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Band-specific atypical functional connectivity pattern in childhood autism spectrum disorder

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HIGHLIGHTS

- Graph theory was used with the phase lag index of a brain network in childhood ASD.
- ASD children frequency-specifically showed atypical functional network patterns.
- Results support the atypical neural network theory of ASD during childhood.

ABSTRACT

Objective: Altered brain connectivity has been theorized as a key neural underpinning of autism spectrum disorder (ASD), but recent investigations have revealed conflicting patterns of connectivity, particularly hyper-connectivity and hypo-connectivity across age groups. The application of graph theory to neuroimaging data has become an effective approach for characterizing topographical patterns of large-scale functional networks. We used a graph approach to investigate alteration of functional networks in childhood ASD.
Method: Magnetoencephalographic signals were quantified using graph-theoretic metrics with a phase lag index (PLI) for specific bands in 24 children with autism spectrum disorder and 24 typically developing controls.
Results: No significant group difference of PLI was found. Regarding topological organization, enhanced and reduced small-worldness, representing the efficiency of information processing, were observed respectively in ASD children, particularly in the gamma band and delta band.
Conclusions: Analyses revealed frequency-dependent atypical neural network topologies in ASD children.
Significance: Our findings underscore the recently proposed atypical neural network theory of ASD during childhood. Graph theory with PLI applied to magnetoencephalographic signals might be a useful approach for characterizing the frequency-specific neurophysiological bases of ASD.

1. Introduction

Autism spectrum disorder (ASD), a polygenetic neurodevelopmental disorder that is strongly influenced by genetic factors (Rutter, 2000; Geschwind, 2011), is characterized by impairment of social communication skills and by repetitive and stereotypic behaviors. Increasing evidence has supported the notion that altered neural connectivity is a key neural underpinning of the brain of ASD individuals (Belmonte et al., 2004; Courchesne and Pierce, 2005; Geschwind, 2011; Wass, 2011; Vissers et al., 2012). However, extensive theoretical and empirical studies have revealed conflicting patterns of brain connectivity, characterized by hypo-connectivity and hyper-connectivity (Picci et al., 2016).

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Recently, specific development-related variations of functional connectivity patterns of ASD have been suggested: a shift from hyper-connectivity to hypo-connectivity during prepuberty (Rudie Jeffrey and Dapretto, 2013; Supekar et al., 2013; Uddin et al., 2013). Indeed, the first decade of life is a time of remarkable transformation of neural network architecture (Innocenti and Price, 2005; Dean et al., 2015; Huang et al., 2015; Schuldiner and Yaron, 2015; Vértes and Bullmore, 2015). The potential contributions of measuring functional connectivity to elucidate atypical development and its clinical relevance have been suggested (Vértes and Bullmore, 2015). Despite the importance of studying a prepuberty population that includes younger children to investigate how atypical connectivity patterns arise in ASD, far fewer studies have addressed this issue (Di Martino et al., 2011; Ghanbari et al., 2013; Keown et al., 2013; Supekar et al., 2013; Bos et al., 2015) than have examined ASD in adulthood.

Phase synchronization of neural oscillations across the brain over multiple frequencies is described as a basis for normally functioning neural networks (Varela et al., 2001; Buzsaki and Draguhn, 2004; Fries, 2005). To assess phase synchronization, magnetoencephalography (MEG) can measure the brain magnetic fields of the cortex directly with excellent temporal resolution, thereby yielding insight into temporal dynamics within physiologically relevant frequency ranges (Wang, 2010). For that reason, it is well suited to measuring whole-brain functional connectivity (de Pasquale et al., 2010; Hipp et al., 2012). When exploring the temporal dynamics of the whole-brain network, graph theoretical approaches offer valuable tools for the characterization of the topological organization of large-scale functional networks (Bullmore and Sporns, 2009; Rubinov and Sporns, 2010). A graph can be made as an illustration of a set of objects (nodes) in which some objects are linked by connections (edges) (Bullmore and Sporns, 2009). Graph theory, which enables viewers to grasp functional segregation and integration in the network architecture, has been associated increasingly with EEG and MEG studies over the last decade (Garcia-Prieto et al., 2017). A key feature of the developing brain is the so-called small-world network (Fair et al., 2007; Power et al., 2010; Boersma et al., 2011; Smit et al., 2012; Bathelt et al., 2013). Small-world architecture is defined as an optimal balance between functional local segregation (high local clustering) and global integration (shorter path length) in the network (Watts and Strogatz, 1998; Sporns and Zwi, 2004). That architecture facilitates efficient spreading of information, with low connection costs (Latora and Marchiori, 2001). Consequently, it contributes to optimal information processing (Langer et al., 2013). Therefore, graph-theoretical explorations of brain network topology have been applied increasingly to the developing brain and its relevance to ASD (Crossley et al., 2014).

This study was undertaken to characterize the functional network properties of childhood ASD in light of functional connectivity and its topological pattern. For that purpose, we derived a MEG device that has been customized for use with young children. We recruited ASD children and typically developing (TD) children of around six years of age. The functional network property, which was characterized using graph theoretic metrics, was investigated in a frequency-band-specific manner during free watching of videos.

2. Methods

2.1. Participants

This study examines 24 children diagnosed with ASD (mean age 71.6 months, age range 57–80, five female) and 24 TD sex-matched, age-matched, and intelligence-matched children (mean age 72.4 months, age range 59–87, seven female) (Table 1). All participants had been patients of the Kanazawa University Hospital and prefectural hospitals in Toyama. Inclusion criteria for the ASD children were diagnosed using the Diagnostic Interview for Social and Communication Disorders (DISCO) (Wing et al., 2002) and/or the Autism Diagnostic Observation Schedule (ADOS) (Lord et al., 1999) at the time of MEG recording. To determine the intellectual ability of the TD group for this study, children with mental processing composite (MPC) scores lower than 60 based on the Kaufman Assessment Battery for Children (K-ABC) (Kaufman and Kaufman, 1983) were excluded. All children with ASD were diagnosed as high-functioning. With full knowledge of the experimental characteristics of the research, all parents agreed to their child's participation in the study. All parents provided informed consent before the experiment began. All study protocols followed guidelines of the Declaration of Helsinki. The Ethics Committee of Kanazawa University Hospital and Toyama University Hospital approved this study.

2.2. Assessment of cognitive function

A trained assistant psychologist (Y.Y.) applied the Japanese version of the K-ABC to assess the children's cognitive function. The K-ABC, an intelligence and achievement test for children between the ages of 2.5–12.5 years, comprises 16 subsets. The K-ABC is divided into two scales: the MPC and the achievement scale. The MPC measures the global child cognitive ability, which is regarded as equivalent to an intelligence quotient. Each index is standardized to a mean of 100 and a standard deviation of 15. The mean MPC score of children with ASD was 100.4 (60–134; SD, 17.8). That of TD was 102.6 (71–125; SD, 13.8). The means did not differ between groups (Table 1).

2.3. MEG recordings

We used a multichannel superconducting quantum interference device (SQUID) 151-channel whole-head coaxial gradiometer MEG customized for children (PQ 1151R; KIT/Yokogawa Electric Corp., Kanazawa, Japan). Before recording, the head position within the helmet was set by measuring the magnetic fields after passing current through coils attached at three locations on the head surface, which served as fiduciary marks for the bilateral mastoid processes and nasion. Magnetic fields were recorded while lying supine comfortably on a bed in a magnetically shielded room (Daido Steel Co. Ltd., Nagoya, Japan). The method of stereographic projection of the MEG sensors onto a planar image is depicted in Fig. 1. After the MEG data were acquired with a sampling rate of 1000 Hz, they were filtered with a 200 Hz low-pass filter. To promote concentration and a consistent state of alertness, all children viewed a video

Table 1
Physical and cognitive characteristics of children.

	ASD children (n = 24)	TD children (n = 24)	P value
Female/male	5/19	7/17	0.51
Age (mo)	71.6 (57–80, 6.0)	72.4 (59–87, 9.6)	0.73
Head circumference (cm)	51.1 (48.0–53.8, 1.47)	51.4 (47.4–54.5, 1.60)	0.59
Mental processing composite score	100.4 (60–134, 17.8)	102.6 (71–125, 13.8)	0.63
ADOS score			
Communication score	2.79 (0–5, 1.4)	NA	
Social interaction score	7 (2–14, 2.9)	NA	
Total score	9.79 (2–16, 3.8)	NA	

Values represent mean (range, SD). Abbreviation: ADOS, autism diagnostic observational schedule.