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Research report

Interhemispheric alpha-band hypoconnectivity in children with autism spectrum disorder

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ABSTRACT

- Diverse genetic and environmental etiologies converge onto circuit level brain dysfunction in autism spectrum disorder (ASD), manifesting at a macroscopic level as aberrant neural connectivity. Previous studies have described atypical patterns of decreased short range and increased long range connectivity in ASD [1]. However, it remains unclear whether group level features of circuit dysfunction are consistently present across the range of cognitive function seen in the autism spectrum.
- The dynamics of neural oscillations in the alpha range (6–12 Hz) are exquisitely sensitive to healthy development of functional and structural connectivity. Alpha-band coherence, measured with high temporal-precision electroencephalography (EEG) therefore represents an ideal tool for studying neural connectivity in developmental populations.
- Here we examined spontaneous alpha phase coherence in a heterogeneous sample of 59 children with ASD and 39 age matched typically developing children. Using a data driven approach, we conducted an unbiased examination of all possible atypical connectivity patterns across all cortical regions.
- Long-range hypoconnectivity was present in children with ASD compared to typically developing children, with temporal interhemispheric connectivity showing the largest difference between the two groups.
- Decreased long range alpha coherence distinguishes a heterogeneous group of ASD children from typically developing children. Interhemispheric temporal hypoconnectivity represents a fundamental functional difference in children with ASD across a wide cognitive and age range that may reflect white matter disturbances or increased signal variability at temporal sites in ASD.

1. Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental condition characterized by core features of social communication impairment, repetitive behaviors and restricted interests. Like many neurodevelopmental disorders, ASD is rooted in aberrant neural connectivity, coined by Geschwind and Levitt as a "developmental disconnection syndrome" [2]. Neuroimaging studies of high risk infants demonstrate early disruptions in the development of both structural and functional connectivity precede the emergence of core symptoms in ASD [3–6].

Various functional and structural imaging methods have been used to quantify spontaneous, or baseline, neural connectivity in ASD and to compare these patterns to those of typically developing individuals. Across studies, a pattern of short range hyperconnectivity and long range hypoconnectivity has emerged [1,7,8]. However, two major gaps exist in this body of research. First, most studies have focused on the individuals with cognitive abilities in the typical range [9], thus excluding the large portion of the ASD population with co-occurring cognitive impairment [10–13]. Secondly, studies often focus on pre-specified, putative networks of interest, such as brain regions involved in language function or social cognition [14,15]. Such a targeted approach may preclude the discovery of unexpected differences in meaningful circuits.

EEG represents a unique and powerful tool that can capture brain dynamics in three important dimensions: space, time and frequency [16]. The complex and multidimensional aspects of brain function that

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EEG captures may reflect changes in many underlying neurobiological processes, from molecular and cellular changes to large scale structural development. Sensitivity to small alterations in any of these dimensions facilitates the detection of neurophysiological patterns associated with both typical and atypical development. EEG also represents a relatively tolerable and scalable research tool to quantify functional connectivity in diverse populations [17].

Of the oscillatory activity underlying large-scale functional networks, coherence in the alpha band (6–12 Hz) is exquisitely sensitive to the healthy development of [18,19], and disruptions to [20], functional and structural connectivity. Alpha oscillations are the dominant signal in the resting brain and therefore yield a high signal to noise ratio in stimulus independent environments [21,22].

Here, we used an electroencephalography (EEG) measures of alpha band phase coherence to quantify functional connectivity in children with ASD across a wide range of cognitive abilities. Employing permutation testing and strict false discovery rate (FDR) control, we studied alpha band coherence between all possible combinations of electrode pairs. This statistical approach obviates the need for a priori assumptions regarding connectivity patterns and allows for an unbiased interrogation of functional interactions in the alpha band across all brain regions.

Coherence is an estimate of the consistency between two neural signals within a particular frequency band, and it depends on both phase consistency and amplitude covariations [23]. Amplitude can be influenced by non-neural anatomical factors, such as skull thickness [24], or by structural brain differences including cortical gyral patterns [25]. These factors can, in turn, bias coherence estimates [25,26]. Therefore, we measured the phase synchrony of signals, which provides a measure of synchronization in the EEG that is independent of signal amplitude [23,27].

We hypothesized that (1) children with ASD would exhibit different patterns of alpha band coherence compared to typically developing (TD) children, particularly in long range networks; and, based on previously reported correlations between alpha band oscillations and cognitive function in ASD [28], we also hypothesized that (2) the network connections that differentiate ASD from TD would relate to cognitive ability, with disruptions in functional connectivity related to cognitive impairment within ASD.

2. Method

2.1. Participants

Sixty-one children with ASD were recruited from the community through the UCLA Center for Autism Research and Treatment (CART). Datasets from participants were pooled across two major studies in order to maximize sample size and reflect a clinically representative range of cognitive function across the autism spectrum. All children entered the study with a prior clinical diagnosis of ASD, made through the California State Regional Center, independent clinical psychologists, child psychiatrists, and/or developmental pediatricians. UCLA psychologists confirmed diagnoses based on DSM-IV or DSM-5 criteria. Exclusionary criteria for children with ASD included active epilepsy, birth-related complications, and uncorrected vision or hearing impairment. Secondary diagnoses were present in seven ASD participants, which included attention-deficit/hyperactivity disorder (ADHD; N = 5), obsessive compulsive disorder (OCD; N = 1), and depression (N = 1). At the time of the study, five participants with ASD were taking psychoactive medication, which included: selective serotonin reuptake inhibitors (SSRI) (N = 2); stimulants (N = 1); partial dopamine antagonist (N = 2); and central alpha agonists (N = 2). Analyses were repeated after removing participants taking medication at the time of the study, with no significant difference in primary measures of interest. Therefore, the results presented here include those taking medication.

Forty typically developing (TD) age- and sex-matched participants were recruited from the community. Exclusionary criteria for TD participants included any neurological abnormalities, birth-related complications, developmental delays, need for special services in school, diagnosis of psychiatric conditions, uncorrected vision or hearing impairment, or a first degree relative with an ASD diagnosis. No TD children were taking psychoactive medications at the time of the study.

The study received ethical approval from the UCLA institutional review board (IRB numbers: 14-001259; 11–000355). Parents provided informed written consent, in accordance with the declaration of Helsinki. Verbal assent was obtained from participants who had sufficient cognitive and language capabilities to understand and agree to the study procedures. Testing was suspended if non-verbal participants became agitated or distressed (e.g. crying, vocal protest). If, following a break, the participant was still distressed, then testing was discontinued.

Two participants with ASD and one TD participant were excluded from further analyses due to excessive artifact throughout the EEG recording (c.f. [28,29]. The final groups included 59 children with ASD and 39 TD children. Verbal and non-verbal IQ (as assessed with standardized tests, described below) were significantly lower in the ASD group, as would be expected when representing the full spectrum of cognitive ability in ASD. See Table 1 for demographic variables. Data from these participants have also been reported in a previous study conducted by our research group (Table 2) [28].

2.2. Behavioral assessments

Cognitive and language assessments were tailored to the ability and age of the child, and ratio IQ was used to facilitate comparison across assessments. Assessments included the Mullen Scales of Early Learning (MSEL; [30], the Differential Abilities Scale-Second Edition (DAS-II; [31]), and the Wechsler Preschool and Primary Scale of Intelligence-Third Edition (WPPSI-III; [32]). From these measures, ratio IQ scores for non-verbal IQ (NVIQ) and verbal IQ (VIQ) were calculated for each child and were used to account for the scores of children who performed outside of the standardized norms for their chronological age. For children who were tested with the WPPSI-III or DAS-II, NVIQ and VIQ were calculated from the protocol-specific subscores. For children who were administered the MSEL, VIQ was calculated using the average of the Receptive Language and Expressive Language subscale scores, and NVIQ was calculated using the average of the Visual Reception and Fine Motor subscale scores [33]. Studies have demonstrated the convergent validity of the WPPSI-III with other cognitive assessments such as the MSEL and the DAS-II, supporting the combination of assessments through standard scores [34–36].

Autism symptoms were assessed in the ASD group using multiple measures due to participants being pooled across two studies conducted by CART in order to represent all levels of cognitive function present in the autism spectrum. Modules one and two of the Autism Diagnostic Observation Schedule (ADOS; [37]) were used to assess communication

Table 1
Demographic variables of participants.

	ASD	TD	Group Comparison
Measure	M(*SD*), range or number (%)	M(*SD*), range or number (%)	Student's *t or X2* *P* value
Age (months)	69.44(24.12), 25–126	71.56(26.58), 29–146	0.68
Sex (N females)	13 (22)	13 (33.3)	0.16
VIQ	68.96(34.35), 12–160	121.12(19.42), 82–168	< 0.001
NVIQ	74.67(33.82), 10–145	112.55(12.07), 88–156	< 0.001