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 when we examined the signals that were coherent with those in the left and right PCC seeds obtained from anatomy templates (WFU PickAtlas 3.03, ANSIR Laboratory). The middle slices were removed to avoid CSF confounds (6mm for each side). Averaged signal time courses from these 2 seed regions and their time derivatives were included in a general linear model with 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 our 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