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Original article

Multi-frequency localization of aberrant brain activity in autism spectrum disorder

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Abstract

Objective: The abnormality of intrinsic brain activity in autism spectrum disorders (ASDs) is still inconclusive. Contradictory results have been found pointing towards hyper-activity or hypo-activity in various brain regions. The present research aims to investigate the spatial and spectral signatures of aberrant brain activity in an unprecedented frequency range of 1–2884 Hz at source levels in ASD using newly developed methods.

Materials and methods: Seven ASD subjects and age- and gender-matched controls were studied using a high-sampling rate magnetoencephalography (MEG) system. Brain activity in delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta (12–30 Hz), low gamma (30–55 Hz), high gamma (65–90 Hz), ripples (90–200 Hz), high-frequency oscillations (HFOs, 200–1000 Hz), and very high-frequency oscillations (VHFOs, 1000–2884 Hz) was volumetrically localized and measured using wavelet and beamforming.

Results: In comparison to controls, ASD subjects had significantly higher odds of alpha activity (8–12 Hz) in the sensorimotor cortex (mu rhythm), and generally high-frequency activity (90–2884 Hz) in the frontal cortex. The source power of HFOs (200–1000 Hz) in the frontal cortex in ASD was significantly elevated as compared with controls.

Conclusion: The results suggest that ASD has significantly altered intrinsic brain activity in both low- and high-frequency ranges. Increased intrinsic high-frequency activity in the frontal cortex may play a key role in ASD.

Keywords: Autism spectrum disorders (ASDs); High-frequency oscillations; Intrinsic brain activity; Mu rhythm; Magnetoencephalography (MEG); Magnetic source imaging

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1. Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder that affects approximately 14.7 per 1000 children at 8 years of age [1]. The onset of this socially debilitating disease is in early childhood, but symptoms persist throughout the lifespan. There is increased evidence that individuals with ASD have aberrant brain activity at resting state as well as during task performance [2,3]. A recent report suggests that children with autism tend to withdraw from social interaction because their brains have elevated activity and connectivity at resting state [4].

The abnormality of brain activity at resting state (or intrinsic brain activity) in ASD is still inconclusive [5–7]. Electroencephalogram (EEG) studies have shown that, at resting state, children with ASD have increased delta activity (1–4 Hz), decreased alpha activity (8–12 Hz) [8], and increased theta activity (4–8 Hz) [9]. Magnetoencephalography (MEG) studies have shown that children with ASD have increased delta (1–4 Hz) and alpha activities (8–12 Hz) [2]. Functional magnetic resonance imaging (fMRI) studies have shown that subjects with ASD have altered intrinsic brain activity in the ventral medial prefrontal cortex/ventral anterior cingulate cortex [10]. Importantly, the increase in intrinsic brain activity is associated with greater core symptom severity, in terms of higher scores on the Social Responsiveness Scale [2]. However, contradictory results have been found pointing towards increased [2] or decreased [8] alpha activity in the occipital area.

The discovery of high-frequency brain activity opens a new window for the study of functional brain abnormalities [11,12]. These findings are especially important in ASD because high-frequency brain activity plays a key role in signal transmission in cortical microcircuits [13], which have been shown to be atypical in ASD [14]. In addition, since high-frequency brain signals can pinpoint epileptogenic zones, and there is a high degree of comorbidity between ASD and epilepsy [15], high-frequency brain signals may also advance our understanding of ASD.

The objective of the present study was to investigate intrinsic brain activity from low- to very high-frequency ranges (1–2884 Hz) in ASD using wavelet and beamforming [16]. We hypothesized that, at resting state, children with ASD would exhibit increased low- and high-frequency brain activities in the frontal and sensorimotor cortices. This hypothesis is based on the observation that the brain generate signals up to 2884 Hz [17] and previous reports children with ASD have aberrant activity and abnormal development in the sensorimotor/frontal cortices [18–20], which has been associated with sensory and motor symptoms. A previous study [2] revealed little about temporal resolution with analysis of up to 120 Hz [2]. Therefore, the present study is the first report to reveal very high frequency brain activities above 120 Hz in ASD children. These findings may significantly contribute to future ASD research.

2. Materials and methods

2.1. Participants

Participants included seven subjects with ASD (average age: 12.7 ± 2.3 years, age range: 10–16 years; 6 boys and 1 girl) and seven age- and gender-matched children with typical development as controls (average age: 12.7 ± 2.3 years, age range: 10–16 years; 6 boys and 1 girl). Six out of the seven ASD subjects were right handed; one of the seven ASD subjects was left handed. The handedness of the controls was matched with the ASD subjects. The inclusion criteria were (1) a clinical diagnosis of ASD; (2) acceptable level of cooperation; and (3) no other neurological disorder or brain injury. Per parent report, all subjects and families ere native English speakers and had no know genetic syndromes or sensor (hearing, visual) impairments. The inclusion criteria for controls were: (1) healthy without history of neurological disorder or brain injury; and (2) normal hearing, vision, and hand movement. The exclusion criteria for all participants were: (1) having metallic implants; and (2) unidentifiable magnetic noise.

Participants with ASD, who were compliant and demonstrated an ability to follow the directions needed to participate in the study, were recruited from the Kelly O'Leary Center for Autism Spectrum Disorders at the Cincinnati Children's Hospital Medical Center (CCHMC). All children screened for inclusion in the ASD sample had received an ASD diagnosis prior to their involvement in the current research. This prior diagnosis was made by a developmental pediatrician following a comprehensive multidisciplinary team assessment (including the Autism Diagnostic Observation Schedule, ADOS [21], and other neuropsychological assessments). Healthy controls were recruited through local advertisements. The study was formally approved by the CCHMC Institutional Review Board and all participants' families gave written informed consent.

2.2. MEG recording

Data were collected using a 275-channel whole-cortex MEG system (VSM MedTech Inc., Coquitlam, BC). Children were scanned in a supine position and were instructed to lie still, try not to fall asleep, and keep their eyes gently closed during a 2-min resting state recording. The built-in audio–video monitor system in the MEG room allowed investigators to observe the participant. To prepare the children for what would happen during the procedure, a story entitled "A Visit to the MEG" was written. Before data acquisition commenced, small