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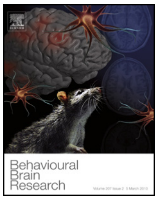

Research report

Functional connectivity in the brain in joint attention skills using near infrared spectroscopy and imaging

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HIGHLIGHTS

- A model was implemented to diffuse optical imaging measurements in response to joint-attention tasks.
- It can detect the strength of autoregressive process and directional propagation.
- No significant difference observed between non-joint attention and rest condition.
- The significant differences in brain connectivity observed between others.

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ABSTRACT

In this study, the changes in activation in terms of Oxy-Hemoglobin (HbO) and Deoxy-Hemoglobin (HbR) were detected in response to join attention based tasks in normal adults using near infrared spectroscopy and imaging. With these detections, functional connectivity between the left and right sides of frontal region of the brain was measured and modeled by a lagged covariance structural equation modeling (SEM). Statistical analysis was performed to assess the difference in the path coefficients amongst different stimuli (joint attention, non-joint attention, and baseline rest). The results demonstrate that the left and right sides of the frontal region of the brain interacted with each other distinctly in response to the joint and non-joint attention based stimuli.

1. Introduction

Brain-behavior studies of joint attention are critical in understanding autism because the early social communication disturbance of autism is exemplified by a chronic developmental failure in this domain [1,2]. Joint attention is the process of sharing one's experience of observing an object or event, by following gaze or pointing gestures, which can be regarded as an outcome of two interacting attention-regulation systems across the anterior and posterior attention systems [3]. The anterior attention system involves a neural network consisting of the parietal and superior cortices, which percept the eye and head orientation of the others and the spatial relations between self, other and the environment. Alternatively, the posterior attention system is supported by the front eye fields, the pre-frontal associated cortex, the orbital frontal cortex and the anterior cingulate, which control volitional, goal-directed attention allocation.

A functional magnetic resonance imaging (*f*MRI) study of joint attention experience [4] demonstrated that the activations identified by contrast of the joint versus non-joint attention were found in the right ventral medial frontal cortex and the left anterior frontal cortex, and other areas such as the cingulate cortex, bilateral caudate nuclei, and right anterior frontal lobe. In particular, the differences amongst these stimuli (i.e. joint, non-joint and baseline rest) were distinctly observed in the frontal cortical brain regions. The similar results were obtained from near infrared spectroscopy and imaging study of brain activation of joint attention experience in normal adults [5]. Near infrared spectroscopy study of gaze following in five-month-old infants demonstrated that the joint attention with another person resulted in the activation localized not only in the left and right frontal cortex but also in the right posterior parietal cortex and left ventral frontal cortex [6]. In addition, right posterior parietal activation and left ventral frontal activation has been reported in other studies of adults [7,8]. However, the static images of brain activation during the joint attention task do not provide enough information for understanding how brain areas interact with each other. Being able to measuring functional connectivity in the brain will allow us to understand the organized

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behavior of cortical regions beyond the simple mapping of their activity.

Functional connectivity is defined as the temporal correlation among spatially remote neurophysiologic events. The widely used method in measuring functional connectivity is based on computing covariance/correlations between spatial units [9]. However, the correlations between different locations may not be able to provide casual directional information on the interaction between distinct regions. This is because the correlation analysis only reveals the degree with which two time courses co-vary with each other. Fortunately, this information can be preserved in the lagged covariance/correlations such that the activity in one area can predict delayed activity with the same or opposite sign in another area. Therefore, the timeline of neural events is taken into consideration.

To integrate the covariance/correlations among cortical areas in humans by using hemodynamic and metabolic measurements, structural equation modeling (SEM) is generally introduced [10–12]. The parameters in the SEM models identify connectivity strengths in the neural network model. Some of applications of this method in healthy subjects include the auditory system [13], the working memory network [14,15], attention [16] and the visual systems [11,17,18]. This method has also been applied to pathological cases such as the motor system of Parkinsonian patients [19] and the memory network of human brains with and without bilateral hippocampal damages [20].

In this study, we applied the lagged covariance SEM for estimating functional connectivity among frontal brain areas in healthy adult subjects under different stimuli, such as joint attention, non-joint attention and rest conditions, with the data obtained from near infrared spectroscopy and imaging. The application of this method to joint attention skills should give new insights into a better understanding of the functional impact of the autistic patients at its earliest stage on the frontal cortical brain network.

2. Materials and methods

2.1. Instrumentation

A frequency-domain based optical imaging system, Imagent (ISS Inc., Champaign, IL) was used to obtain the measurements as an input for studying functional connectivity. The Imagent has laser diodes and four photomultiplier tube (PMT) detectors. Laser diodes are divided into 16 lasers at 690 nm and 16 lasers at 830 nm. The light sources are electronically multiplexed at a frequency of 100 Hz (10 ms on-time per laser diode) to time-share the four detectors. Both laser diodes and PMTs are modulated at 110 MHz since this frequency is optimal towards improved depth penetration of the optical signals [21]. In addition, four laser diodes and four PMTs are used for our study wherein these are coupled to a custom-built optical cap via optical fibers (details provided in the following subsection). The entire instrument is computer controlled and the frequency-domain measurements (I_{AC} and θ) are obtained from different source-detector locations using a Fast-Fourier-Transform data acquisition card.

2.2. Experimental design and task

Totally, 11 normal, right-handed subjects were enrolled in this study. The Florida International University IRB approved this study and all subjects gave written consent. Imaging studies were performed in the frontal cortical regions, which were chosen based on systemic analysis of the regions of the brain where joint-attention related stimulus distinctly generated an activation signal. Moreover, optical signals are better recovered from the frontal cortical surfaces over deeper locations such as the cingulated cortex or the bilateral caudate nuclei. The frontal region of the brain were imaged by placing two paired laser diodes (each containing two different wavelengths) at the middle electrode points (Fpz, AFz), and the four PMTs at the left electrode points (Fp1, AF3), and right electrode points (Fp2, AF4) (total imaging area of $3 \times 7\,\mathrm{cm}^2$) of the 10–20 electrode placement system, respectively, via the customized built optical cap. Each source was placed at the center of two detectors, in order to understand the connectivity patterns between the right and left cortical regions symmetrically. The video clips developed by other researchers [4] were used to engender an experience of joint attention, non-joint attention and rest. During data acquisition, the subjects were instructed to watch a video clip with minimal or no head movement. In the case of joint attention, the subject follows a red dot on the video clip in congruent with the person on the video clip; whereas during the non-joint attention the subject follows the red dot although not in congruent with the person on the video clip. Under the rest condition, the subject just watched a blank screen. A block experimental design was chosen in stimulating the subjects with the following sequence: joint-attention clip (J), followed by a non-joint attention clip (NJ), and followed by a baseline rest (R). The sequence of tasks (J-NJ-R, 30 s each task) was repeated five times during an experiment and the entire experiment was repeated 3 times for each subject.

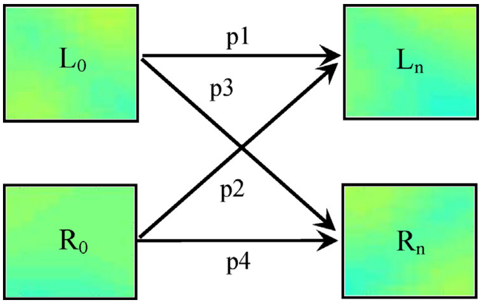

Fig. 1. Schematic representation of the path model. The regions of interest Left (*L*) and Right (*R*) are taken at two different lags (0 and *n*). The path coefficients p_1 and p_4 represent the autoregressive process, predicting activation in a ROI (left/right) from previous activation within the same ROI (left/right), and the path coefficients p_2 and p_3 represent the directional propagation of activation from right side to left side or vice versa.

2.3. Data extraction

Optical measurements were obtained in real-time in response to the different stimulus for the entire experimental period, for each subject. In the current studies, the average of the modulated light signal (i.e. DC signal) was employed in post-processing two-dimensional (2-D) hemodynamic responses using HomER (Hemodynamic Evoked Response), a graphical interface program developed by Photon Migration Imaging (PMI) lab (MGH, Harvard, http://www.nmr.mgh.harvard.edu/PMI). Using this program, band pass filters were chosen appropriately (between 0.0016 and 0.3 Hz) in order to eliminate slow drifts and cardiac pulsation [22]. Regions of time showing significant motion were rejected from the analysis. The filtered data was further processed automatically and finally averaged, or deconvolved with the stimulus, to obtain a hemodynamic response function (HRF) of HbO and HbR. The embedded back-projection technique allowed for the reconstruction of activation maps for each subject, stimulation condition and latency.

2.4. Lagged covariance structural equation model

To analysis the correlation between the earlier activity and later activity in different areas, one can use all the voxels in the entire frontal region as a region of interest (ROI). However, this approach would be computationally intense and redundant. For simplicity, we chose left and right sides of frontal region of the brain as the ROIs. Therefore, the two-way interactions are considered in the lagged covariance SEM method for studying functional connectivity of frontal region of the brain. The schematic representation of the path model is illustrated in Fig. 1, showing the interaction of ROIs at two time lags at a time.

Totally, 12 different models were generated, each including two time periods simultaneously, that is a lag of zero and one of the other lags $n = (1, \ldots, 12)$ so that each model was based on a 2.5-s time delay (for a 30-s stimulus), where all models include lag zero due to the relative latency of the processes of interest in each side unknown, using custom scripts in MatLab, rather than with HomER. Therefore, we obtained twelve 4×4 matrices and each of them is partitioned into the four 2×2 matrices:

$$\sum_{n} = \begin{bmatrix} \sum_{ij}(0) & \\ \sum_{ij}(n) & \sum_{ij}(0) \end{bmatrix}$$

where $i = 1, 2$; $j = 1, 2$; and $n = 0, \ldots, 12$. Here $\sum_{ij}(0)$ represent the zero-lag cross correlation matrices, and $\sum_{ij}(n)$ are the matrices of cross correlation at lag n. Assuming that we only consider the state of the system at two points in time $t = 0$ and n, we have 4 observed variables: L_0, R_0, L_n an R_n (*L* is left and *R* is right). An appropriate mathematical formulation for such path model can be constructed as follows:

$$L_0 = d_1$$

$$R_0 = d_2$$

$$L_n = p_1 L_0 + p_2 R_0 + d_3$$

$$R_n = p_3 L_0 + p_4 R_0 + d_4$$