Alteration in medial prefrontal cortex in relation with symptom severity in autism spectrum disorder as revealed by resting state fMRI

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Introduction

We investigated the default mode network (DMN) in adolescents with autism spectrum disorders (ASD) to examine the difference from typically developing (TD) counterparts in relation with clinical assessment of social impairment. Among the DMN, we specifically examined the medial prefrontal cortex (MPFC) because accumulating evidence suggests its strong correlation with the social impairment (e.g., theory of mind) [1], which is the core symptom of individuals with ASD. The social responsiveness scale (SRS) was developed as a reliable and valid assessment tool for autistic trait in general population and its score could indicate the severity of symptoms [2]. We applied this score as the clinical behavioral index to investigate the correlation with parameters from DMN image results. The posterior cingulated cortex (PCC) is considered to be the core region in the DMN and taken as the seed region in our resting-state fMRI [3-4].

Methods

Sixteen adolescents with ASD (including high functioning autism and Asperger's syndrome whom were formally diagnosed by child psychiatrists and confirmed by the ADI-R; aged 14.2±1.91 years) and 16 TD adolescents (matched in age, gender, and handedness; aged 14.2±1.86 years) were recruited in this study. All the participants and their parents had written the informed consent. All images were acquired with a 3T MR scanner with a 32-channel phased array coil (Trio Tim, Siemens, Erlangen, Germany). A GE-EPI sequence was employed using the following parameters: TR/TE = 2000 ms/24 ms, flip angle = 90 deg, 34 slices, 3 mm thick with no gap interleaved, FOV 256 mm, matrix size 64 x 64, and 180 volumes per run with additional 2 volumes of dummy scans in advance. We discarded the first 3 volumes and used the remaining 177 volumes. We used SPM8 program (http://www.fil.ion.ucl.ac.uk/spm/) [5] and in-house MATLAB codes for analyses. Individual images were preprocessed with the slice timing, realignment and spatial normalization to the MNI space, low-pass filtered at 0.08Hz, and spatially smoothened with FWHM 6mm. We placed two seeds using the left and right PCC masks obtained from anatomy templates (WFU_PickAtlas 3.03, ANSIR Laboratory). The midline portions were removed to avoid CSF confounds (6mm for each sides). Averaged signal time courses from these 2 seed regions and their time derivatives were included in a general linear model of the first level statistics for each subject with regressors of spurious sources by the realign parameters and average intensity values from CSF and white matter regions. We computed three kinds of contrasts: left, right and bilateral PCC; the resultant contrast images showed cortical regions whose signal changes were significantly coherent with those in the left, right or bilateral PCC, respectively. The second level random-effects group statistics were performed using the 3 contrasts ($p<0.001$, uncorrected). To obtain an activation index in the MPFC, we first generated left and right MPFC masks using the results from the bilateral PCC contrast of the TD (i.e., signals that were coherent with signals from both sides of PCC) [3]. Next, we applied those MPFC masks to the 3 kinds of the DMN contrast files (i.e., spmT*.img files) to calculate the averaged voxel T value within the MPFC masks. Two-sample t-test was applied to compare these values between the two groups. We also computed the Pearson correlation coefficients between the individual SRS score and the averaged voxel T-value within the MPFC.

Results and Discussion

We obtained a DMN activation pattern including the MPFC, inferior parietal lobule and middle temporal portion in each hemisphere (Figure 1). Signals in the left DMN regions were specifically coherent with the left PCC signals, whereas the right DMN regions were specifically coherent with the right PCC signals; these patterns were quite similar between both groups. However, when we examined the signals that were coherent with those in both left and right PCC seeds, a remarkable difference was revealed in the MPFC; the TD group exhibited the MPFC activation, but the ASD group did not, which showed a consistency with a previous study [6]. The absence of activation in the MPFC in the ASD group might reflect the alteration in the self-reflective function such as "theory of mind" [7]. Two-sample t-test revealed that the averaged voxel T-values in the left, right and both MPFC were larger in the TD group than in the ASD group ($t=-3.106$, $p= .03$; $t= -2.41$, $p= .023$; $t=-3.057$, $p= .005$ respectively) (Figure 2). The finding further suggested that the MPFC was primarily associated with the alteration in ASD. Furthermore, we found negative correlations between the SRS score and the voxel T-value of left MPFC and both MPFC ($r= - .436$, $p= .029$ and $r= - .389$, $p= .005$), which indicated that the severity of autistic behaviors was negatively associated with the the level of synchronization between the MPFC and bilateral PCC (Figure 3).

Conclusion

The DMN was clearly defined in our ASD and TD groups. A similar pattern was shown in both groups when using left and right PCC seeds individually. A difference between the ASD and TD groups was found in the MPFC activation coherent with the bilateral PCC seeds, revealing a lack of the activation in the ASD group. The MPFC demonstrated better signal synchronization with the bilateral PCC in the TD group, and the SRS scores moderately negatively correlated with the synchronization index in the MPFC with the PCC. Our findings suggested that the functional connectivity index in resting state, specifically in the MPFC, might be a possible candidate marker to distinguish the autistic trait in adolescents.

References

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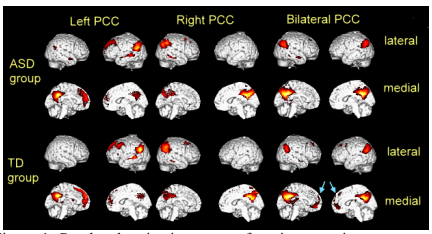

Figure 1. Rendered activation maps of resting state in two groups. left PCC, cortical regions that showed signal changes specifically coherent with left PCC. Right PCC, those with right PCC. Bilateral PCC, those with both left and right PCC. The blue arrows indicate the MPFC activated in the TD group but not in the ASD group in bilateral PCC seeds

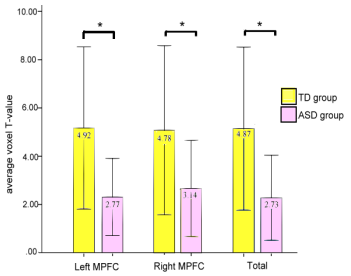

Figure 2. Synchronization index (e.g., average voxel T-value) of the MPFC with the PCC in two groups

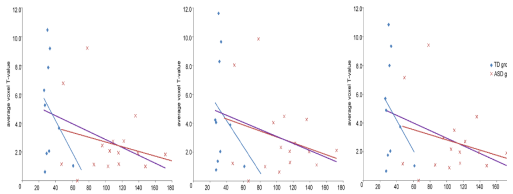

Figure 3. The symptom severity and synchronized activation of the left, right and both MPFC with bilateral PCC in two groups. The left diagram shows the relation between SRS and left MPFC activation in two groups, the purple slope indicates a negative trend between the SRS and synchronized activation index of left MPFC; the middle diagram for the right MPFC shows the similar but flatter trend which did not yield significant level; the right diagram represents the relation between SRS and both MPFC activation, suggesting the negative correlation between these two indices.