ALTERED FUNCTIONAL AND STRUCTURAL CONNECTIVITIES WITHIN DEFALUT MODE NETWORK IN ADOLESCENTS WITH AUTISM SPECTRUM DISORDER

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Purpose: Default mode network (DMN) is an important brain network for processing human cognitive functions. Previous studies have consistently demonstrated functional connectivity (FC) of DMN hubs including posterior cingulate cortex (PCC) and medial prefrontal cortex (mPFC) during human resting state. The direct white matter connection, cingulum, was also found between these two regions, providing evidence for the structural connectivity (SC) within DMN [1]. Autism spectrum disorder (ASD) is a neurodevelopmental disorder mainly featured in deficient social cognitive functions. Cumulating evidence has documented the atypical FC within DMN at different age stages of this population [2]; other studies also found reduced integrity of cingulum in ASD [3, 4]. However, there are few ASD studies investigating the FC and SC within DMN simultaneously, especially in adolescents with ASD. Furthermore, previous studies reported the positive FC-SC correlation within DMN in neurotypical adults [5]; however, the FC-SC correlation patterns in normal adolescents and in adolescents with ASD are still unknown. Therefore, the purpose of the study was to compare the FC and SC between PCC and mPFC, the key regions of DMN, and the FC-SC correlation patterns between ASD and TD adolescents.

Method – imaging acquisition: We used resting-state fMRI (rs-fMRI) and diffusion spectrum imaging (DSI) to investigate the FC and SC, respectively. **Rs-fMRI** data were acquired on a 3-Tesla Siemens Tim Trio system (6-minute scan with eyes closed). Parameters: 180 echo planar imaging (EPI) volumes; TR = 2000 ms; TE = 24 ms; flip angle = 90°; field of view (FOV) = 256×256 mm^2; matrix size = 64×64; 34 axial slices acquired in an interleaved descending order; slice thickness = 3 mm; voxel size = 4×4×3 mm^3. **T1-weighted images** of the whole brain 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 sequence, TR/TE = 9600/130 ms, imaging 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 bmax = 4000 s/mm^2 were applied to sample the grid points in a half sphere of the 3D q-space with $|q| \leq 3.6$ units.

Method – data analysis: After image preprocessing, the final sample recruited 41 adolescents with ASD and 37 TD (Table1) with age, gender and FIQ matched. Rs-fMRI data were preprocessed using the DPARSF toolbox (http://rfmri.org/DPARSF) with SPM8. Motion artifact was corrected by nuisance regression against 24-autoregressive motion parameters at an individual level. The DMN FCmap with significant activation of PCC and mPFC was constructed with the seed centered in PCC (-1, -59, 31) from the previous literature [6]. To analyze the SC and FC with anatomical consistency, the bilateral PCC from Automatic Anatomical Labeling system (AAL) and the 6mm sphere centered in the peak value of mPFC (0, 60, 0) were selected as the ROIs for FC analysis. Temporal correlations of the ROIs were calculated as the FC indices. Bilateral cingulum tracts were reconstructed on a DSI standard template by an expert using cingulate cortex as ROIs defined in AAL and the individual generalized fractional anisotropy (GFA) values were sampled as SC indices. (Figure 1) We used two sample t-test to compare the FC and SC between the two groups, and Pearson product-moment correlation coefficient to compare the FC-SC correlation patterns between normal adolescents and adolescents with ASD.

Results: The GFA values of the right cingulum were significantly lower in ASD group compared to TD group (p = .003). Although not reaching significance, the ASD group showed trend-level lower values of all the other indices (left FC: p = .054; right FC: p = .069; left cingulum: p = . 073) (Figure 2). In the comparison of FC-SC correlation patterns, the ASD group showed a significantly positive FC-SC correlation on the right side (r = 0.391, p = .012), while the TD group showed a trend-level negative correlation (r = -0.249, p = .09). Comparing the two correlation coefficients with fisher's z transformation, there was a significant difference between the FC-SC correlations of the two groups on the right side (p = .0048) (Figure 3).

Discussion: At the age of adolescence, we observed moderate differences in the FC and SC within DMN between TD and ASD. During this important stage of developing social cognitive functions, our results implicate the delayed or abnormal development of DMN which causes the deficits in the social behavior of adolescents with ASD. Furthermore, the FC-SC correlation patterns are distinct and even opposite between the two groups. To our surprise, the normal adolescents showed a negative FC-SC correlation, which is different from the previous DMN studies showing positive correlation in normal adults. In contrast, ASD adolescents showed a positive correlation pattern. These findings imply different FC-SC patterns in different age stages in both TD and ASD people, which should be taken into consideration in the brain connectivity studies of ASD.

Conclusion: In the present study, we investigated the FC and SC within DMN in normal adolescents and adolescents with ASD. We found that all the indices tended to be lower in adolescents with ASD compared to TD, especially in the SC of the right cingulum. Furthermore, the FC-SC correlation patterns showed opposite directions on both sides and were significantly different on the right side between the two groups. This might imply the abnormal DMN development in individuals with ASD during their adolescence.

References : [1] Greicius et al. (2009) *Cereb Cortex.* [2] Uddin et al. (2013) Front Hum *Neurosci.* [3] Ikuta et al. (2014) *Psychiatry Res.* [4] Ameis et al. (2013) *Acta Neuropsychiatrica* [5] van den Heuvel et al. (2008) *J Neurosci.* [6] Fransson et al. (2008) *Neuroimage.*

Table 1 demographic table

	ASD (N=41)	TD (N=37)
age	14.89 (0.22)	14.85 (0.31)
gender	Male= 37	Male =28
FIQ	104.5 (2.07)	105.5 (2.02)

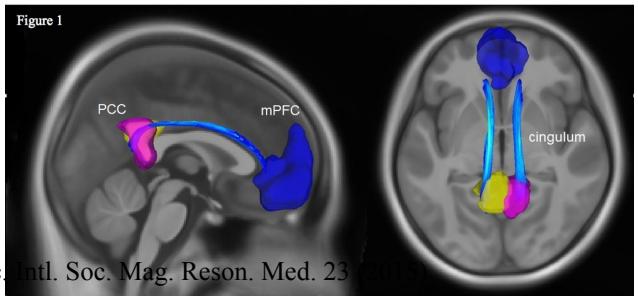

Figure 2. between-group comparison of (A) functional connectivity and (B) structural connectivity

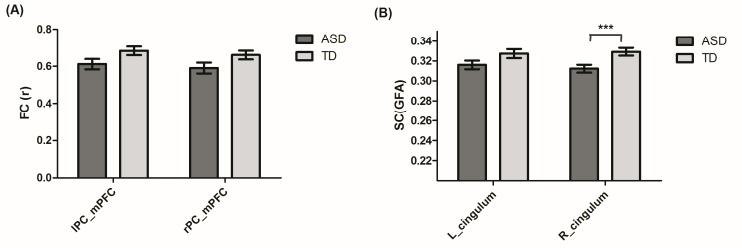

Figure 3. FC-SC correlations of (A) left and (B) right PCC-mPFC (cingulum) in ASD and TD