Default mode network abnormalities in children with autism spectrum disorder detected by resting-state functional magnetic resonance imaging

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Abstract: Purpose: The purpose of this study was to investigate changes in the functional connectivity of the default mode network (DMN) in normal aging and in children with autistic spectrum disorder (ASD) by using resting-state functional magnetic resonance imaging (rsfMRI) and independent component analysis. Methods: Thirty-one healthy controls (HC) in four age groups (1-3, 4-8, 20-29, and 50-59 years) and 14 childhood ASD cases (1-8 years of age) were examined by rsfMRI echo-planar imaging on a clinical 3-T MRI scanner. Imaging of all children (1-8 years) was conducted under sedation, while adults were scanned in the awake state with eyes closed. Results: The regions of DMN functional connectivity in the bilateral inferior parietal lobule and posterior cingulate cortex were smaller in HC children than in HC adults, and smaller in the ASD group than in the HC children. Conclusion: It is possible to observe developmental and pathological changes in the DMN by rsfMRI. Reduced DMN functional connectivity in children may be a useful biomarker for ASD diagnosis. J. Med. Invest. 63: 204-208, August, 2016

Keywords: default mode network, resting state MRI, autism spectrum disorder, inferior parietal lobule, posterior cingulate cortex

INTRODUCTION

Functional blood oxygen level dependent (BOLD) magnetic resonance imaging (MRI) studies without task-related stimulation have revealed a widespread resting-state neural network characterized by spontaneous low-frequency (0.01-0.1 Hz) BOLD fluctuations (intrinsic activity), termed the resting-state functional MRI (rsfMRI), which plays important roles in various brain functions such as default mode network (DMN), executive control, salience, dorsal attention, and auditory, visual, and sensorimotor mechanisms (1). The DMN is an attractive rsfMRI manifestation for clinical applications because it is unbiased by task performance (e.g., finger tapping), which may vary among subjects. Moreover, this technique is applicable to patients with disturbance of consciousness or disabilities. Indeed, rsfMRI measures have revealed specific regional DMN abnormalities in patients with psychiatric and/or neurological disorders such as Alzheimer’s disease, schizophrenia, and bipolar disorder and may aid in clinical diagnosis. For instance, it was reported that patients with Alzheimer disease (2) and schizophrenia (3) exhibit lower DMN functional connectivity in the posterior cingulate cortex (PCC) compared with healthy controls (HC).

Autism spectrum disorder (ASD) commonly manifests as behavioral signs and symptoms during the first 2 to 3 years of life, such as delayed speech, communication disorders, and repetitive behaviors. Clinical signs of ASD emerge even earlier, particularly brain overgrowth between 1 to 2 months and 6 to 14 months of age (4) due to accumulation of an excess number of neurons in the prefrontal cortex (5). Several recent reports have assessed brain function in ASD using rsfMRI (6-9) but none has specifically examined DMN abnormalities in children with ASD. To address this issue, it is first necessary to describe the functional changes in the DMN during normal brain development. The aims of this study were to describe differences in functional connectivity in the DMN of HC during normal aging by comparing multiple age groups (1-3, 4-8, 20-29, and 50-59 years) and then to compare functional DMN connectivity in developmentally normal children (1-8 years) and age-matched children with ASD.

MATERIALS AND METHODS

Subjects

Four age groups of HC subjects, 1-3 years (7 male, mean age 2.3±1.0), 4-8 years (7 male and 1 female, mean age 4.8±1.5 years), 20-29 years (7 male and 1 female, mean age 22.5±0.8 years), and 50-59 years (7 male and 1 female, mean age 55.9±2.8 years) as well as a group of children with ASD aged 1-8 years (15 male, 1 female, mean age 3.4±1.8 years) were examined by rsfMRI. All children with ASD were diagnosed by two experienced pediatric neurologists according to the criteria of DSM-IV-TR. All of the children were sedated with triclofos sodium (Triclyrol, 0.5 mL/kg body weight) 30 min before the measurement following the guidelines for monitoring and management of pediatric patients during and after sedation published by the American Academy of Pediatrics (10). The adult subjects were instructed to keep their eyes closed and not to fall asleep during scanning.

This study was approved by the Institutional Review Board of Tokushima University Hospital. Permission was obtained from the parents of all children, and when possible, the assent of the child.
was obtained. Informed consent was also obtained from all adult subjects after they received an explanation of the content and purpose of this study.

fMRI data acquisition

Imaging data were acquired on a 3.0-T whole-body scanner (Discovery MR 750, GE Healthcare, Waukesha, WI) with an 8-channel phased array coil. High-resolution anatomical images were acquired using a T1-weighted fast spoiled gradient recalled echo sequence. Measurement conditions were as follows: repetition time (TR)=8.7 ms, echo time (TE)=3.6 ms, flip angle=15°, field of view (FOV)=240 mm², matrix size=256x320, axial slices=86, slice thickness=1.8 mm. Resting state fMRI data were acquired using a T2*-weighted gradient-echo echo-planer imaging sequence. Measurement conditions were as follows: TR=2000 ms, TE=27 ms, flip angle=90°, FOV=240 mm², matrix size=128x128, axial slices=35, slice thickness=4.0 mm, no gap. Ninety-six functional volumes were acquired over a total imaging time of 3 min 18 s. The first 3 images of the scan were not included in the data analysis.

fMRI data analysis

Resting-state functional images were preprocessed using SPM8 (Wellcome Department of Imaging Neuroscience, London, UK). First, images were time corrected (slice timing) and subsequently realigned using rigid transformation. Next, functional and anatomical images were coregistered. Both the functional and anatomical images were normalized to the Montreal Neurological Institute space with a voxel size of 3³ mm in the T1 template of SPM8. Finally, the normalized images were spatially smoothed with an 8 mm³ FWHM Gaussian kernel.

Spatial independent component analysis (ICA) was conducted for rsfMRI data acquired from the 31 HC and 14 ASD subjects using GIFT software (http://icatb.sourceforge.net/). The number of components was determined using the minimum description length criteria, which yielded 22 components for the HC group and 26 for the ASD group. The individual subject components were converted to Z-values using the z-shift GIFT utility. For analysis, we selected DMN components including the PCC and inferior parietal lobe (IPL). Individual contrast maps of the DMN for HC and ASD groups were entered into a full factorial second-level analysis in SPM8. These maps were used to create masks for analyses using the Masking toolbox (http://www0.cs.ucl.ac.uk/staff/g.ridgway/masking/).

RESULTS

Differences in default mode network functional connectivity among the healthy control age groups

In all four HC age groups, the results of ICA revealed typical DMN activity (P<0.001 with family-wise error [FWE] and k=2 voxels) (Fig. 1A), including strong functional connectivity between the PCC and bilateral IPL (Figure 2). The regions of DMN functional connectivity in the PCC and bilateral IPL, as measured by total significant voxel cluster number, were smaller in HC children (1-3 years and 4-8 years) compared with adults aged 20-29 and 50-59 years (Table 1).

The maximum Z-scores for the PCC did not differ significantly between HC children and adults (Fig. 1B), while the score for the right (R)-IPL was significantly smaller in the 1-3 years HC group compared with the 20-29 years HC group (P=0.015) and the 50-59 years HC group (P=0.002). Similarly, the maximum Z-score for the R-IPL was significantly smaller in the 4-8 years HC group compared with the 20-29 years HC group (P=0.011) and the 50-59 years HC group (P=0.001). The maximum Z-score for the left (L)-IPL was also significantly smaller in the 4-8 years HC group compared with the 50-59 years HC group (P=0.015) (Fig. 1B).

Differences in default mode network functional connectivity between healthy control children and children with autism spectrum disorder

Comparison of the 14 ASD and 15 age-matched HC children (1-8 years) revealed typical DMN activity (P<0.05 with FWE and k=2 voxels) and structure (Fig. 3). However, regions of DMN functional connectivity in the bilateral IPL and PCC were smaller in the ASD group. Significant differences in DMN functional connectivity were observed in the bilateral angular gyrus, cuneus, calcarine gyrus, and superior occipital gyrus (P<0.001 and k=9 voxels) (Fig. 4, Table 2).

Figure 1. (A) Functional connectivity of the default mode network in the healthy control (HC) group. The statistical threshold was set at P = 0.001 with family-wise error and k=2 voxels. (B) Mean maximum Z-score in three regions of the DMN are shown: PCC (-3, -55, 28), right (R) -IPL (42, -70, 37), and left (L)-IPL (-39, -64, 43). Z-scores were compared among regions and HC age groups by Mann-Whitney U test. *P<0.05 and **=P<0.01.
Figure 2. Maps of default mode network functional connectivity for each healthy control (HC) age group. The statistical threshold was set at $P=0.001$ and $k=8$ voxels.

Table 1. Regional default mode network functional connectivity in the healthy control age groups

<table>
<thead>
<tr>
<th>Age groups</th>
<th>Region</th>
<th>MNI coordinates</th>
<th>Cluster level (voxels)</th>
<th>t-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3 years</td>
<td>L precuneus</td>
<td>-9 -58 16</td>
<td>912</td>
<td>10.13</td>
</tr>
<tr>
<td></td>
<td>R angular gyrus</td>
<td>42 -58 43</td>
<td>60</td>
<td>5.80</td>
</tr>
<tr>
<td></td>
<td>L angular gyrus</td>
<td>-51 -70 37</td>
<td>41</td>
<td>5.72</td>
</tr>
<tr>
<td>4-8 years</td>
<td>L precuneus</td>
<td>0 -55 28</td>
<td>1437</td>
<td>11.04</td>
</tr>
<tr>
<td></td>
<td>R angular gyrus</td>
<td>45 -70 37</td>
<td>6</td>
<td>5.01</td>
</tr>
<tr>
<td></td>
<td>R inferior parietal lobule</td>
<td>45 -55 46</td>
<td>7</td>
<td>4.94</td>
</tr>
<tr>
<td></td>
<td>L middle occipital gyrus</td>
<td>-30 -70 40</td>
<td>183</td>
<td>8.19</td>
</tr>
<tr>
<td>20-29</td>
<td>R precuneus</td>
<td>6 -52 28</td>
<td>1223</td>
<td>11.79</td>
</tr>
<tr>
<td></td>
<td>R angular gyrus</td>
<td>42 -64 37</td>
<td>244</td>
<td>9.27</td>
</tr>
<tr>
<td></td>
<td>L angular gyrus</td>
<td>-39 -67 43</td>
<td>270</td>
<td>7.98</td>
</tr>
<tr>
<td>50-59</td>
<td>R precuneus</td>
<td>-3 -55 28</td>
<td>1332</td>
<td>11.69</td>
</tr>
<tr>
<td></td>
<td>L angular gyrus</td>
<td>39 -73 34</td>
<td>369</td>
<td>11.75</td>
</tr>
</tbody>
</table>

The statistical threshold was set at $P=0.05$ with family-wise error and $k=3$ voxels. MNI, Montreal Neurological Institute; L, left; R, right.
DISCUSSION

We observed developmental increases in DMN functional connectivity in the PCC and bilateral IPL, as well as reduced connectivity in the PCC and bilateral IPL in children with ASD compared with age-matched developmentally normal children using spatial ICA of rsfMRI data. As rsfMRI does not rely on specific cognitive or motor tasks, it can reveal DMN changes in subjects spanning a wide range of ages and functional abilities, including patients with cognitive and motor deficits. Thus, changes in DMN may be a valuable biomarker for the diagnosis and prognosis of neurological diseases, including ASD.

In the first phase of this study, we showed that DMN structure was similar between developmental normal children (1-8 years) and adults (20-29 and 50-59 years), although the DMN functional connectivity in the PCC and bilateral IPL was weaker in children. Using ICA as in this study, Onoda et al. (2012) reported that adults 36-86 years showed decreased DMN functional connectivity during normal aging (11), and Jones et al. (2011) reported that adults 64-91 years showed decreased functional connectivity, particularly in the posterior DMN (2). Moreover, age-related weakening of DMN functional connectivity was associated with cognitive dysfunction (2, 12). Few studies have conducted similar comparisons between adults and young children, but most reported a similar trend of stronger connectivity from childhood to young adulthood.

![Figure 3](image1.png)

**Figure 3.** Default mode network functional connectivity in healthy control (HC) children and age-matched children with autism spectrum disorder (ASD). The statistical threshold was set at $P=0.05$ with family-wise error and $k=2$ voxels.

![Figure 4](image2.png)

**Figure 4.** Regions with significant differences in default mode network functional connectivity between children with autism spectrum disorder (ASD) and age-matched healthy control (HC) children (HC > ASD). The statistical threshold was set at $P=0.001$ and $k=9$ voxels.

<table>
<thead>
<tr>
<th>Region</th>
<th>MNI coordinates</th>
<th>Cluster level (voxels)</th>
<th>t-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>R cuneus</td>
<td>15 -82 31</td>
<td>19</td>
<td>5.96</td>
</tr>
<tr>
<td>R angular gyrus</td>
<td>42 -52 37</td>
<td>112</td>
<td>5.14</td>
</tr>
<tr>
<td>L calcarine gyrus</td>
<td>-9 -73 16</td>
<td>29</td>
<td>4.61</td>
</tr>
<tr>
<td>L superior occipital gyrus</td>
<td>-18 -82 40</td>
<td>17</td>
<td>4.48</td>
</tr>
<tr>
<td>L angular gyrus</td>
<td>-36 -64 34</td>
<td>15</td>
<td>4.13</td>
</tr>
</tbody>
</table>

The statistical threshold was set at $P=0.001$ and $k=9$ voxels. MNI, Montreal Neurological Institute; L, left; R, right.
Alteration of default mode network in children with autism spectrum disorder

middle age, despite using different approaches such as graph theory (13) and seed-based analysis (14).

In the second phase of this study, we showed weaker DMN functional connectivity in the PCC and bilateral IPL in children with ASD compared with age-matched controls. These results are consistent with findings in adult ASD (6, 7). Buckner et al. (2008) reported that the core regions associated with the DMN include the ventral medial prefrontal cortex, posterior cingulate/retrosplenial cortex, IPL, lateral temporal cortex, dorsal medial prefrontal cortex, lateral temporal cortex, dorsal medial prefrontal cortex, and hippocampal formation (15). DMN function has been associated with self-relevant, internally directed information processing (16) with each DMN region related to different features. The PCC was associated with episodic memory retrieval (17) and visuospatial imagery (18). Furthermore, Sestieri et al. (2011) reported an interaction of the DMN with other networks during episodic memory retrieval (19), including activation of the anterior cingulus gyrus (a subregion of the inferior parietal lobe) and PCC/precuneus. Therefore, we suggest that the change in functional connectivity between PCC and IPL is associated with specific impairments in ASD, such as social cognition and communication disorders.

Several factors are known to disrupt DMN functional connectivity as measured by rsfMRI, including both sedation and stimulation. However, not using sedation in children introduces interference from motion artifacts and sensory (visual) activation. The effects of sedation on DMN are inconsistent across studies. Stamatakis et al. (2010) reported that the anesthetic agent propofol increased connectivity with the PCC, including from areas outside the DMN (20). On the other hand, Greicius et al. (2008) reported significantly reduced functional connectivity in the PCC during conscious sedation (21). Although we cannot rule out an effect of sedation, both the ASD and HC children where sedated with the same dose, so the sedative is unlikely to have contributed to the difference in DMN connectivity observed between these two groups.

In conclusion, we demonstrated both age-dependent and ASD-associated changes in the DMN. It is critical that normal developmental changes in the DMN are fully described in order to identify abnormal neurodevelopmental changes in the DMN associated with ASD in childhood. We propose that rsfMRIs may be a useful modality for assessing DMN changes in ASD and that these changes may be helpful biomarkers for ASD diagnosis.

CONFLICT OF INTERESTS

The author has no conflicts of interest to disclose concerning the paper.

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