18
Cognitive TOM (PT+F)	43.4 (7.4)	49.5 (8.1)	.067
Affective TOM (EC+PD)	42.2 (7.1)	45.2 (6.9)	.304

*IRI: Interpersonal Reactivity Index, ASD: Autism Spectrum Disorder, TDC: Typically Developing Control, SD: Standard Deviation

4. Functional MRI

A) Brain regions showing significant group differences between ASD and TDC group

In Table 4 and Figure 2, brain areas showing greater activation in the ASD group than the TDC group and regions reaching cluster-level significance at $p<0.001$ uncorrected, $k>35$ for the contrast of interest are shown. For Cognitive ToM task (COG > PHY), ASD group recruited a region within the bilateral medial frontal cortex (BA 9) and right superior temporal gyrus (BA 22), left anterior cingulate gyrus to a greater extent, compared to TDC group. In affective ToM tasks (AFF > PHY), only right medial frontal cortex (BA 10) was engaged to a greater degree relative to

TDC group. However, right superior temporal gyrus (BA 22), right prefrontal regions (superior, inferior, and medial frontal gyrus, BA 6,8,9) and right putamen are more activated relative to controls, uncorrected at the cluster level when the threshold was lowered to $p<0.005$, $k>20$. Neither AFF > COG nor COG > AFF contrasts reached the statistical threshold of $p<0.001$, uncorrected.

Table 4. Brain regions showing significant group differences between ASD and TDC group ($p<0.001$, uncorrected at the cluster level)

Anatomical region	Side	BA	(.....)			*k*	*Z*
			x	*y*	*z*		
(TDC < ASD) x (COG > PHY)							
Medial frontal gyrus	R	9	22	34	36	78	4.45
Superior temporal gyrus	R	22	48	-18	2	52	4.35
Anterior cingulate	L	24	-4	36	10	63	4.02
Medial frontal gyrus	L	10	-8	52	8	37	3.60
(TDC < ASD) x (AFF > PHY)							
Medial frontal gyrus	R	10	12	48	10	28	3.72

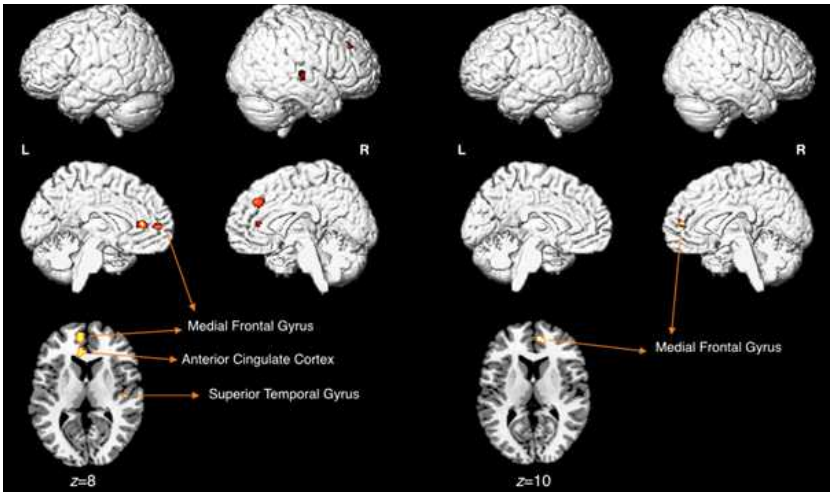

Figure 2: Brain regions showing significant differences between the ASD and the TDC group, at $p<0.001$, uncorrected at the cluster level for contrasts Cognitive ToM > PHY, Affective ToM > PHY

B) Brain regions showing a significant effect of Condition (COG, AFF) in ASD group

There was a significant effect of COG > PHY contrast, in bilateral prefrontal regions (Rt. medial frontal gyrus, Lt. middle frontal gyrus, precentral gyrus: BA6) and bilateral Inferior frontal gyrus (BA 45,46,47), middle temporal gyrus (BA 39), inferior parietal lobule (BA 40), right precuneus (BA 19) and left cingulate gyrus. The AFF > PHY contrast showed activations in the lateral PFC (the right inferior and middle frontal gyrus ; BA 9, 45, 46), superior temporal gyrus (BA 22), middle and medial frontal gyrus (BA 6), middle temporal gyrus

(BA 37, 19) bilaterally, anterior cingulate, cerebellum, cuneus and thalamus. These activations are shown in Table 5 and Figure 3. For AFF > COG, significant clusters were found in right insula, middle frontal gyrus, and precentral gyrus. The reverse contrast COG > AFF did not show any significant activation.

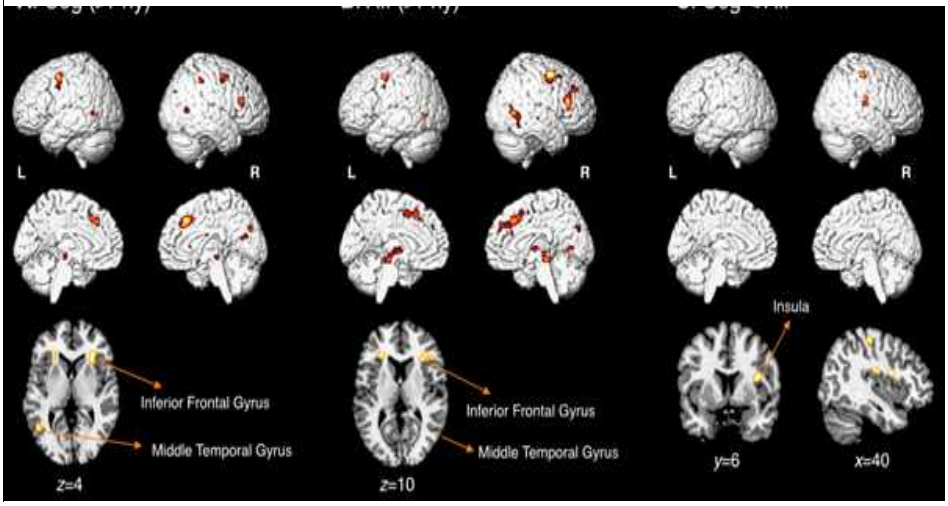

Figure 3. Brain regions showing significant differences for (A) Affective ToM > PHY (B) Cognitive ToM > PHY (C) Affective ToM > Cognitive ToM at $p<0.001$, uncorrected at the cluster level in ASD group.

Table 5. Regions showing a significant effect at p<0.001, uncorrected at the cluster level for contrasts Affective ToM>Cognitive ToM, Cognitive ToM>PC and Affective ToM>Cognitive ToM in ASD group

Anatomical Name	Side	BA	MNI coordinates (mm)			*k*	*Z*
			x	*y*	*z*		
COG < AFF							
Insula	R	13	40	6	18	61	4.14
Insula	R	13	36	-14	20	162	4.02
Middle Frontal Gyrus	R		32	28	22	62	4.00
Precentral Gyrus	R	4	38	-26	56	68	3.80
COG > PHY							
Medial Frontal Gyrus	R	6	8	28	40	249	4.59
Middle Frontal Gyrus	L	6	-40	-2	50	205	4.29
Precentral Gyrus	L	6	-34	0	38		3.84
Inferior Frontal Gyrus	R	47	32	30	4	180	4.26
Inferior Frontal Gyrus	R	46	38	34	10		3.64
Claustrum	L		-24	30	8	77	4.17
Inferior Frontal Gyrus	L	46	-32	32	10		3.70
Claustrum	L		-24	20	-2		3.11
Middle Temporal Gyrus	L	39	-48	-60	4	37	3.95
Medial Frontal Gyrus	R	9	20	32	34	42	3.90
Middle Frontal Gyrus	R	9	26	38	38		3.24
Middle Frontal Gyrus	R	6	44	-2	54	91	3.78
Precentral Gyrus	R	6	36	-4	46		3.55
Inferior Parietal Lobule	R	40	46	-38	48	34	3.74
Inferior Frontal Gyrus	R	45	50	26	22	74	3.74
Precuneus	R	19	24	-76	32	39	3.56
Cingulate Gyrus	L	32	-6	20	46	102	3.56
AFF > PHY							
Inferior Frontal Gyrus	R	45	50	26	22	342	4.29
Inferior Frontal Gyrus	R	46	38	32	10		3.72
Middle Frontal Gyrus	R	46	54	30	32		3.67
Superior Temporal Gyrus	R	22	46	-20	0	32	4.13
Medial Frontal Gyrus	R	6	10	26	40	171	4.03
Cingulate Gyrus	R	32	14	18	44		3.50
Middle Frontal Gyrus	R	6	42	-2	54	444	4.00
Middle Frontal Gyrus	R	6	30	0	56		3.73
Middle Frontal Gyrus	R	6	32	-2	48		3.46
Middle Temporal Gyrus	R	37	42	-58	2	182	3.96
Sub-Gyral	R	37	46	-52	-8		3.52
Middle Temporal Gyrus	R	19	52	-64	14		3.24
Inferior Frontal Gyrus	R	9	36	6	24	70	3.89

Inferior Frontal Gyrus	L	45	-26	30	10	39	3.88
Cerebellum (Culmen)	R		8	-28	-10	137	3.81
Brainstem (Red Nucleus)	L		-4	-28	-14		3.73
Brainstem (Red Nucleus)	L		-6	-20	-2		3.58
Middle Frontal Gyrus	R	9	26	36	36	74	3.76
Anterior Cingulate	R	32	18	30	24		3.33
Middle Frontal Gyrus	L	6	-32	0	54	89	3.70
Middle Frontal Gyrus	L	6	-40	-4	50		3.65
Medial Frontal Gyrus	L	8	-6	18	50	128	3.70
Medial Frontal Gyrus	L	6	-14	4	52		3.53
Posterior Cingulate	R	30	22	-66	4	34	3.59

C) Brain regions showing a significant effect of Condition (COG, AFF) in TDC group

There was no significant effect of COG > PHY contrast in TDC group, except one left sub-gyral region at threshold of $p<0.001$, uncorrected, but when the threshold was lowered to $p<0.005$, $k>20$, the ToM related regions such as m PFC, STG were indeed activated in cognitive ToM condition. The AFF > PHY contrast showed the significantly greater activation in bilateral thalamus, precentral gyrus (BA 6), precuneus, inferior parietal lobule (BA 7,40), insula, middle and inferior frontal gyrus (BA 9) and middle temporal gyrus (BA 39). For AFF > Cog contrast, significant activations were found in bilateral thalamus, right putamen, right middle temporal gyrus (BA 39), left insula, parahippocampal gyrus. (Table 6)

Table 6. Regions showing a significant effect at p<0.001, uncorrected at the cluster level for contrasts Affective ToM > Cognitive ToM, Cognitive ToM > PHY and Affective ToM > Cognitive ToM in TDC group

			MNI coordinates (mm)				
Anatomical Name	Side	BA	*x*	*y*	*z*	*k*	*Z*
COG < AFF							
Putamen	R		30	-10	8	88	3.86
Insula	L	13	-34	-46	12	35	3.73
COG > PHY							
Sub-Gyral	L		-28	28	18	49	4.17
AFF > PHY							
Thalamus	R		22	-34	4	83	4.37
Thalamus	L		-6	-24	4	204	4.11
Precentral gyrus	R	9	38	6	36	133	4.08
Inferior frontal gyrus	R	9	44	8	30		3.70
Insula	L	13	-28	28	18	78	3.65
Precentral gyrus	L	6	-38	-10	36	41	3.86
Middle frontal gyrus	L	6	-40	-4	50	62	3.79
Precuneus	R	7	28	-46	46	55	3.74
Inferior parietal lobule	R	40	32	-46	56		3.36
Cerebellum (Declive)	R		8	-72	-26	51	3.72
Middle frontal gyrus	L	9	-44	6	38	183	3.63
Inferior frontal gyrus	L	9	-46	2	28		3.49

*COG: cognitive ToM, AFF: affective ToM, PHY: physical control

D) The relationship between autistic symptomatology and brain activation in the ASD group

Correlational analyses explored the relationship between patterns of brain activation to the contrasts exhibiting Group x Condition interactions and the severity of symptoms of the ASD group, by using correlations between signal intensity in the clusters for COG > PHY and social subscales of the ADOS. Figure 4 illustrates that signal intensity in m PFC and ACC were inversely correlated with symptoms of reciprocal social interaction as measured by ADOS social subscale (m PFC: r= -0.71, p= 0.03, ACC: r= -.66, p=0.05, Figure 4). In other words, greater m PFC and ACC activation predicted less autism symptoms in the social domains.

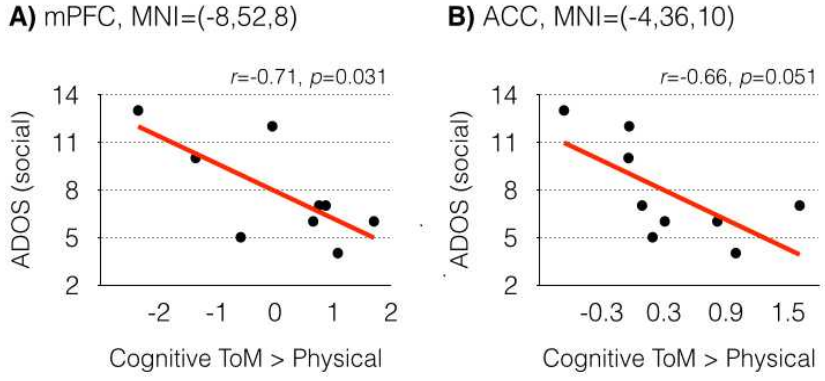

Figure 4. The relationship between autistic symptomatology and brain activation in the mPFC/ACC. Correlation scatterplots show individual participant's signal intensity values in the mPFC/ACC in COG > PHY contrast and ADOS social subscale scores. r values reflect correlation coefficients.

*Abbreviation- mPFC: medial prefrontal cortex, ACC: anterior cingulate cortex, COG: cognitive ToM, PHY: physical controlC and ACC for COG

E) The correlation between IRI subscale scores and signal intensity in each brain region

Correlation analysis between contrasts of interest and IRI subscales were conducted across the whole sample (Table 7). For the Affective ToM > PHY contrasts, there was a negative relationship between IRI empathic concern subscale score and BOLD response in mPFC and STG. For Cognitive ToM > PC, there was also a negative relationship between IRI Cognitive (perspective taking subscale) or affective ToM score and signal intensity in the m PFC.

Table 7. The correlation between IRI subscale scores and signal intensity in each brain region

	mPFC (22,34,36)		mPFC (12,48,10)		STG (48,-18,2)	
Contrast Name	*r*	*p*	*r*	*p*	*r*	*p*
IRI (Cognitive ToM)						
COG > PHY	-0.05	0.834	-0.57*	0.004	-0.30	0.157
AFF > PHY	-0.44*	0.031	-0.54*	0.006	-0.52*	0.010
IRI (Affective ToM)						
COG > PHY	-0.03	0.895	-0.42*	0.042	-0.31	0.14
AFF > PHY	-0.26	0.218	-0.36	0.087	-0.43*	0.038
IRI (Perspective taking)						
COG > PHY	-0.20	0.351	-0.60*	0.002	-0.29	0.169
AFF > PHY	-0.43*	0.036	-0.55*	0.006	-0.37	0.079

IRI (Empathic concern)						
COG > PHY	-0.18	0.404	-0.48*	0.018	-0.38	0.069
AFF > PHY	-0.51*	0.011	-0.48*	0.018	-0.48*	0.017

mPFC: medial prefrontal cortex, STG: superior temporal gyrus,
IRI: Interpersonal reactivity index, ToM: theory of mind, COG: cognitive ToM, AFF: affective ToM, PHY: physical control, * $p<0.05$, significant correlation

Discussion

To the best of my knowledge, this is the first study to examine the contrast between neural correlates of cognitive and affective ToM processes in ASD children and adolescents.

1. Group differences in brain activation between ASD and TDC group

The comparison between brain activation in the ASD and TDC groups showed a number of interesting findings. First, ToM-related regions, such as medial frontal cortex, superior temporal gyrus and cognitive control region, such as mPFC and anterior cingulate cortex showed increased activation in ASD group relative to TDC group in cognitive ToM condition and medial frontal cortex in affective ToM condition. In contrast, no brain regions showed more activation in the TDC group. This finding is consistent with the results from recent studies showing hyperactivation of ToM-related brain regions in ASD.[21,22] However, other previous studies have also reported under-activation or no differences in activation of the ToM network.[1,23,24,25] In sum, atypical mentalizing-related

brain activity in ASD group can be both over and under-activation.[26] Though the reasons for these contradictory findings from different studies are unclear, one possible explanation regarding over-versus-under-activation in ASD patients is the characteristic of the task employed in each study. For example, one task-specific factor potentially influencing the brain activation is the use of implicit versus explicit tasks.[27,28] In an implicit task, participants are not explicitly instructed to engage ToM processes, and so it may be that ASD subjects fail to engage ToM processes, and therefore underactivate ToM-related regions. However, Yoni task employed in our study is an example of explicit task and involved a few complex cognitive functions, such as processing of verbal cue, eye gaze as well as ToM ability. Therefore, this task place higher demands on attention and working memory, because both Yoni's cues and those of the other faces on the screen had to be cognitively processed at the same time.[20] Cognitive components of ToM (eg. mentalizing and cognitive control) may become more and more automated and require fewer neural resources in TDC, reflecting decreased effort when solving a task. In contrast, increases in brain activation in ASD may result from a greater effort or compensatory strategies to solve the cognitive or emotional requirement of the ToM task, hence over-activating the ToM network. Such increase in PFC activation might be an evidence of impaired ToM circuitry, indicating greater effort/compensatory mechanism in order to attain normal level of behavioral performance. In fact, data from other disorders validated the possibility that psychopathological states may be associated with hyperactivation of relevant brain regions.[20] Or ASD patients may also have

taken a more cognitive approach to the task, increasing the recruitment of cognitive control regions such as mPFC or ACC when solving ToM task.[20] Previous findings also indicated anomalous recruitment of cognitive control brain regions in social contexts in ASD.[31] Considering the lack of significant differences in accuracy scores between the two groups, this compensatory mechanism appears to be working to a satisfactory level in our task.

Another possible explanation of our finding of increased ToM–related activation in ASD is that our subject were mainly in the age range of adolescent period. In contrast to the adult samples more prevalent in previous research, studies of typically developing adolescents have revealed increased activation of mPFC compared with adult subjects. [15,29] If ToM development is substantially delayed in autism,[30] this delay may be reflected in neural response, leading to increases rather than decreases in mentalizing-related brain activity during adolescence.[31] However, this assumption is speculative, since such questions can be investigated only in a longitudinal design.

2. Neural correlates of cognitive and affective ToM in ASD patients

On the basis of previous findings regarding the subtypes of ToM (cognitive vs affective ToM), our second objective was to investigate the difference of these two concepts at the neural level in ASD patients. As hypothesized, cognitive and affective ToM tasks engaged similar areas of brain including prefrontal cortex and STS. Their activation in both ToM conditions suggests that both cognitive and affective ToM require an

ability to infer mental states.[32] However, in affective ToM condition, activation in other additional brain areas (insula, precentral gyrus in ASD group, thalamus, putamen, insula and parahippocampal gyrus in TDC group) have been observed in both ASD and TDC group. This result implies that both ASD and TDC subjects seem to engage these brain area to a greater extent when performing affective ToM tasks compared to Cognitive ToM Tasks.

The data on the recruitment of subcortical structures in ToM tasks, such as basal ganglia and insula, has been scarce in previous studies, though several neuroimaging studies have reported the activity of these structures during ToM tasks.[33-35] Specifically, ToM tasks related to identifying emotional state from observable cues recruited emotion-related brain regions, such as the amygdala, anterior insula, thalamus and inferior frontal gyrus (IFG).[36] The involvement of the subcortical structures in ToM processing coincides with its role in facilitating the interface between cortical and subcortical information.[36]

However, in contrast to the previous study that ventromedial PFC (vmPFC) may be required for affective but not cognitive ToM and the affective ToM condition activated m PFC more than did the cognitive ToM condition,[9,11] our result showed that task activations of m PFC was observed in both cognitive and affective ToM conditions. Actually, mixed evidences from fMRI studies about the role of the vmPFC in affective ToM is currently reported, suggesting that m PFC may not be affect specific, but is related to various executive function.[15]

Besides, more insula activation was observed in AFF > COG

condition, especially in ASD group in our study. The insular cortex is known as being involved in visceral-sensory processing of internal body states, including states of emotional arousal and is known to be related to dispositional differences in empathy.[37] In recent meta-analysis, common loci of dysfunction in ASDs were identified in insula region.[38] Our result suggests our ASD group depend more on explicit processes such as internal awareness of feelings and bodily sensations during affective ToM task (relative to cognitive ToM), as reflected by an increased insular activation. Our TDC group showed increased activation in insula but the extent of increased activation was less than that of ASD. This result in TDC group might imply that, during typical development, the assessment of own emotional reactions during empathizing draws less on explicit processes, such as internal awareness of feelings and bodily sensations. Instead, monitoring of self-related emotional states may become increasingly automatic and less relevant for affective ToM task in TDC.[38] In support of this notion, previous study reported a negative correlation between insula activation and self-rated empathy in TDC group.[38] Additionally, in TDC group, AFF > COG contrast showed increased activation in putamen and insula. Regarding putamen activation, prior study employing the same task as ours also found the similar pattenrs of activation in basal ganglia (BG).[35] It has been proposed that perceiving other's emotional states triggers mirroring this emotion in the recipient and that the BG are involved in this connection.[40] Alternatively, the BG might be involved in affective ToM due to their role in emotion recognition and facial expression decoding.[41] In our task, mirroring or simulating mental

states of others is thought to be associated with the affective ToM subcomponent.[42]

3. Correlational analysis between clinical or ToM scales and fMRI signal intensity

A) ADOS social subscale

The inverse relationship between autistic symptoms of social impairment and fMRI functional response for COG > PC contrasts suggests that greater activation of the mPFC/ACC regions was associated with less symptom severity in ASD patients. We examined the role of m PFC in ToM task in previous section of this article. The anterior cingulate activation is associated with effortful control of attention, cognition, and emotion in situations that involve selecting among potentially competing responses. Also, the differentiation of self-other agency (i.e. me versus not-me) is registered in different regions of the medial cingulate gyrus. We interpreted this hyperactivation of mPFC/ACC in the context of a compensatory mechanism, in line with similar reports in previous studies.[43] That is, ASD individuals with less severe symptoms were capable of engaging such compensatory mechanisms to a relatively greater degree than those with more severe symptoms.[43]

B) IRI cognitive and affective empathy subscales

We also explored the correlations between self-reported empathic abilities measured by IRI and BOLD response across ASD and TDC

groups during the task. Our results suggest that in some m PFC area, both IRI cognitive and affective empathy subscale scores correlate with BOLD response in both cognitive and affective ToM tasks. The correlation of IRI cognitive empathy subscale with BOLD response of affective ToM tasks can be explained by the possibility that affective ToM and cognitive empathy are often defined in similar ways, in terms of understanding emotions.[32]

Significant correlations between the IRI empathy subscale and contrasts of interest in cross-group were in the negative direction, and this association was mainly driven by the results from the TDC group. In other words, these brain regions responded to a greater extent for the contrasts in individuals reporting lower levels of cognitive and affective empathy. In the case of frontal control regions, such as m PFC, especially TDC participants low in empathy score may have taken a more cognitive approach to the task, increasing the contribution of cognitive control regions such as m PFC. Taken together, the direction of association was opposite between the TDC and ASD group. Those TDC individuals high in empathy score needed less brain activation but less symptomatic ASD individuals showed greater compensatory brain activation to cope with environmental demands. Stated another way, it may be that brain function in the context of similar performance was different in TDC and ASD individuals. Less severe individuals with ASD does not necessarily mimic brain function observed in TDC individuals, but rather reflects relatively greater compensatory brain activation.[43]

4. Limitation

The present study should be interpreted with caution under the following limitations. The majority of the subjects were boys and only ASD subjects with normal IQ was included to this study. Therefore, this result cannot be generalized to girls or ASD subjects with low IQ. However, ASD is more common in males, and therefore data on neural correlates on ToM in males is useful, since there is differing trajectories of structural brain development between males vs females during adolescence. Therefore, averaging results across both boys and girls might produce noisy data that cannot represent the characteristics of either sex.[15] Small sample size are also a problem. This limitation may have led to a reduced power in detecting brain activations in both group. Also, this study employed the event-related design, which also has the reduced power to detect changes in brain activation, compared to the block design. Also, several of ASD subjects were comorbid with other psychiatric disorders (ADHD, depressive disorder, anxiety disorder) and taking medication, and this can be a confounding factor, causing the differences in brain activation. Another limitation of this study is Yoni task itself. This task appears to be too simple to operationalize such a complex concept as ToM. However, the task has been validated before and shown to be positively correlated with verbal measures of ToM such as false belief stories, which suggests that Yoni task also measure similar ToM components. However, this task cannot disentangle which components of ToM processing (eg. basic processing of affective cues, emotional

contagion, more conscious affect sharing) might be driving the group differences in the reported regions of the significant activation difference. Therefore, for more complete understanding of the ToM processing, future studies should aim to disentangle these processes.

V. CONCLUSION

Despite some limitations, the current study provides useful insight to the neural correlate of ToM processing in children and adolescents with ASD. In sum, our findings may extend results from other previous studies, demonstrating the neural bases of cognitive and affective ToM in ASD patients. From a clinical perspective, our data suggests that the recruitment of additional prefrontal resources can compensate for the successful performance in the ToM task at behavioral level in children and adolescents with ASD. The results of this study can be used for establishing the rationale for strengthening the prefrontal function, such as cognitive control, in the intervention strategy for enhancing ToM abilities in ASD patients.

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<ABSTRACT(IN KOREAN)>

자폐 스펙트럼 장애 소아청소년에서의 마음이론의 정서적, 인지적 요소에 대한 신경반응

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Objective: 자폐스펙트럼장애 소아 청소년은 마음이론 능력이 손상된 특성이 있다고 알려져 있다. 최근 연구들에 따르면, 마음이론의 두 가지 측면, 즉 마음이론의 인지적, 정서적 측면이 자폐스펙트럼장애 환자에게 구별되어 손상되어 있다고 알려져 있다. 이 연구에서 우리는 정상발달 소아청소년과 비교하여 자폐스펙트럼장애 소아청소년에서 인지적, 정서적 마음이론의 신경학적 기반을 살펴 보는 것을 목표로 하였다.

Methods: 자폐스펙트럼장애 진단을 받은 12 명의 소아청소년 (남아 11 명, 평균 나이 12.4 세) 과 나이와 지능이 맞추어진 12 명의 정상발달 소아청소년 (남아 11 명, 평균 나이 11.7 세) 이 기능적 뇌 자기공명영상 연구에 참여하였다. 마음이론 과제는 언어적, 시선 자극에 바탕을 둔 만화 주인공의 인지적, 정서적 정신 상태를 알아맞히는 과제로 구성되었다. 인지적, 정서적 마음이론 과제 수행시 나타나는 자폐스펙트럼장애와 정상발달아동의 뇌 활성도 차이를 비교하였다.

Results: 인지적 마음이론 과제에서, 자폐스펙트럼장애 환아의 전두엽 (medial prefrontal cortex, anterior cingulate cortex)과 상부 측두엽 (superior temporal gyrus) 영역의 뇌활성화 정도가 정상군보다 더 큰 것으로 나타났다. 정서적 마음이론 과제에서는 자폐스펙트럼장애 환아에서 insula, middle frontal gyrus, precentral gyrus, 정상군에서는 우측 putamen, 우측 insula 에서 유의미한 활성도가 나타났다. 상관관계분석에서는 자폐 증상 중 사회성 저하와 인지적 마음이론 과제의 MRI 기능적 활성도 사이에 음의 상관관계가 나타났으며, 이런 결과는 mPFC/ACC 영역의 더 큰 활성도를 보이는 환자가 자폐 증상의 심각도가 덜한 것을 시사한다.

Conclusion: 본 연구는 자폐스펙트럼장애 소아청소년의 마음이론의 신경학적 기반을 기능적 뇌영상을 통해 연구하였다. 임상적 관점에서는, 우리 연구는 부가적인 전두엽 영역의 동원을 통해 자폐스펙트럼장애 환자가 마음이론과제를 성공적으로 수행할 수 있었음을 보여 준다. 이는 자폐스펙트럼장애 소아 청소년의 마음이론능력을 향상시키기 위해 전두엽 기능을 향상시키는 방향으로 치료프로그램이 개발되어야 함을 시사한다.

핵심되는 말 : 마음이론, 인지적 마음이론, 정서적 마음이론, 자폐스펙트럼장애, 기능적 뇌 자기공명영상