STRUCTURAL DEFICITS OF MIRROR NEURON SYSTEM IN AUTISM SPECTRUM DISORDER

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Purpose: Imitation plays an important role in human social skills. A successful social process requires the ability to perceive others' action and expressions, deciding a proper response, and form the social interactions. Mirror neuron system (MNS), which has been known for its activation during both self-action and when observing others' action, is responsible for this imitation mechanism. Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder, which features the apparent social deficits, especially the lack of social interactions with others. Previous studies reported that the ASD patients showed less activation in pars opercularis (POP), which is a part of MNS and lies in the inferior frontal gyrus (IFG), when performing the social cognitive task to observe and imitate the emotional expressions [1], presenting the functional neural deficit in MNS. The structural and anatomical studies of MNS in ASD are relatively few, only one study showed that the cortical thicknesses of MNS brain areas were thinner in ASD group [2]. To our knowledge, there is no study focusing on the tractography of MNS in ASD patients except for the reported abnormal arcuate fasciculus, which is a possible fiber tract related to MNS. [3] To further clarify the structural deficits of MNS in ASD, in the present study, we focused on bilateral POP and supramarginal gyrus (SMG), the specific brain areas included in MNS, as our regions of interest (ROI), analyzing their cortical thickness using *freesurfer* software, and the white matter fiber tracts connecting each two of the ROIs using diffusion spectrum imaging (DSI) and the template-base tract-specific analysis. [4] We hypothesized that the cortical thickness of these ROIs would be thinner in ASD group; moreover, the generalized fractional anisotropy (GFA) of the tracts may be different in the two groups, since the structural connectivity may influence the functional connectivity, and have some impact on the MNS as well as the social skills of ASD patients.

Methods: We recruited 13 adults with ASD and 13 typically developed (TD) adult control as our subjects. The two groups were both age and IQ matched (Table 1). T1-weighted images of the whole head were acquired using a 3D magnetization-prepared rapid gradient echo (MPRAGE) sequence, repetition time (TR)=2530 ms; echo time (TE)=3.4 ms; slice thickness=1.0 mm; matrix size=256×256; and field of view (FOV)=256×256 mm. DSI data were acquired by a twice-refocused balanced echo diffusion echo planar imaging (EPI) sequence, TR/TE = 9600/130 ms, image matrix size = 80 x 80, spatial resolution = 2.5 x 2.5 mm^2, and slice thickness = 2.5 mm. 102 diffusion encoding gradients with the maximum diffusion sensitivity b_{max} = 4000 s/mm^2 were sampled on the grid points in a half sphere of the 3D q-space with $|q| \leq 3.6$ units. *Freesurfer* software (http://surfer.nmr.mgh.harvard.edu/) was used to automatically segment the whole brain areas of each subject, and to calculate the cortical thickness and other cortical statistics. We used two sample t-test to determine the group result of bilateral POP and SMG cortical thickness. To get the proper ROIs for DSI fiber tracking, the average T1 image engendered from the DSI template was also segmented using *freesurfer* to decide the positions of POP and SMG in the template space (Fig. 1). Tract-specific analysis was performed using a template-based approach, which would first make a study-specific template, and four targeted tracts were reconstructed on this template using DSI studio (http://dsi-studio.labsolver.org/) (Fig. 2). These tracts were then transformed back to each subject's native DSI space and were used to sample the GFA values along each individual tract. We used two sample t test to evaluate the group differences. Finally, we checked the positions of the POPs and SMGs in each subject, and confirmed that the tracts we found in the study-specific template would definitely connect the ROIs.

Results: We found that the cortical thickness in bilateral POP was significantly thinner in ASD group compared to TD group (lPOP p=.014, rPOP p=.0003), but there was no significant difference in that of bilateral SMG between two groups. Moreover, the ASD group had significant left lateralization in POP cortical thickness when the laterality index was compared between the two groups [5]. In tract-specific analysis, we found that the GFA values of commissural fibers connecting the bilateral POP were significantly lower in ASD group compared to the TD group (p=.024), while the other three tracts showed no significant difference in the GFA values.

Discussion: The results of the cortical thickness are consistent with a previous study [2] reporting abnormal thinner cortical thickness of bilateral POP in ASD patients. According to this study, the cortical thickness of bilateral SMG was also significantly thinner in ASD group; while in our study, the SMG cortical thickness is thinner in ASD but does not reach the significance. This inconsistency may be due in part to the relatively big ROIs that are not specific enough to represent the MNS in each individual, and to a small sample size used in this study. The left lateralization of POP cortical thickness shows the abnormal leftward asymmetry in ASD patients while a previous study shows the right lateralization of IFG in normal subjects [6]. This abnormal lateralization in POP may be related to the altered hemispheric specialization for language abilities in ASD [7] and also influence their social communication abilities. The lower GFA values of commissural fiber in ASD patients may imply the aberrant white matter structure which results in the poor signal transmission between bilateral POPs, and further influences the MNS functions.

Conclusion: In the present study, abnormal thinner cortical thickness of POP and its left lateralization are found in ASD patients; moreover, the GFA values of the commissural fiber connecting them are significantly lower in the ASD group than in the TD group. These structural variances imply the structural abnormality of MNS in ASD patients. More specific relationships between these structural variances and clinical symptoms or cognitive functions need to be clarified in the future studies.

References: [1] Dapretto et al. (2005) Neuroscience. [2] Hadjikhani et al. (2006) Cereb Cortex. [3] Kana et al. (2011)Neurosci Biobehav Rev. [4] Hsu et al. (2012) Neuroimage.[5] Seghier et al. (2008) Magn Reson Imaging. [6] Luders et al. (2006) Cereb Cortex. [7] Kleinhans et al. (2008) Brain Res.

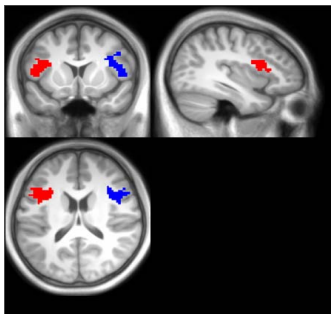

Figure1. bilateral POP in average T1 image segmented by *freesurfer*

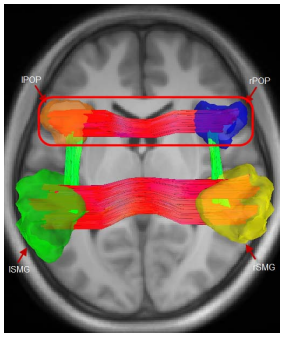

Figure2. Fiber tracts and cortical regions of MNS

	ASD (N=13) Mean±SD	TDC (N=13) Mean±SD	p value
Age (range 9-17)	21.027±3.18	20.962±4.25	.9652
Handedness	Right=13	Right=13	.
Full-scale IQ	102.692±18.74	107.308±7.34	.421
Performance IQ	99±16.98	106.385±13.87	.237
Verbal IQ	101±18.30	106.769±9.82	.33

Table1. Demographic features of the participants