Atypical prefrontal cortical responses to joint/non-joint attention in children with autism spectrum disorder (ASD): A functional near-infrared spectroscopy study

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Abstract: Autism spectrum disorder (ASD) is a neuro-developmental disorder, characterized by impairments in one’s capacity for joint attention. In this study, functional near-infrared spectroscopy (fNIRS) was applied to study the differences in activation and functional connectivity in the prefrontal cortex between children with autism spectrum disorder (ASD) and typically developing (TD) children. 21 ASD and 20 TD children were recruited to perform joint and non-joint attention tasks. Compared with TD children, children with ASD showed reduced activation and atypical functional connectivity pattern in the prefrontal cortex during joint attention. The atypical development of left prefrontal cortex might play an important role in social cognition defects of children with ASD.

OCIS codes: (170.2655) Functional monitoring and imaging; (170.5380) Physiology; (170.3880) Medical and biological imaging.

References and links
1. Introduction

Functional near infrared spectroscopy (fNIRS), as a non-invasive optical method for brain imaging, measures cerebral hemodynamic parameters closely reflecting the neuronal activity through neurovascular coupling [1–3]. fNIRS has high temporal resolution and reasonable
spatial resolution. By providing a non-invasive and convenient imaging environment, it can be easily applied to study not only adolescents and adults, but also infants, toddlers, children and patients with neurological disorders.

Autism spectrum disorder (ASD) is a brain developmental disorder, characterized by impaired social interactions, communication deficits, restricted interests and repetitive and stereotyped behaviors [4]. It is marked by degeneration in joint attention as early on as 8–15 months of age [5]. Joint attention is a process whereby two individuals share the focus of attention on the same object or event as one is following the gaze or pointing gestures of the other. This is critical for the development of social, language and cognitive abilities, so the neuroimaging studies of joint attention are crucial for understanding autism spectrum disorder deeply [6,7].

fNIRS studies on typical developing (TD) infants [8,9] and adults [10] as well as functional magnetic resonance imaging (fMRI) studies on adults [11,12] have revealed that the frontal cortex is the region mainly associated with joint attention experiences, and the left and right sides of the frontal cortex interact with each other distinctly by contrasting joint/non-joint attention responses. Before this work, an earlier fNIRS study used two sources and four detectors to assess the joint attention response in a child with ASD and four TD children [13]. We supposed larger sample size and more optical channels should be used to reveal the pattern of response on the frontal cortex of children with ASD during joint and non-joint attention.

As the activity of the frontal cortex has been shown by many previous studies to be most relevant with joint attention experiences, we proposed to use fNIRS with more channels to provide more specific cortical response in terms of activation and functional connectivity (or correlation) in the prefrontal cortex. We supposed that, comparing to TD children, children with ASD would show atypical pattern of activation and functional connectivity in the prefrontal cortex to joint attention stimuli.

2. Materials and methods

2.1 Participants and experimental protocol

The participants were 21 children (mean age = 8.75 ± 1.34, median = 9, range from 6.5 to 11 years) who were diagnosed as ASD and 20 age-matched TD children (mean age = 8.09 ± 1.27, median = 8, range from 6 to 10 years). Children with ASD were diagnosed under DSM-IV-TR, which characterizes autism by delays or abnormal functioning before the age of three in one or more of the following domains: (1) social interaction; (2) communication; and (3) restricted, repetitive, and stereotyped patterns of behavior, interests, and activities [14]. Children were diagnosed by experienced clinicians in qualified hospitals according to instruments, substantial behavioral observations and parents' interviews [14]. In the current study, 21 children with ASD (included 20 children with autism and 1 child with Asperger syndrome) participated in the experiment. We further validated the diagnosis by adopting the Chinese version of the Autism Spectrum Quotient: Children's Version (AQ-Child) [15]. The mean score of AQ of children with ASD was 83.900 ± 6.688. All participants with ASD had higher scores of AQ than the cut off score (76). TD children were recruited from a local primary school. All participants were right-handed.

In order to remove the motion artifact from our study and make sure the data were qualified for analysis and interpretation, we introduced the same training procedures as our previous studies on children with ASD [16]. During the experiment, noticeable head movement and touching the optics fibers or helmet were not allowed. After training and screening, child who met the standard that the frequency of interference (such as any kind of small head movement) was less than once in a minute would be recruited to experiment. Furthermore, children were also informed not to move their heads but only to use eyes to follow the red dot in the experiment (see Fig. 1). Although fNIRS measurement is less
sensitive to head movement than MRI by fixing the optical sources and detectors tightly (but still comfortably) on the scalp by helmet, the data from children who moved their heads obviously during the experiment would be excluded from the analysis. Before the experiment, we randomly sampled 24 children with ASD. After training, 3 children with ASD did not meet the standard of experiment and 1 child with ASD still moved his head to follow the red dot during the experiment. All 20 TD children meet the standard. Thus, data from 20 children with ASD and 20 TD children were analyzed.

After the optic fibers and the helmet were placed on the prefrontal head, each measurement channel was adjusted to record data properly. Each participant was seated beside a child size desk (length: 80cm, wide: 50cm, height: 56cm). Upon the desk was a 70-cm-wide display for presenting the task. The distance between the nasion of each child and the display was fixed at 70cm. This distance between the display and the eyes of the child would ensure the child could see the screen clearly and no need to move his/her head to follow the dot. During the experiment, children were asked to watch 8 video clips successively for a total of 8 minutes. Children with and without ASD were all instructed to use their eyes to follow the red dot. Based on the paradigm used in the earlier fMRI study [11], the video clips were made to arouse joint/non-joint attention. Details about how to create and display video clips could be seen in [11]. Each video clip consisted of 30s baseline (black screen) followed by 30s task including 10 joint/non-joint attention stimuli (Fig. 1). The 8 video clips were composed of 4 joint and 4 non-joint attention stimuli respectively. Unlike previous studies, we improved the experiment by adopting a presentation order of A-B-B-A-B-A-B-A-B (A: 30s black screen followed by 30s joint stimuli, B: 30s black screen followed by 30s non-joint stimuli) to counterbalance the order of joint and non-joint conditions. The experiment protocol was approved by the Institutional Review Board of Guangzhou Rehabilitation and Research Center for Children with ASD where the study was carried out.

![Screen captures of video clips in the experiment: (a) Joint attention (see Media 1) and (b) non-joint attention (see Media 2).](image)

2.2 fNIRS measurements

Measurements were performed with a fNIRS system (FOIRE-3000, Shimadzu Corporation, Kyoto, Japan) working at three wavelengths, 780 nm, 805 nm and 830 nm, with a sampling rate of 14.286 Hz (time resolution = 70ms). The absorptions of near infrared light were then transformed into concentration changes of oxy hemoglobin (HbO), deoxy hemoglobin (Hb) and total hemoglobin (HbT) by the modified Beer-Lambert law [17]. The distance between the emitter and detector was fixed at 3 cm. The measured area and the optical channel locations are shown in Fig. 2. We located Channel 7 at FPZ and Channel 16 at AFZ according to the 10-10 system [18]. The fNIRS data were recorded in sync with the beginning of the experiment. During the collection of the data, the operator should watch the real-time recording as well as the subjects’ events and add marks manually to the data if any motion or disturbance occurred.
Fig. 2. The positions of the 22 optical channels over the prefrontal cortex. We located Channel 7 at FPZ and Channel 16 at AFZ according to the 10-10 system [18]. Regions of interest (ROIs): Channels 1, 5, 6, 10, 14, 15, 19 were defined as the left prefrontal cortex; Channels 4, 8, 9, 13, 17, 18, 22 were defined as the right prefrontal cortex.

2.3 Data analysis

Only HbO data was included in the analysis. Before analyzing the activation and functional connectivity, we preprocessed the raw data in several steps. Firstly, we checked all the raw data and removed the blocks containing motions or disturbance from further analysis. In total, about 10% of the blocks from children with ASD and 5% from TD children were removed. Secondly, we specified the initial time as the baseline of the data. Thirdly, we chose hemodynamic response function (HRF) (with time and dispersion derivatives) as the basic functions to model the hemodynamic response. Under this model, we specified the vector of onset and duration for each experiment condition (joint and non-joint attention). In our design, we define the onset of joint attention at 30s, 210s, 330s, and 390s, the onset of non-joint attention at 90s, 150s, 270s, and 450s. The duration of the task was 30s (see the black line in Fig. 3). Then, the wavelet-minimum description length (MDL) detrending algorithm was applied to decompose fNIRS measurements into global trends (participant's movement, blood pressure variation, and instrumental instability), hemodynamic signals and uncorrelated noise components as distinct scales. Detrending by wavelet-MDL, the average HbO time series were estimated by convolving each HRF with the relevant experimental paradigms, which could improve the signal-to-noise ratio, and provides more specific activation signals than a conventional method such as simple filtering (for comparison, see Fig. 3) [19]. Fourthly, in order to correct temporal autocorrelation in fNIRS data, the precoloring method [20] was adopted to attenuate high frequency components and smooth the data. This procedure was realized by the NIRS-SPM toolbox in Matlab [21].
Fig. 3. Comparison between different preprocess methods on the hemodynamic changes of Channel 14 of a TD child. The red line is HbO, the blue line is Hb and the green line is HbT. The black line shows the overall stimulated of joint attention and ideal estimate of increase of HbO. (a) Raw time course data of the channel. (b) Preprocessed with 0.0016-0.3Hz band pass filter, the same filter as the previous study [10]. (c) Preprocessed with the wavelet-MDL detrending algorithm and hemodynamic response function filter. The wavelet-MDL provides more specific activation signals than simple filtering.

For average activation analysis, the maps and the time course wave forms were generated. Firstly, the brain activation data obtained from fNIRS are relative values, and thus we cannot average or compare fNIRS data directly across different participants or channels before transforming to z-scores. We transformed the preprocessed time series data of each participant into z-scores defined as: each raw score minus the mean of each channel of each participant and then divided with the standard deviation of each channel of each participant. The transformed data of each participant were separated into 8 segments (8 blocks). Each segment included 30 s of resting state and 30 s of stimuli response. We used the data during the 30 second stimuli to analyze the effects of joint and non-joint stimuli on the prefrontal cortex of the brain. Each preprocessed data segment of each channel was calculated by using one point baseline adjustment (minus the value at the start point of the stimuli). For HbO maps, the 30s data were averaged for each channel at each condition. Then, we averaged all the participants of children with ASD or TD children to obtain the averaged channel values (z-scores) in each group under joint/non-joint conditions. The average values were mapped onto the channel geometry, and the blank area between the adjacent channels was filled via interpolation. For time course wave forms, we used z-scores to average all the block epochs for each channel at each time point under joint/non-joint task to obtain a ground averaged time course wave form of each channel. Then, we averaged all the wave forms from channels within ROIs. The time course wave forms were obtained from computing the mean and standard deviation for all the participants in ASD/TD group. To quantitatively compare the
differences between children with ASD and TD children, we performed a General Linear Model (GLM) to test the effects of task (within group factor: joint vs. non-joint attention), ROIs (within factor: the left prefrontal cortex and the right prefrontal cortex), and group (between factor: ASD vs. TD) on the changes of HbO. Bonferroni method was used for correction the possible problem of multiple comparisons.

Functional connectivity of the brain is defined as the synchronization of neural activity. In the present study, we analyzed the synchronization of the bilateral prefrontal cortex during joint/non-joint attention to reveal the different role of the left and right prefrontal cortex on joint attention. Firstly, we used the preprocessed time series data in joint/non-joint conditions (30s for each block and 4 blocks for each condition) and calculated the time course Pearson correlation coefficient $r$ between all symmetrical channels within ROIs (for examples, Channels 19 and 22, Channels 14 and 18 in Fig. 2). To estimate the left-right connectivity between the prefrontal cortices during joint or non-joint attention, all the $r$ values between all symmetrical channel pairs were averaged. To compare the differences between children with ASD and TD children, we used a GLM to test the effects of task (within group factor: joint vs. non-joint attention) and group (between factor: ASD vs. TD) on the left-right connectivity between bilateral prefrontal cortex. For the functional connectivity maps, we chose one or two channels within ROIs as the seeds and calculated the Pearson correlation coefficient $r$ between the time course of the seed channel and all the other channels during stimuli (joint or non-joint). The averaged $r$ value for each channel was mapped onto the channel geometry with interpolation to fill the blank area. The average correlation values of the ASD/TD group during different experiment condition were estimated by converting $r$ values to $z$ values with Fisher’s $r–z$ transformation for each participant, and then converting back from averaged $z$ values to the averaged $r$ values. The Matlab2013a was used for generating activation and connectivity maps.

3. Results

3.1 Activation analysis

The mean HbO maps as well as the time course of wave forms of different children under joint and non-joint conditions were shown in Fig. 4 and Fig. 5, respectively. From Fig. 4(a), no obvious activation could be seen in the prefrontal cortex in children with ASD during joint attention. Comparing the joint and non-joint attention, there was no obvious distinction between the activation patterns in the prefrontal cortex for children with ASD. However, for TD children, there was significantly more activation in the bilateral prefrontal cortex during joint attention than non-joint attention. From Fig. 4(b), we could find that both the left and the right frontal cortices were activated during joint attention in TD children. According to the activation area (with red color), we defined Channel 1, 5, 6, 10,14,15,19 as the left prefrontal cortex and Channel 4, 8, 9, 13, 17, 18, 22 as right prefrontal cortex (as boxed with the red line in Fig. 2).
Figure 4. Comparisons of HbO activation (z-scores) during joint (left column) and non-joint (right column) attention, of ASD children (upper row) and TD children (bottom row). Black numbers on the maps represent the measured channels with the same distribution as in Fig. 2.

Figure 5 showed the averaged time course wave forms (HbO) of ASD/TD children during joint/non-joint attention in the bilateral prefrontal cortex. From Fig. 5(a), no obvious activation but a decrease of HbO in the first 10 s could be seen in the prefrontal cortex in children with ASD during joint attention. In the right prefrontal cortex of children with ASD, there was an increased response to non-joint attention during the time window of 13s to 20s compared with joint attention. In the left prefrontal cortex of children with ASD, there was no obvious distinction between joint and non-joint attentions. However, for TD children, Fig. 5(b) showed steady increased responses after 8 seconds to the joint attention in the bilateral prefrontal cortex. There were also short decreased responses from the star point to the non-joint attention in the bilateral prefrontal cortex. After 15 seconds, the left prefrontal cortex of TD children showed more increased HbO to joint attention and more decreased HbO to non-joint attention.
Fig. 5. The time course of mean HbO change of two groups to joint/non-joint stimuli in the bilateral prefrontal cortex. Error bars are standard error of mean across participants. The temporal profiles of changes of HbO in the left prefrontal cortex (blue lines) and the right prefrontal cortex (red lines) to joint (dark lines) and non-joint (light lines) attention.

Table 1. Mean and standard deviation of the changes of HbO (z-scores) across all participants during different tasks in different ROIs.

<table>
<thead>
<tr>
<th>ROI</th>
<th>Task</th>
<th>ASD</th>
<th>TD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left prefrontal cortex</td>
<td>Joint attention</td>
<td>−0.323 ± 2.979</td>
<td>2.041 ± 2.025</td>
</tr>
<tr>
<td></td>
<td>Non-joint attention</td>
<td>−0.596 ± 2.871</td>
<td>−1.543 ± 3.010</td>
</tr>
<tr>
<td>Right prefrontal cortex</td>
<td>Joint attention</td>
<td>0.025 ± 2.475</td>
<td>1.829 ± 2.625</td>
</tr>
<tr>
<td></td>
<td>Non-joint attention</td>
<td>0.285 ± 2.710</td>
<td>−0.620 ± 3.744</td>
</tr>
</tbody>
</table>

We calculated the sum of the values of channels within each ROI for statistical analysis. Table 1 contains the average values (z-scores) for HbO in the left and right prefrontal cortex across all children in each group. Results of GLM showed that the interaction effect of task and group ($F = 9.024$, $P = 0.005$, $\eta_p^2 = 0.192$) as well as the main effect of the task ($F = 9.105$, $P = 0.005$, $\eta_p^2 = 0.193$) was significant. Further post hoc analysis showed that during joint attention, children with ASD exhibited significantly reduced strength of activation than TD children in prefrontal cortex ($P = 0.008$), while the comparison between two groups under non-joint attention was not significant ($P = 0.316$). Other interaction and main effects did not reach the statistical significance ($P_{min} = 0.070$).

3.2 Connectivity analysis

Since Channel 14 in the left prefrontal cortex and Channel 8 in the right prefrontal cortex obtained the most salient activation in Fig. 5, we chose Channel 14 and Channel 8 as the seeds to generate the correlation maps for the functional connectivity, as shown in Fig. 6. For TD children, the left prefrontal cortex showed reduced symmetry in correlation maps during joint attention than non-joint attention, while the right prefrontal cortex did not show such a
distinction during joint and non-joint attentions. Children with ASD seemed to show almost the same interhemispheric correlation within the ROIs during joint attention than non-joint attention. Moreover, in the right prefrontal cortex, both TD children and children with ASD did not show obvious distinction between joint and non-joint attentions. Children with ASD showed a weaker synchronization between the right prefrontal seed and other channels than TD children.

![Fig. 6](image)

The functional connectivity maps during joint (left column) and non-joint (right column) attention, for ASD children (a) and TD children (b). In each group, the upper row showed the correlation maps when the seeds were located in the left prefrontal cortex (Channel 14); The bottom rows showed maps when the seeds were located in the right hemisphere (Channel 8). Black numbers on the maps represent the measured channels with the same distribution as in Fig. 2. The seed channels were colored with yellow.

Table 2 contained the average values of interhemispheric correlation within the ROIs in each group. Results of GLM analysis showed that the interaction effect of task and group was marginally significant ($F = 3.794, P = 0.059, \eta_p^2 = 0.091$). The main effect of task was significant ($F = 6.788, P = 0.013, \eta_p^2 = 0.152$). Further post hoc analysis (t-test with Bonferroni correction for multiple comparison) showed that the prefrontal cortex of TD children exhibited significantly lower interhemispheric correlation during joint attention than non-joint attention ($P = 0.003$), while the interhemispheric correlation of the prefrontal cortex of children with ASD did not show significant difference between joint and non-joint attention ($P = 0.645$). The main effect of group did not reach the statistical significance ($F = 0.092, P = 0.763, \eta_p^2 = 0.002$).
Table 2. Mean and standard deviation of the interhemispheric correlation across all participants during different tasks within the ROIs.

<table>
<thead>
<tr>
<th>Task</th>
<th>ASD</th>
<th>TD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joint attention</td>
<td>0.535 ± 0.318</td>
<td>0.458 ± 0.299</td>
</tr>
<tr>
<td>Non-joint attention</td>
<td>0.553 ± 0.221</td>
<td>0.586 ± 0.318</td>
</tr>
</tbody>
</table>

4. Discussion

In the past twenty years, fNIRS has been rapidly developed to be an effective and easy-to-operate tool to monitor human brain function and has been widely applied in various fields, especially for studies on children with ASD [22, 23]. In the present study, we employed fNIRS to detect the prefrontal response to joint and non-joint attention stimuli in terms of activation and functional connectivity and compared the differences between ASD and TD children. We hypothesized that, compared with TD children, children with ASD would show atypical pattern of activation and functional connectivity in the prefrontal cortex under joint attention condition.

Considering the group differences, the analysis of activation showed that during joint attention, children with ASD exhibited significantly reduced strength of activation than TD children in prefrontal cortex, while the comparison between the two groups under non-joint attention was not significant. The analysis of functional connectivity showed that the prefrontal cortex of TD children exhibited a much more obvious lateralization to the left hemisphere during joint attention than non-joint attention, manifesting as reduced interhemispheric correlation in term of strength. Furthermore, when the seed was located in the left prefrontal cortex, TD children showed reduced symmetry in correlation maps during joint attention. However, children with ASD did not show any similar pattern. Children with ASD did not show altered interhemispheric correlation in joint attention compared with non-joint attention. Thus, TD children' prefrontal network were influenced by the gaze direction whereas the children with ASD's were not. Some previous study on adults with ASD supported the underconnectivity of prefrontal cortex of ASD during task [24, 25]. An electroencephalographic study on adults with ASD in resting state showed increased local coherence in frontal regions in the theta (3-6Hz) frequency range [26]. A fNIRS study in task-free state showed children with ASD had a significantly increased inter-hemispheric connectivity with 0.02-Hz fluctuation [27]. The present study did not show the strength of interhemispheric connectivities were different between children with and without ASD. However, results showed the social information could influence the cortical organization of the prefrontal cortex of TD children, but not for children with ASD.

To further discuss the meaning of our findings, we should analyze the basic cognition process underlying the joint/non-joint attention task in our experiment. We assumed that there were two major cognitive aspects involved: maintaining the attention to the red dot in the video clips and utilizing the social information (gaze direction). We inferred that the altered frontal-cortical activation and functional connectivity in children with ASD were induced by the abnormalities in both maintaining attention and social cognition. According to a previous behavioral study, children with ASD showed the lack of sustaining attention on imposed stimuli, which could be caused by delay of development or lack of motivation but not a primary impairments [28]. In an fMRI study, even though participant with ASD showed in general the same cortical area of the brain with a similar strength in an executive function task, they showed reduced neural synchronization between different areas of the brain [24]. There are evidences shown that children with ASD failed to use the information of eyes to infer mental state of a person [29]. According to our observation, children with ASD did follow the red dot, while TD children might spontaneously look at the actress’s face in the videos to see whether the actress was also looking at the red dot. TD children might feel more interested in the task when the actress shared common attention with them and consequently...
the HbO response obviously increased during joint attention. Also, TD children might feel more disappointed when the actress did not follow the red dot with them and the HbO decreased during non-joint attention. Children with ASD might avoid the actress’ face and thus would not be affected by the actress. Considering the failure of utilizing the information of eyes, there was evidence showed that children with ASD response larger skin conductance (SCR) than TD children to faces with direct and averted gaze [30]. The accuracy of face recognition was negatively correlated with the amplitude of SCRs to direct gaze but not to averted gaze among children with ASD, meaning that eye contacts would cause more arousal for children with ASD and they would avoid the eye contacts to reduce the arousal [30]. Thus, in order to further reveal the cognitive mechanism of atypical response of frontal area during joint attention of ASD, eye-tracking records should be add to the experiment to detect the intention distribution and social information utilization of children with ASD.

Some of the theoretical models as well as studies in typical adults proving the prefrontal cortex was not only a domain-general region of the brain function for working memory, scheduling and inhibition [31, 32], but the left prefrontal cortex also served as a domain-specific area for memory and language [33]. A study on typical adults showed that both left and right prefrontal cortex was involved in joint attention [10]. However, there were growing evidences supporting the importance of the left prefrontal cortex and lateralization of prefrontal cortex in neurodevelopment for social cognition. For example, previous fNIRS studies showed that the left dorsal prefrontal cortex of five-month-old infants could response to eye contacts and triadic social interactions [8, 9]. A fMRI study has revealed that the ventromedial frontal cortex, the left superior frontal gyrus (BA10), cingulate cortex, and caudate nuclei of typical adults was activated during joint attention [11]. Although a fNIRS study support the role of right prefrontal cortex in self-face cognition [34]. In line with some previous studies, our results showed the importance of prefrontal cortex in joint attention experience of TD children, and revealed the atypical activation and connectivity pattern of the left prefrontal cortex during joint attention of children with ASD. Moreover, our study confirmed the critical role of left prefrontal cortex in atypical development of social cognition of children with ASD.

5. Conclusion

In summary, by using fNIRS to investigate the cortical response of ASD and TD children in the prefrontal cortex to joint and non-joint attention stimuli, we have observed that, in contrast to TD children, children with ASD showed reduced activation and atypical functional connectivity pattern in the bilateral prefrontal cortex during joint attention. These results imply that the atypical prefrontal cortical activation and connectivity pattern may be related to the impairment of joint attention in autism spectrum disorder. The atypical development of the left prefrontal cortex played an important role in social cognition defects of children with ASD.

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