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EEG Coherence Patterns in Autism: An Updated Review

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Abstract

Recent electrophysiological studies suggest that autism spectrum disorder is characterized by aberrant anatomical and functional neural circuitry. During normal brain development, pruning and synaptogenesis facilitate ongoing changes in both short- and long-range neural wiring. In developmental disorders such as autism, this process may be perturbed leading to abnormal neural connectivity. Careful analysis of electrophysiological connectivity patterns using EEG coherence may provide a way to probe the resulting differences in neurological function between people with and without autism. There is general consensus that EEG coherence patterns differ between individuals with and without autism spectrum disorders, however the exact nature of the differences and their clinical significance remain unclear. Here we review recent literature comparing EEG coherence patterns between patients with autism spectrum disorders or at high risk for autism and their non-autistic or low risk for autism peers.

I. Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by clinically recognized deficits in social communication and repetitive and restricted behaviors and interests [1]. While the behavioral symptoms of ASD are fairly well defined, researchers have yet to determine the underlying neural contributors of the disorder. Recent electrophysiological studies pinpoint aberrant functional neural circuitry as a key underlying feature in this disorder [2]. Pruning, synaptogenesis, and myelination are key processes that facilitate ongoing changes in neural wiring during typical brain development [3]. Theoretically, disruptions in one or more of these processes leads to an array of atypical neural networks that then manifest as a very recognizable and stereotypic behavioral phenotype [3–5].

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There is evidence that synaptic dysfunction in ASD occurs both at the local level of single axons and at the global level of neural networks [6,7]. Careful analysis of electrophysiological patterns across the brain using electroencephalogram (EEG) coherence is one way to noninvasively evaluate this synaptic dysfunction. EEG coherence characterizes the consistency and magnitude of a relationship between simultaneously recorded and spatially separated oscillatory nodes. When two signals in the same frequency are active with a consistent phase relationship over time, they are considered coherent and we assume there is a high degree of coordinated activity between the underlying brain regions producing those two signals [2,8,9]. It is assumed that the two signals do not originate from the same generator when their phases are coupled but not identical [10]. EEG coherence is currently one of the only proxies for network organization in the brain. Its principal limitation is that the connectivity of deep brain structures must be inferred given the surface location and timing of activity measured at the scalp [8]. Nonetheless, while somewhat lacking in spatial resolution, EEG coherence is excellent at providing temporally precise information on global network processing.

Given the strengths of EEG coherence, its quantification in diverse samples of ASD provides a promising path towards discovering a proximal biomarker that potentially could reflect differences in behavioral function, not only between people with and without the disorder, but also between subtypes of the disorder with different underlying etiologies. Over the past ten years, there have been several studies using EEG to compare coherence patterns between individuals with ASD and non-autistic, age-matched peers, as well as between infants at high and low risk for developing ASD. While these studies generally agree that coherence patterns are different in those with, or at risk for, ASD, there remains considerable debate about the details and their significance.

Here, we critically reviewed recent research on EEG coherence in ASD, focusing on studies that could be considered moderately powered, with sample sizes of at least twenty subjects. To constrain the number of compiled studies, we limited our review to task-based studies from the past five years and resting-state and sleep-based studies from the past ten years. The scope of the review was functional coherence as defined by linear and nonlinear methods of spectral coherence (most commonly computed through magnitude-squared coherence (MSC), which considers both magnitude of the spectral power and phase relationship as a frequency-domain correlation between signals) and phase lag coherence (which only considers the correlation of the two signals' phases and does not consider the magnitude). We did not address past literature that investigated effective connectivity (e.g., entropy, graph theory, or granger causality) [6]. Because chronological maturation has significant effects on EEG morphology and coherence in typical development, we segmented research based on the developmental stage of their subject cohorts [11–14]. In addition, this review followed the convention of organizing neural connectivity into separate frequency bands: delta (0.3-4 Hz), theta (4-7 Hz), alpha (8-12 Hz), beta (13-25 Hz), and gamma (25-60 Hz). Prior research has provided partial evidence for associations between these various frequency bands and corresponding cognitive tasks [15–18]. Organizing coherence based on frequency band allowed for us to make occasional inferences about the effectiveness of signal transmission during these cognitive processes. Finally, we attempted to simplify the disparities in what different research groups call "long-" and "short-" range

connections by considering the location and distance of the channel electrodes used in the computation of coherence. To draw parallels between studies, we used the following guidelines: 1) long-range connections referred to frontal to posterior parietal or occipital channel pairs and left temporal to right temporal channel pairs, 2) short-range connections referred to adjacent channel pairs in a 10-20 system, and 3) medium-range connections referred to any other channel pair connection. Overall, this review sought to highlight the degree to which findings of perturbed long- and short-range, intra- and inter-hemispheric connections in ASD vary based on chronological age, behavioral phenotype, and setting of EEG recording. Furthermore, we aimed to direct future research by pinpointing distinct methodological discrepancies in data quality, in paradigm design, and in focus of analysis that significantly limit the conclusions researchers can make at this time about aberrant neural functioning in ASD, despite the abundance of studies on the topic.

II. Early Development: Infants at Risk, Toddlers, and Preschoolers

II. a. Infants: Eliciting Functional Patterns of Coherence

The primary objective of studying EEG coherence in infants who are considered at high risk for developing ASD is to identify early ASD-specific biomarkers, electrophysiologic endophenotypes, and developmental trajectories of neural integration and coordination during the most critical stage of postnatal brain development [19,20]. Infants are most often considered at high risk for ASD when they have an older sibling diagnosed with ASD, as the prevalence of receiving an ASD diagnosis when a sibling carries the diagnosis rises from approximately 1% in the general population to around 19% [21]. Because EEG is a noninvasive technology, is somewhat tolerant to motion, and does not require an active response from the participant whose brain is being measured, it is an ideal tool to be used on infants for the evaluation of very young subjects.

The largest study reviewed in this early developmental stage included 46 at low-risk (low-risk controls, or LRC) and 49 high-risk (high-risk for ASD, or HRA) infant subjects [17]. The study's primary focus was on left-right hemispheric lateralization of event-rated gamma-band MSC coherence between intra-hemispheric frontal-posterior pairs during a face processing task [17]. The authors chose to look at gamma activity because it is thought to represent neural integration between local, specialized networks and therefore may be pertinent to the neural integration of facial features during face processing [17]. In addition, based on prior research, the authors suspected that the neurotypical response to viewing faces would be to recruit from the right hemisphere more so than the left [17,22]. The study showed that at 12 months, HRA infants had significantly increased left-lateralized intra-hemispheric coherence when viewing faces compared to LRC infants [17]. Furthermore, through a retrospective analysis of a subsample of 36 infants who were clinically assessed for ASD at 18, 24, and 36 months, the study revealed that HRA infants later diagnosed with ASD (HRA+) had displayed the greatest leftward lateralization at 12 months of age, while HRA infants who were not later diagnosed with ASD (HRA−) had exhibited an intermediate level of lateralization between their HRA+ counterparts and LRC infants [17]. From these results, the authors hypothesized that aberrant, left-lateralized gamma coherence patterns during facial processing at a very early age may precede the atypical behavioral

manifestations of facial processing and encoding that are more apparent by 18-36 months when children are diagnosed with ASD [17,23].

In a smaller set of infants, this same research group had previously conducted a similar study in which they investigated intra-hemispheric event-related gamma-band linear coherence, but this time between anterior and posterior scalp regions while subjects heard speech sounds [24]. During this speech-listening task, HRA infants had significantly lower MSC coherence at 12 months than LRC infants [24]. Similar to their later study, retrospective analysis revealed tiered levels of coherence at 12 months of age, with HRA− infants showing an intermediate degree of linear coherence between the LRC and HRA+ infants [17,24]. Together, these studies provide evidence for the early presence of disrupted patterns of neural integration in response to social stimuli, whether it visually or aurally presented, in those with a familial or genetic risk for ASD.

The only other moderately sized study investigating patterns of EEG coherence in infant siblings from the past five years came from the British Autism Study of Infant Siblings (BASIS) [25]. In this study, EEG activity was recorded from 26 LRC and 28 HRA infants as they watched social and non-social movies [25]. This time, alpha activity was selected *a priori* due to its association with active and attention-driven preparedness for cognitive and top-down processes [25,26]. The authors found that HRA infants later diagnosed with ASD had significantly increased bilateral frontal-central alpha phase-lagged coherence [25]. In addition, the degree of alpha coherence during this task positively correlated with later measurements of repetitive and restricted behaviors and interests in the HRA+ children, as measured by the Autism Diagnostic Interview, Revised [25,27]. This research highlights the potential to detect connectivity-related biomarkers of ASD in infancy before behavioral manifestations of ASD are clearly apparent.

II. b. i. Toddlers and Preschoolers: Eliciting Functional Patterns of Coherence

In addition to studies investigating infants, two other studies published over the past five years have focused on young children shortly after their initial diagnosis of ASD in task-based settings. One was a large study of 103 two-to five-year old children who had ASD or were typically developing (TD) [28]. The authors used an alternative form of MSC referred to as the ‘Imaginary Part of Coherency’ to calculate synchronized activity at a given time lag as children viewed emotional faces [28,29]. The authors found that during the viewing, those with ASD had particularly high concentrations of connections with increased coherence over the posterior scalp region in the delta and theta frequencies, as well as increased delta, theta, and alpha coherence intrahemispherically in the left hemisphere when compared to controls [28]. The study also found statistically significant differences in frontal-parietal connections, mostly representing decreased coherence in children with ASD [28]. While the previously described study by Keehn and colleagues solely investigated gamma-band coherence while infants viewed faces, the analysis of coherence here was of all bands *except* gamma [17,28]. Therefore, while both studies found altered connectivity during face processing in those with and at risk for developing ASD, the differences in analyses between the two studies prevent substantial comparison of their findings [17,28]. Furthermore, there is some question about the robustness of these findings in toddlers because the researchers did not statistically

account for multiple comparisons despite the consideration of multiple frequency bands, electrode pair connections, and time intervals around their stimuli [28]. The other recent task-based study of note included 12 ASD and 19 TD toddlers and preschool children (mean age 3.5 years), during which children passively watched pictures of cars or faces [30]. Relative to TD children, young children with ASD displayed reduced global phase lag in the alpha to beta frequency band (10-25 Hz) during the activity [30]. These differences were apparent when the cars and faces conditions were combined and were actually more pronounced in the cars-only condition [30].

II. b. ii. Toddlers and Preschoolers: Default Network and Sleep Coherence

Only one study from the past ten years has investigated resting-state as well as sleepbased connectivity in young children recently diagnosed with ASD [31]. This large study evaluated 137 two- to six-year-old children with either ASD, developmental delay matched with the ASD group by non-verbal intelligence (DD), or typical development [31]. The authors measured functional coherence across three states: awake, slow wave sleep (SWS), and Rapid Eye Movement (REM) sleep [31]. After adjusting for multiple comparisons, the authors found relatively increased MSC between frontal-parietal regions during SWS and REM sleep across all frequency bands in toddlers with ASD relative to the TD group [31]. In contrast, there were no observed differences during the awake resting-state following multiple comparison correction [31]. There were also far fewer differences in MSC between ASD and DD groups, with the ASD group predominantly showing increased MSC in a small group of electrode pairs in the frontal/central-parietal region during SWS and REM sleep [31]. In addition, children with ASD showed a reduction in phase lag coherence compared to TD controls, almost exclusively during SWS and most notably in long-distance electrode pairs [31]. Phase lag coherence differences between ASD and DD children were prevalent, but the pattern was diffuse across states, bands, and electrode locations [31]. These findings mirror Boersma and colleagues' findings of reduced phase lag, particularly in the beta frequency, in young children with ASD [30,31].

Overall, the three-way comparison that included children with a developmental delay without ASD effectively allowed for better detection of ASD-specific features of functional connectivity that are distinct from those attributable to developmental delay and intellectual disability more broadly [31]. Given the clear distinction in group differences based on whether connectivity was measured when the children were awake or asleep, this study suggests that the investigation of clinical disturbances in connectivity during sleep may provide unique insights into ASD [31]. In particular, by focusing on REM and SWS, researchers may gain critical insights into how young children with ASD rebalance synaptic homeostasis, engage in neuronal plasticity, and more broadly, consolidate memories [13]. At this point, more longitudinal studies are needed to compare functional coherence in infants and young children in order to determine the extent to which those who develop ASD present a unique trajectory of neural maturation over the first five years of life. From the reviewed research, we suspect that alterations in the trajectory of dynamically changing systems that underlie neural coherence in early development may significantly contribute to the deficits seen in ASD.

III. School-aged Children: Default Network Coherence

III. a. Group Differences Between ASD and Typically Developing Children

Numerous researchers have examined resting-state neural activity in ASD in order to study global processing and ascertain a baseline, unprovoked pattern of default mode network oscillations [32]. In theory, all studies with resting, awake-state recording are not linked to any specific task. In reality, resting-state recordings are likely to include some measure of non-rest-like processing and cognition. For instance, individuals may have a heightened sensory awareness to their environment because they are in an unfamiliar setting and are wearing a piece of EEG equipment on their head. Subjects are also strategically distracted during these resting-state tasks, whether it be with music, a movie, a screen-saver, or bubbles. In more controlled paradigms that seek to avoid unquantifiable levels of sensory processing, subjects are instructed to focus on a visual point for the duration of the resting-state recording. Such structured resting-state conditions are usually feasible only with subjects that are at least school-aged and do not have an intellectual disability. While task-based paradigms generally introduce latent factors such as an individual's attention on a task and level of anxiety when performing a high-pressure task, resting-state paradigms seek to somewhat circumvent such issues.

Our review found that researchers have mixed conclusions whether or not school-aged children with ASD without cognitive impairment display a reduction or an increase in the coherence patterns of the lowest frequency bands, delta and theta. For instance, in one study of resting-state connectivity, children ages 6 to 11 diagnosed with ASD showed reductions in delta and theta frontal-occipital MSC, both intra- and interhemispherically, relative to TD, agematched controls [33]. Another study of boys with ASD, ages 5-7, also found highly significant patterns of reduced theta coherence from the frontal to temporal and posterior regions during resting state [34]. In direct contrast, Machado and colleagues found significant increases in delta and theta MSC in the left hemisphere, generally defined by long-range connections between the anterior and posterior regions [33–35]. However, these contradictory findings are less compelling because the total sample size was less than two-thirds the size of that in the Coben et al. study [33] and did not uniformly correct for multiple comparisons [35]. Elhabashy and colleagues also found evidence for increased interhemispheric coherence over the temporal region in the delta frequency, despite general reductions between the frontal and central regions [36]. Along with these significant, but apparently contradictory, findings of reduced and increased low-frequency coherence, there were two moderately sized studies that reported no intra- and interhemispheric differences between ASD and TD children during resting-state [37,38].

There has been a greater consensus on the patterns of coherence in higher frequency bands: alpha, beta, and gamma. Generally, researchers have found a reduction in alpha, beta, and gamma in short- and medium- range connections in school-aged children with ASD who have average-or-higher intellectual functioning, relative to TD peers. In a study of subjects during eyes-closed resting state, Carson and colleagues found reductions in interhemispheric alpha coherence particularly over the frontal lobe and temporal-parietal lobe [39]. Clarke and colleagues, who also measured eyes-closed resting state, found these same

interhemispheric alpha-based differences but only over the frontal lobe [38]. Coben and colleagues measured subjects during eyes-open resting state and found alpha-based differences solely over the temporal-posterior brain regions [33]. In addition, Clarke et al. and Coben et al. found similar results of reduced interhemispheric coherence but in the beta frequency band [33,38]. Elhabashy also found reductions in alpha coherence among short- and medium- connections spanning between the frontal, temporal, and posterior regions as well, but intrahemispherically within the left and right hemispheres, in children with ASD during eyes-open resting state [36]. In contrast, Sheikhani and colleagues found only a few statistically significant reductions in the beta frequency over the left temporal-posterior region in the ASD group [40]. Elhabashy et al. and Carson et al. did not focus on the analysis of beta or gamma band frequency, while Clarke et al., and Coben et al. did not analyze gamma, so no information about those bands can be inferred [33,36,38,39]. Findings on long-range connections in these higher frequency bands are more mixed, with a few studies showing an ASD-specific increase in long-range coherence but most finding no significant differences between groups. In particular, medium- to long-range gamma coherence between temporal lobe regions and other brain regions have been noted as increased in children with ASD [35,40]. Global increases in beta and gamma coherence have also been noted as prominent in medium- and long-range connections stemming from the temporal and posterior regions [34].

While the results described in this literature form a somewhat coherent message about how communication between brain networks occurs during an unsolicited baseline of neural functioning in ASD, there are several constraints. Each reviewed study on ASD resting-state connectivity in school-aged children tended to cover a wide age range and only included children with average-or-higher intelligence (high functioning autism, or HFA). Compiling data across multiple stages of child development obscures specific information about brain maturation that might be most evident in narrow developmental time windows. Furthermore, by only focusing on HFA children, the results cannot be applied to a substantial portion of children with ASD. Despite these limitations, the results described provide useful information about default mode network functioning within various frequency bands during non-task related paradigms in children who are diagnosed with ASD and have unaffected intellectual functioning.

III. b. Discrimination of ASD Subtypes in Children

Given that ASD is a highly heterogeneous disorder with likely a host of different etiologies, researchers have begun to look for electrophysiological markers that distinguish different clinical manifestations of the disorder. Here, we reviewed a series of studies that sought to not only classify whether a child had ASD or not, but also identify subgroups within children with ASD.

Within the past ten years, the largest study to conduct such an analysis was one on children ages 2 to 12, comprised of 430 children diagnosed with Autistic Disorder (AD) or Pervasive Developmental Disorder, Not Otherwise Specified (PDD-NOS), 26 children diagnosed with Asperger’s syndrome, and 554 TD children [2,41]. For purposes of our review, the group diagnosed with AD and PDD-NOS was referred to as ASD and Asperger’s syndrome was

classified as synonymous with high-functioning autism (HFA). First, the authors used a data-driven method to distinguish solely between pediatric ASD and TD subjects based on EEG MSC [2]. Predictive modeling identified 40 factors, representing bands in the theta, alpha, and beta range, that could explain 51% of the variance in their total sample [2]. These 40 factors were then used in a discriminant function analysis to discriminate between the two major groups [2]. The algorithm was highly accurate in differentiating individuals based on ASD or non-ASD diagnosis both *across* all children ages 2-12 and *within* three separate age groups: 2-4, 4-6, and 6-12 [2]. These factors were primarily driven by a pattern of reduced short-range coherence and a mix of reduced and increased medium-range coherence in the ASD group [2]. Analysis failed to show any pattern of lateralization or regionalization among coherence factors [2]. Overall, 70% of the coherence factors identified were associated with reduced coherence in the ASD sample, and two of the four factors most commonly employed for discrimination represented reduced ASD coherence [2]. When HFA children were then included in this analysis, discriminant factor analysis with the same 40 factors successfully classified 96% of the HFA group as a part of the ASD group, suggesting some degree of similar neurophysiological underpinnings between the two groups, at least relative to TD children [41]. Then, when the HFA group was compared solely to the ASD group, the factor analysis successfully discriminated the two groups with 92% accuracy [41]. The most utilized factor in both the differentiation between ASD and TD groups and the differentiation between HFA and ASD groups represented *reduced beta coherence between the anterior and posterior left temporal region, an area most commonly associated with language processing* [2,41–43]. Surprisingly, this beta-driven factor revealed even further reduction of coherence in the HFA group compared to the main ASD group [41]. The authors propose that these results may be driven by a compensatory factor in the HFA group, which showed greater beta-band coherence in the HFA group relative to the ASD group [41]. Given that the principal differences occur in the left temporal region, the results suggest the utility of EEG coherence to determine whether underlying language systems function differently in ASD depending on the cognitive and clinical degree of impairments.

In a slightly different comparison, Peters and colleagues investigated theta and alpha MSC in young children with and without ASD and with and without comorbid tuberous sclerosis (TSC), a genetic disorder known to be associated with ASD [44]. The 16 subjects with non-syndromic ASD were 2-5 years of age, the other three comparator samples had much wider age ranges including subjects ages 0 to 25 [44]. Taking into account only the non-syndromic ASD sample, investigators found no difference in alpha or theta coherence relative to the TD sample, but did find a significantly decreased ratio of “long-” over “short-” range alpha coherences [44]. In addition, the broader ASD cohort, inclusive of those with TSC comorbidity, had the same pattern of proportionally increased short-range coherence and decreased long-range coherence compared to the non-ASD cohort [44]. These results support the hypothesis that an altered ratio of short- to long-range connectivity in theta and alpha oscillatory activity may be characteristic of ASD and that the contribution of TSC to its aberrant neural signature is negligible [44]. However, these results must be taken with caution for several reasons. For example, the uneven distribution of subjects in each age range makes direct comparison between groups difficult given the extensive changes in

neuromaturation that occur during the first 25 years of life. In addition, history of seizures is highly prevalent in TSC, even more so than in ASD, and epileptiform activity is thought to significantly impact EEG-based recordings, and a history of seizures was not accounted for as a covariate in this study's analysis [45,46]. Furthermore, the study of neural distance through short- and long- ranges is particularly challenging in the context of this study, which includes children with TSC whose tubers in their neural structures may make it difficult to predict the actual neural distance of network connections [47]. With these limitations in mind, we acknowledge the unique opportunity and continued importance to study ASD through genetic disorders like TSC and others that are highly associated with ASD.

Several other studies have compared ASD subtypes based on intellectual functioning and ASD severity in more conventional between-group analysis approaches. Comparing 8- to 17-year-old children with low-functioning ASD (LFA) to children with high-functioning ASD (HFA), as determined by IQs below and above 70, respectively, Han and colleagues found that LFA children had increased theta coherence within the frontal region, across the left hemisphere, and between interhemispheric connections [48]. It is possible that other differences between groups would have emerged at other frequency bands, as well; however, to increase their power to analyze multiple electrode pairs, the investigators limited their analysis solely to coherence in the theta band due to its association with executive functioning in frontal brain regions [48,49]. In addition, Barttfeld and colleagues compared HFA adolescents and adults with TD age-matched controls, with a focus also on low frequency, but in the delta range [50]. Subjects with HFA had increased short-range delta coherence in the lateral-frontal regions of the scalp but also reduced medium- and long-range coherent connections across frontal-frontal and frontal-occipital connections [50]. In addition to these group differences, this pattern became more pronounced with increasing ASD severity as determined by the Autism Diagnostic Observation Scale, a gold-standard diagnostic tool for diagnosing ASD [50,51]. While it seems unlikely that a measure of globally synchronized activity can capture the same traits as a 10- point severity scale, these last results support the inclination that patterns of neural connectivity and behavioral manifestations of the disorder share a common origin.

Together, these studies highlight the possibility that individuals with greater cognitive deficits and ASD severity have characteristically different coherence patterns, especially in low frequency bands [41,48,50]. Because it is clear that ASD is a heterogeneous disorder composed of multiple subtypes, this work differentiating groups by neural signatures is a critical step towards understanding the underlying contributors of synaptic dysregulation in individuals with ASD. The study of various known genetic disorders associated with ASD will also help to identify common patterns of aberrant connectivity that underlie each group with ASD that are uncharacteristic in non-ASD forms of those genetic disorders.

IV. School-aged Children: Eliciting Functional Patterns of Coherence

Despite the well-known heterogeneity across the ASD spectrum, there are certain core symptoms associated with the disorder. Reliable methods for recording functional connectivity should be applied to core symptom-related tasks to illuminate differences in specific regions in a hypothesis-driven fashion. This approach has employed tasks designed

to elicit brain networks recruited for performing audio-visual processing and integration, social communication, and executive functioning [52–56]. Photic stimulation, while not an active task, has also been explored in ASD; it is thought to capture local potential oscillators at specific frequencies and perhaps tap into rhythmic activity in a way that general resting-state recordings cannot [37].

IV. a. Audio-Visual Integration

Audio-visual integration has been postulated to be an inherent deficit in ASD, with individuals unable to effectively integrate signal inputs across two domains [52,53]. Recent work has primarily characterized this process through means other than EEG coherence, like behavioral tasks, eye-tracking, and event-related potentials [57,58]. The only study to investigate coherence in this field over the past five years has been by Machado and colleagues [35]. Machado et al. sought to address audio-visual integration by instructing two groups of children, one with ASD and one without, to watch a cartoon under conditions that either did or did not include audio [35]. Children with ASD demonstrated greater coherence across both short- and long-range intra- and interhemispheric connections [35]. Both groups showed a reduction in delta through gamma, bilateral coherence during the task relative to resting baseline condition [35]. The ASD group, however, tended to have even lower coherence in the right hemisphere in the absence of audio compared to when audio was present, whereas the typical group showed no significant differences between these conditions [35].

IV. b. Social Communication Tasks

Attention to socially directed gaze, or joint attention, and general face processing, are both considered to be severely impacted components of social communication in those diagnosed with ASD [54,55]. However, like audio-visual integration, little recent work addressing these deficits has been conducted specifically looking at EEG coherence. Jaime and colleagues investigated neural connectivity in this domain by recording EEG from cognitively unimpaired ASD and TD adolescents while they watched a series of videos where a red dot was paired with either an actor's congruent or incongruent gaze [59]. After combining the data recordings across three conditions (congruent gaze, incongruent gaze, and an eyes-open baseline resting state), the investigators found the ASD cohort to have significantly reduced alpha coherence over the temporal-central scalp region [59]. There were no clear differences in either group between congruent and incongruent conditions, which the authors explain may have resulted from instructing subjects to follow the red dot and thus inadvertently directing their attention away from the actor's gaze [59].

Deficits of EEG coherence during social interaction have also been examined by comparing ASD and TD children as they watched a video in which either a familiar or an unfamiliar person read a story [39]. While alpha interhemispheric temporal-parietal coherence did not change significantly across familiar, unfamiliar, or resting-state baseline conditions within the ASD or TD groups, coherence was significantly lower in children with ASD compared to typical controls during both task conditions and at baseline [39]. Alpha interhemispheric frontal coherence decreased during the two social tasks relative to baseline for the TD group, whereas the ASD group showed no significant change in across the three conditions [39].

The lack of alpha suppression by the ASD group under this condition may reflect atypical modulation of executive focus, but given the small sample size of the study, this warrants further investigation [39].

IV. c. Executive Functioning Tasks

Executive functioning refers to a host of higher-order cognitive processes, including working memory, reasoning, and attentional control, all of which have been considered to be affected in those with ASD [56]. Of the recent studies that looked at EEG coherence during an executive functioning task, the largest came from Lushchekina and colleagues, who analyzed data from 51 young boys with ASD and typical development [34]. Using an eyes-closed cognitive loading task where children counted numbers, investigators found that during the cognitive task relative to a baseline period, the TD control group exhibited significant increases in the high frequency ranges, beta and gamma, while the ASD group showed only minor changes [34]. In contrast, the ASD group showed increased delta coherence, especially interhemispherically at the frontal-temporal and temporal-posterior regions, while TD controls showed only minor changes in delta between conditions [34]. While in TD children, theta coherence in the right frontal and central-temporal regions decreased during the task, theta coherence decreased significantly more so in the left frontal and bilateral posterior regions in ASD children during that task [34]. The authors hypothesized that these results collectively implied that a simple cognitive task, like counting, may be supported by a completely separate mechanism in ASD than that utilized in the neurotypical brain [34]. The study did also include a psychodiagnostic scale to assess the degree to which each subject could complete verbal and nonverbal cognitive, social, and motor tasks [34]. The psychodiagnostic scale revealed that the ASD sample differed from typical controls in terms of their attention skills [34]. Furthermore, the authors note that some children could not complete the psychodiagnostic tasks even with high levels of support [34]. Therefore, while the authors claimed to have ensured that all subjects were completing the silent counting task during the EEG, it is possible that task compliance was not comparable between groups given the ASD group’s documented attentional deficits and required levels of adult support [34].

Chan and colleagues also examined the degree to which children with ASD differ in terms of their working memory, but they did so by measuring object recognition memory rather than with cognitive loading [60]. The authors designed an object recognition memory task to test both working memory and resistance to interference, using a set of twelve memorized target images from a validated library, along with 12 distractors images [60]. The task was performed during EEG recording, and theta coherence was chosen *a priori* for analyses [60]. During this recall-based task, children with ASD presented increased long-range frontal-parietal-occipital theta coherence, both within the left hemisphere and between the left anterior and right posterior brain regions [60]. Furthermore, in those with ASD, anterior-posterior intrahemispheric theta coherence negatively correlated with memory performance during the task [60]. While these results resemble those of Lushchekina and colleagues [34], it is difficult to determine the extent to which connectivity differences are due to the task, because data acquired during the task was not compared relative to a baseline, non-task condition [60]. Furthermore, given that performance scores on this task were lower in ASD,

the results may be partially attributable to misdirected attention or a misunderstanding of the directions.

IV. d. Intermittent Photic Stimulation

Intermittent Photic Stimulation (IPS) has been used on several occasions by one group of researchers in particular to measure rhythmic oscillatory activity in individuals with ASD [37,61,62]. In recent work, this group found that by presenting children with 3-24 Hz photic driving stimulations, children with ASD showed reduced interhemispheric theta, alpha, and beta coherence [37]. These findings built off of prior work showing a less symmetric distribution of highly coherent interhemispheric connections in children with ASD [37]. In particular, photic driving led to an increase in alpha and beta coherence that was largely restricted to the left hemisphere [37]. This study's interhemispheric deficit in ASD provided further evidence that IPS may be extremely beneficial in revealing latent differences between groups that are unobservable in spontaneous resting-state EEG [37].

V. School-aged Children: Sleep Coherence

As mentioned, resting-state paradigms can mitigate latent factors such as individual level of attention and anxiety that may be present during task-based measures. Sleep-based paradigms may be even more effective in reducing these additional factors by allowing neural activity to be measured when all subjects are engaged in physiologically comparable sleep states and are not actively engaged with external sensory stimuli. Sleep may be a potentially important contributor to altered neurodevelopment in ASD and may result in abnormal processes of memory consolidation and behavioral regulation [63,64]. Within the past decade, the sole study to investigate MSC as well as phase correlations during sleep in school-aged children was by Lázár and colleagues in 2010 [65]. Standard all-night EEG sleep parameters were obtained from 18 unmedicated subjects with ASD and 14 TD controls ranging from 7 to 22 years of age [65]. MSC and phase coherence measures were computed for multiple frequency bands specifically during NREM sleep. After correcting for multiple comparisons, investigators found significant reductions in short-range frontal-central connections in delta, theta, and alpha coherence on the right side of the brain and alpha only on the left side of the brain [65]. Because delta and theta bands are associated with slow wave sleep, entrainment to sensory stimuli, and working memory, these results may be indicative of abnormal slow wave regulation [15,16].

VI. Adults: Default Network Coherence

In the past decade, only five studies have investigated coherence in adults with ASD. Three of those focused on eyes-closed resting state alpha coherence in high-functioning adults with ASD and presented conflicting results. By measuring alpha coherence during eyes-closed states, all three studies mitigate the interference that external sensory input can have on alpha activity [66]. The first, by Murias and colleagues, found significant reductions at the global level both within the frontal region and between the frontal region and other scalp locations [67]. The second found that central-central interhemispheric alpha coherence was significantly increased in ASD (with comorbid diagnoses of anxiety, attention-deficit/ hyperactivity disorder, or neither) relative to TD adults, as well as to non-ASD adults with

anxiety, but not adults with attentiondeficit/hyperactivity disorder (ADHD) [63]. Finally, the third study of similar design detected no ASD-TD group differences in either eyes-closed or eyes-open, resting-state alpha coherence [68].

Studies that focus on delta and theta coherence have also produced mixed results [50,63,67,69]. Two eyes-closed resting-state paradigms generally agree that adults with ASD present locally elevated levels of delta and theta band frequencies in the frontal and temporal regions [50,67]. A third eyes-closed study found theta coherence to increase in the left central and parietal regions associated with a linear increase of autism severity as determined by the Autism-spectrum Quotient in both ASD and TD adults [68,70]. In contrast, two studies that measured eyes-open cross-fixation resting-state theta coherence – one comparing ASD and TD adults and the other involving ASD, TD, Anxiety Disorder, and ADHD adults – did not find significant group differences [63,69]. Unfortunately, in the study with a four-group comparison, the statistical analysis was conducted at the group level across all four groups and did not include (or permit) any direct comparison between the ASD and TD groups alone [63].

VII. Adults: Eliciting Functional Patterns of Coherence

Similar to pediatric executive functioning tasks, Catarino and colleagues studied HFA adults using a matching task that involved face and object recognition components and incorporated response inhibition [71]. Group-by-task performance interaction approached but did not reach significance and was driven by the ASD group's significantly lower behavioral performance on the face task compared to typical controls [71]. Alpha and theta interhemispheric coherence was significantly decreased in ASD during both face and object recognition conditions for all studied electrode pairs [71]. However, after correcting for multiple comparisons, the only remaining significant group difference was reduced alpha coherence between a left temporal and right temporal electrode pairing (T7-T8), specifically only during the face recognition task, around 300 milliseconds post-stimulus onset [71].

In a task more geared towards social skills, Tseng and colleagues examined the degree to which neural synchrony differed in HFA adults engaged in an emotional identification task [69]. Participants were instructed to categorize neutral, angry, and happy faces, presented as either black and white photographs or line-based drawings [69]. When they were engaged in categorizing black-and-white photographs, adults with ASD had reduced delta-theta phase synchronization locally between midline central-parietal channels and nearby channels spanning in all directions compared to controls [69]. When the stimuli to be categorized switched to line-drawings, both controls and ASD subjects demonstrated increased long-range phase locking, and there was no difference between groups [69]. Higher frequency bands, alpha and beta, were not significantly different between groups [69].

VIII. Adults: Sleep Coherence

Only one small study to date has considered EEG coherence in adults with ASD during sleep [72]. Léveillé et al. reported on 9 young adults with ASD and 13 age-matched TD controls, specifically during REM sleep [72]. Adults with ASD had increased delta and theta

coherence, particularly between a few short-and long-range connections in the left occipital region [72]. One short-distance electrode pairing in the right frontal region also showed reduced theta coherence [72]. No differences were apparent based on interhemispheric coherence [72]. The analysis of higher frequency bands (alpha and beta) did not result in group differences [72]. The results, while they cannot stand alone and need further validation, do suggest sleep-based differences in collaborative information processing between visual networks and other networks [72].

IX. Major Conclusions

Uncovering the degree to which the brain in ASD differs from typical development in its ability to efficiently synchronize local and global neural networks is critical. ASD as a disorder of neural connectivity may be understood as a condition of altered complex global processing whereby the collaborative integration of circuits responsible for joining specialized regions of the brain does not occur normally. In particular, complex global processing encompasses visualauditory integration to aid in affect perception, gestalt processing to decipher communicative intent, and the necessary seamless communication between attentional networks and sensory processing networks that facilitate the encoding of pertinent information [73,74].

The reviewed publications often focus their analyses on certain bands of interest, guided by *a priori* assumptions about the underlying function of certain oscillatory patterns. For instance, desynchronization of alpha activity is thought to be important for attentional processes while heightened coherence in the beta frequency has been related to better cognitive processes [18,39,59,75]. Theta and alpha coherences have been further postulated to be related to working memory and other higher-order cognitive processes [26,60,71]. In line with theories that individuals with ASD are specifically prone to deficits in executive functioning and altered inhibition, our review found that for all task-based studies reporting differences in alpha coherence, there was relatively lower alpha coherence in ASD [34,37,39,59,71]. Of the five task-based studies reporting differences in theta coherence, three reported increased coherence during visual working memory, passive face viewing, and mental calculation tasks [34,40,60], and two reporting decreased coherence were during working memory and IPS [37,71].

Task-based and rest-based EEG coherence studies have been routinely deployed to interrogate networks in ASD. Studies measuring EEG coherence during tasks provide key information about global processing of external stimuli and about active cognitive processes relative to resting baseline, whereas measurements of resting-state coherence can be considered to characterize oscillations of a default mode network [32]. Atypical patterns of connectivity within the default mode network may be of particular interest in ASD as an indication of internal or self-referential contemplation and general synchronized attention to external stimuli [76]. In addition, capturing network connectivity during sleep or with sensorystimulating paradigms such as Intermittent Photic Stimulation offers alternative strategies that can be effective in eliminating differing and uncontrollable responses to unstructured external sensory inputs.

From a developmental perspective, we found that infants at high familial risk for ASD, displayed atypical alpha and gamma coherence, especially in the left hemisphere, during social stimuli paradigms [17,24,25]. High frequency oscillations are especially relevant to the appropriate functioning of inhibitory networks which, in turn, may be particularly salient to infant neuromaturation [77]. While promising, these studies did not quantify group differences within other frequency bands, leaving an avenue of research still to be explored. Task-based studies on children who have matured to toddler age revealed greater differences in low frequencies like delta and theta, as well as alpha [28]. These differences became particularly pronounced during SWS and REM sleep, stages that are speculated as critical for the consolidation and optimization of synaptic connections [13,31]. In school-aged children, several research groups found a reduction in higher frequency bands, particularly among short- and medium-range connections, in ASD relative to TD controls during rest. Given that in typical child development from infancy to adolescence, coherence in high frequencies linearly increases between short-medium inter-electrode connections, this significant reduction may represent a clear developmental delay in ASD [11,12]. Unfortunately, it was difficult for us to consider the developmental trajectory of abnormalities within school-aged children because the reviewed experiments often chose to include subjects across a wide age range in order to acquire a greater sample size. In adults, we found limited evidence for abnormal coherence [63,68,69]. The transition from significant differences observed in childhood that are no longer apparent in adulthood may represent a degree of cortical maturation and accompanying increase of broadband coherence that allows individuals' brains to "catch up" [78]. However, it could also be the case that the observed change in cognitive functioning across chronological development results from differences in the composition of cognitive functioning in various age groups. Cohorts of ASD adults tended to be exclusively high-functioning and cohorts of ASD children tended to include a more diverse cognitive range. Cognitive level in typically developing populations is associated with EEG coherence and therefore also should be considered when evaluating clinical populations like ASD [11].

X. Methodological Considerations and Constraints

The majority of studies reviewed analyzed only a few minutes of data, in part given the time constraints when studying a clinical population at rest. However, studies with less data to analyze should be wary of significant findings between groups in the slower frequency bands, especially delta [79]. This is because fewer cycles of rhythmic activity, for instance in delta frequency, occur in the same amount of time as a higher frequency bands and therefore result in less data, which can, in turn, also be subject to further loss due to movement artifact. While awake-based studies tended to have five minutes or fewer of resting-state data prior to artifact rejection and post-processing, sleep-based measures exceed that amount of data collected and can thus allow for a more specific and reliable calculation of coherence in the slower frequencies. We also found that a high proportion of the reviewed studies did not report on frequencies in the gamma range (above 25 Hz). This is often attributed to researchers' caution in analyzing and interpreting gamma given its susceptibility to noise artifacts from movement and extraneous electrical signals. However, it may make sense for ASD-related research to make an effort to always include gamma, as it is thought that the

inhibition of cortical interneurons, primarily through the neurotransmitter Gamma-Aminobutyric Acid (GABA), is the main driver of high-frequency activity in the brain [77,80,81] Abnormally dampened higher frequencies in ASD may represent an aberrantly high ratio of excitatory-to-inhibitory connections, offering a theory-driven rationale for the investigation of gamma-based differences in ASD [82].

A fair amount of inconsistencies across results were driven by methodological variation. The reviewed studies used different recording techniques including both scalp electrodes and electrode nets with widely varying numbers of electrodes, affecting both the quality and quantity of the collected data. Studies also varied in terms of chosen electrode pairs to be included in analyses, making it difficult to compare between studies. In addition, some studies only reported general areas of significance and vague descriptions of “short-” and “long-” range connections, but did not report which pairs from the analyses the significance pertains to, making it difficult to interpret and replicate results. This is particularly relevant to consider given the inconsistencies in the literature over the use of the terms “long-” and “short-” distance between electrodes. The methods to calculate coherence, including the type and amount of data that was used and the type of mathematical computations completed to achieve coherence values, also differ amongst studies.

Studies that employed *a priori* hypotheses allowed for more focused and more statistically-powered research, but run the risk of overlooking other potentially important information. Exploratory studies, on the other hand, report data from many connections across the brain but are limited by the need to control for multiple comparisons. The type of multiple comparisons and statistical thresholds used for significance also play a role, and did vary between the reviewed studies [71,83]. For instance, a portion of studies examined used False Discovery Rate, another set used Bonferroni-type corrections, and a third group failed to correct for multiple comparisons at all by any method. Choosing not to statistically correct for multiple comparisons is only valid if the degrees of freedom afforded by the sample size is larger than the number of comparisons that the researchers conduct; in other words, the sample size would have to be larger than the number of analyses done for each electrode pair in each frequency.

Beyond the methodological differences, there were inconsistencies in how subject cohorts were defined that limited our ability to directly compare studies. First, ASD is composed of multiple subtypes. The variation in how studies confirm ASD diagnosis (e.g., gold-standard behavioral observation and parent report versus use of a former diagnosis and a 10-item checklist) and the diagnostic samples they include (whether it is high-functioning or low-functioning or by some other metric) is very relevant. Not every study even included a method of diagnosis. The variation in age, especially when some studies are narrow in range and others include both young and adolescent children as subjects, was also problematic. Furthermore, the majority of the reviewed studies did not control for co-occurring conditions such as anxiety or attention deficits in ASD or control groups, both factors that might impact coherence findings [84,85]. Finally, the majority of reviewed studies did not attain a sample size of thirty subjects per cohort. This makes each analysis more susceptible to confounding factors and limits the generalizability of the data due to potential Type I and Type II errors and lack of moderate power [60].

XI. Future Directions

Leveraging the greater temporal resolution of EEG studies relative to imaging studies has allowed researchers to parse coherence patterns across multiple frequency bands and further dissect the study of brain connectivity. The unique properties of MRI and EEG allow for different representations of the brain that both contribute to a more cohesive understanding of the complex and highly nuanced brain patterns that define the social animal. From a practical perspective, EEG methods are arguably the most viable way to investigate brain dysfunction in those with ASD and other clinical disorders that have sensory and behavioral issues. They require less compliance from the subject to stay still and can be implemented at a much lower cost than MEG or MRI methods. However, scalp EEG is currently only usable as an estimation for underlying strength, coordination, and source localization of neural firing rates. Advances are needed in the construction of computational models that reflect deep-brain connectivity and its resulting scalp-based, EEG measures, as well as in EEG technology itself to better counteract muscle artifacts and scalp impedances. These advances will foster greater synthesis of research on large-scale global connectivity and local network functionality.

Our review also highlighted that there is a dearth of ASD research on the sleeping brain. Out of the 28 papers reviewed, we were only able to identify three that characterized coherence in ASD over the past ten or more years [31,65,72]. Sleep provides a rare opportunity to study basic neural network coherence, unaffected by either external stimuli or complex internal thought processes. Sleep studies are especially useful in ASD cohorts whose resting-state and task-related studies are often confounded by the inability to follow directions and stay somewhat still. Moreover, sleep is critical for the regulation of synaptic connections and more broadly, neural plasticity. Therefore, we recommend that future research rely more on sleep-based paradigms to tap into the progression of neural and synaptic development in ASD [13].

While the current literature suggests that there are differences in synchronized neural activity between ASD and TD populations, there are certainly methodological inconsistencies that prevent sweeping generalizations. At the present moment, we are unable to state that any particular behavior is reflective of any particular coherence pattern or that any particular electrophysiologic pattern is predictive of any observable, clinical phenotype. In addition, given that neurodevelopment is a dynamic process and ASD is a developmental disorder, coherence patterns are likely to be changing both naturally and with the introduction and success of behavioral interventions. Future research would benefit from more rigorous characterization of ASD etiology and case presentation within cohort samples to guide better interpretation of electrophysiological data. Defining sleep-mediated changes in coherence across development in ASD and even in typical development will also contribute to potential identification of biomarkers of neural circuitry specific to neurodevelopmental trajectories.

References:

[1]. Association Psychiatric Association. DSM-5. American Psychiatric Association; 2013.

[2]. Duffy FH, Als H. A stable pattern of EEG spectral coherence distinguishes children with autism from neuro-typical controls - a large case control study. BMC Med 2012;10:64. doi: 10.1186/1741-7015-10-64. [PubMed: 22730909]

[3]. Geschwind DH. Genetics of autism spectrum disorders. Trends Cogn Sci 2011;15:409–16. doi: 10.1016/j.tics.2011.07.003. [PubMed: 21855394]

[4]. Voineagu I, Wang X, Johnston P, Lowe JK, Tian Y, Horvath S, et al. Transcriptomic analysis of autistic brain reveals convergent molecular pathology. Nature 2011;474:380–4. doi:10.1038/nature10110. [PubMed: 21614001]

[5]. Zikopoulos B, Barbas H. Changes in Prefrontal Axons May Disrupt the Network in Autism. J Neurosci 2010;30:14595–609. doi:10.1523/JNEUROSCI.2257-10.2010. [PubMed: 21048117]

[6]. Ameis SH, Catani M. Altered white matter connectivity as a neural substrate for social impairment in Autism Spectrum Disorder. Cortex 2015;62:158–81. doi:10.1016/j.cortex.2014.10.014. [PubMed: 25433958]

[7]. De Rubeis S, He X, Goldberg AP, Poultney CS, Samocha K, Ercument Cicek A, et al. Synaptic, transcriptional and chromatin genes disrupted in autism. Nature 2014;515:209–15. doi: 10.1038/nature13772. [PubMed: 25363760]

[8]. Srinivasan R, Winter WR, Ding J, Nunes PL. EEG and MEG coherence: measures of functional connectivity at distinct spatial scales of neocortical dynamics. J Neurosci Methods 2007;166:41–52. doi:10.1016/j.biotechadv.2011.08.021.Secreted. [PubMed: 17698205]

[9]. Fries P A mechanism for cognitive dynamics: neuronal communication through neuronal coherence. Trends Cogn Sci 2005;9:474–80. doi:10.1016/j.tics.2005.08.011. [PubMed: 16150631]

[10]. Singer W Neuronal Synchrony: A Versatile Code for the Definition of Relations? Neuron 1999;24:49–65. doi:10.1016/S0896-6273(00)80821-1. [PubMed: 10677026]

[11]. Thatcher RW, North DM, Biver CJ. Development of cortical connections as measured by EEG coherence and phase delays. Hum Brain Mapp 2008;29:1400–15. doi: 10.1002/hbm.20474. [PubMed: 17957703]

[12]. Barry RJ, Clarke AR, McCarthy R, Selikowitz M, Johnstone SJ, Rushby JA. Age and gender effects in EEG coherence: I. Developmental trends in normal children. Clin Neurophysiol 2004;115:2252–8. doi:10.1016/j.clinph.2004.05.004. [PubMed: 15351366]

[13]. Kurth S, Achermann P, Rusterholz T, LeBourgeois M. Development of Brain EEG Connectivity across Early Childhood: Does Sleep Play a Role? Brain Sci 2013;3:1445–60. doi: 10.3390/brainsci3041445. [PubMed: 24535935]

[14]. Tarokh L, Carskadon MA, Achermann P. Developmental changes in brain connectivity assessed using the sleep EEG. Neuroscience 2010;171:622–34. doi:10.1016/j.neuroscience.2010.08.071. [PubMed: 20833232]

[15]. Sauseng P, Griesmayr B, Freunberger R, Klimesch W. Control mechanisms in working memory: a possible function of EEG theta oscillations. Neurosci Biobehav Rev 2010;34:1015–22. doi: 10.1016/j.neubiorev.2009.12.006. [PubMed: 20006645]

[16]. Knyazev GG. EEG delta oscillations as a correlate of basic homeostatic and motivational processes. Neurosci Biobehav Rev 2012;36:677–95. doi:10.1016/j.neubiorev.2011.10.002. [PubMed: 22020231]

[17]. Keehn B, Vogel-Farley V, Tager-Flusberg H, Nelson C a. Atypical Hemispheric Specialization for Faces in Infants at Risk for Autism Spectrum Disorder. Autism Res 2015:1–12. doi:10.1002/aur.1438. [PubMed: 24850670]

[18]. Knyazev GG. EEG correlates of personality types. Neth J Psychol 2006;62:78–87. doi: 10.1007/BF03061054.

[19]. Johnson MH. Functional Brain Development in Humans. Nat Rev Neurosci 2001;2:475–83. doi: 10.1038/35081509. [PubMed: 11433372]

[20]. Andersen SL. T rajectories of brain development: Point of vulnerability or window of opportunity? Neurosci Biobehav Rev 2003;27:3–18. doi:10.1016/S0149-7634(03)00005-8. [PubMed: 12732219]

[21]. Ozonoff S, Young GS, Carter A, Messinger D, Yirmiya N, Zwaigenbaum L, et al. Recurrence Risk for Autism Spectrum Disorders: A Baby Siblings Research Consortium Study 2014. doi: 10.1542/peds.2010-2825.

[22]. Kanwisher N, McDermott J, Chun MM. The fusiform face area: a module in human extrastriate cortex specialized for face perception. J Neurosci 1997;17:4302–11. doi :10.1098/Rstb. 2006.1934. [PubMed: 9151747]

[23]. Dawson G, Webb SJ, McPartland J. Understanding the nature of face processing impairment in autism: Insights from behavioral and electrophysiological studies. Dev Neuropsychol 2005;27:403–24. doi:10.1207/s15326942dn2703_6. [PubMed: 15843104]

[24]. Righi G, Tierney AL, Tager-Flusberg H, Nelson C a. Functional Connectivity in the First Year of Life in Infants at Risk for Autism Spectrum Disorder: An EEG Study. PLoS One 2014;9:e105176. doi:10.1371/journal.pone.0105176. [PubMed: 25140874]

[25]. Orekhova E V, Elsabbagh M, Jones EJ, Dawson G, Charman T, Johnson MH. EEG hyper-connectivity in high-risk infants is associated with later autism. J Neurodev Disord 2014;6:40. doi:10.1186/1866-1955-6-40. [PubMed: 25400705]

[26]. Klimesch W, Sauseng P, Hanslmayr S. EEG alpha oscillations: The inhibition-timing hypothesis. Brain Res Rev 2007;53:63–88. doi:10.1016/j.brainresrev.2006.06.003. [PubMed: 16887192]

[27]. Lord C, Rutter M, Le Couteur A. Autism Diagnostic Interview-Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. J Autism Dev Disord 1994;24:659–85. [PubMed: 7814313]

[28]. Dominguez G, Stieben J, Perez Valazquez L, Shanker S. The Imaginary Part of Coherency in Autism: Differences in Cortical Functional Connectivity in Preschool Children. PLoS One 2013;8:e75941. doi:10.1371/journal.pone.0075941. [PubMed: 24098409]

[29]. Nolte G, Bai O, Wheaton L, Mari Z, Vorbach S, Hallett M. Identifying true brain interaction from EEG data using the imaginary part of coherency. Clin Neurophysiol 2004;115:2292–307. doi: 10.1016/j.clinph.2004.04.029. [PubMed: 15351371]

[30]. Boersma M, Kemner C, de Reus M a., Collin G, Snijders TM, Hofman D, et al. Disrupted Functional Brain Networks in Autistic Toddlers. Brain Connect 2013;3:41–9. doi:10.1089/brain. 2012.0127. [PubMed: 23259692]

[31]. Buckley AW, Scott R, Tyler A, Mahoney JM, Thurm A, Farmer C, et al. State-Dependent Differences in Functional Connectivity in Young Children With Autism Spectrum Disorder. EBIOM 2015;2:87. doi:10.1016/j.ebiom.2015.11.004.

[32]. Chen ACN, Feng W, Zhao H, Yin Y, Wang P. EEG default mode network in the human brain: Spectral regional field powers. Neuroimage 2008;41:561–74. doi:10.1016/j.neuroimage. 2007.12.064. [PubMed: 18403217]

[33]. Coben R, Clarke AR, Hudspeth W, Barry RJ. EEG power and coherence in autistic spectrum disorder. Clin Neurophysiol 2008;119:1002–9. doi:10.1016/j.clinph.2008.01.013. [PubMed: 18331812]

[34]. Lushchekina EA, Khaerdinova OY, Novototskii-Vlasov VY, Lushchekin VS, Strelets VB. Synchronization of EEG Rhythms in Baseline Conditions and during Counting in Children with Autism Spectrum Disorders. Neurosci Behav Physiol 2016;46:382–9. doi: 10.1007/ s11055-016-0246-5.

[35]. Machado C, Estévez M, Leisman G, Melillo R, Rodriguez R, DeFina P, et al. QEEG Spectral and Coherence Assessment of Autistic Children in Three Different Experimental Conditions. J Autism Dev Disord 2015;45:406–24. doi:10.1007/s10803-013-1909-5. [PubMed: 24048514]

[36]. Elhabashy H, Raafat O, Raafat H, Abdullah K. Quantitative EEG in autistic children. Egypt J Neurol Psychiatry Neurosurg 2015;52:176–82. doi:10.4103/1110-1083.162031.

[37]. Lazarev V V, Pontes A, Mitrofanov AA, DeAzevedo LC. Reduced Interhemispheric Connectivity in Childhood Autism Detected by Electroencephalographic Photic Driving Coherence. J Autism Dev Disord 2015;45:537–47. doi:10.1007/s10803-013-1959-8. [PubMed: 24097142]

[38]. Clarke AR, Barry RJ, Indraratna A, Dupuy FE, Mccarthy R, Selikowitz M. EEG activity in children with Asperger ' s Syndrome. Clin Neurophysiol 2016;127:442–51. doi:10.1016/j.clinph. 2015.05.015. [PubMed: 26187351]

[39]. Carson AM, Salowitz NMG, Scheidt R a., Dolan BK, Van Hecke AV. Electroencephalogram Coherence in Children With and Without Autism Spectrum Disorders: Decreased Interhemispheric Connectivity in Autism. Autism Res 2014;7:334–43. doi :10.1002/aur.1367. [PubMed: 24623657]

[40]. Sheikhani A, Behnam H, Mohammadi MR, Noroozian M, Mohamamadi M. Detection of abnormalities for diagnosing of children with autism disorders using of quantitative electroencephalography analysis. J Med Syst 2012;36:957–63. doi:10.1007/s10916-010-9560-6. [PubMed: 20711644]

[41]. Duffy FH, Shankardass A, McAnulty GB, Als H. The relationship of Asperger's syndrome to autism: a preliminary EEG coherence study. BMC Med 2013; 11:175.doi: 10.1186/1741-7015-11-175. [PubMed: 23902729]

[42]. Scott SK. Identification of a pathway for intelligible speech in the left temporal lobe. Brain 2000;123:2400–6. doi:10.1093/brain/123.12.2400. [PubMed: 11099443]

[43]. Friederici AD. Pathways to language: fiber tracts in the human brain. Trends Cogn Sci 2009;13:175–81. doi:10.1016/j.tics.2009.01.001. [PubMed: 19223226]

[44]. Peters JM, Taquet M, Vega C, Jeste SS, Fernandez IS, Tan J, et al. Brain functional networks in syndromic and non-syndromic autism: a graph theoretical study of EEG connectivity. BMC Med 2013;11:54. doi:10.1186/1741-7015-11-54. [PubMed: 23445896]

[45]. Crino PB. Evolving neurobiology of tuberous sclerosis complex. Acta Neuropathol 2013; 125:317–32. doi:10.1007/s00401-013-1085-x. [PubMed: 23386324]

[46]. Spence SJ, Schneider MT. The role of epilepsy and epileptiform eegs in autism spectrum disorders. Pediatr Res 2009;65:599–606. doi:10.1203/PDR.0b013e31819e7168. [PubMed: 19454962]

[47]. Curatolo P, Bombardieri R. Hamartomatous disorders of cellular lineage Tuberous sclerosis 2008;87.

[48]. Han YMY, Chan AS, Sze SL, Cheung M-C, Wong C, Lam JMK, et al. Altered immune function associated with disordered neural connectivity and executive dysfunctions: A neurophysiological study on children with autism spectrum disorders. Res Autism Spectr Disord 2013;7:662–74. doi: 10.1016/j.rasd.2013.02.011.

[49]. Mizuhara H, Yamaguchi Y. Human cortical circuits for central executive function emerge by theta phase synchronization. Neuroimage 2007;36:232–44. doi:10.1016/j.neuroimage.2007.02.026. [PubMed: 17433880]

[50]. Barttfeld P, Wicker B, Cukier S, Navarta S, Lew S, Sigman M. A big-world network in ASD: Dynamical connectivity analysis reflects a deficit in long-range connections and an excess of short-range connections. Neuropsychologia 2011 ;49:254–63. doi:10.1016/j.neuropsychologia. 2010.11.024. [PubMed: 21110988]

[51]. Lord C, Risi S, Lambrecht L, Cook EH, Leventhal BL, DiLavore PC, et al. The Autism Diagnostic Observation Schedule—Generic: A Standard Measure of Social and Communication Deficits Associated with the Spectrum of Autism. J Autism Dev Disord 2000;30:205–23. doi : 10.1023/A:1005592401947. [PubMed: 11055457]

[52]. Grossman RB, Steinhart E, Mitchell T, Mcilvane W. "Look who's talking!" Gaze Patterns for Implicit and Explicit Audio-Visual Speech Synchrony Detection in Children With High-Functioning Autism. Autism Res 2015;8:307–16. doi:10.1002/aur.1447. [PubMed: 25620208]

[53]. Foxe JJ, Molholm S, Del Bene VA, Frey HP, Russo NN, Blanco D, et al. Severe multisensory speech integration deficits in high-functioning school-aged children with autism spectrum disorder (ASD) and their resolution during early adolescence. Cereb Cortex 2015;25:298–312. doi:10.1093/cercor/bht213. [PubMed: 23985136]

[54]. Mundy P, Sullivan L, Mastergeorge AM. A parallel and distributed-processing model of joint attention, social cognition and autism. Autism Res 2009;2:2–21. doi:10.1002/aur.61. [PubMed: 19358304]

[55]. Mundy P, Newell L. Attention, Joint Attention, and Social Cognition. Curr Dir Psychol Sci 2007;16:269–74. [PubMed: 19343102]

[56]. Geurts HM, de Vries M, van den Bergh SFWM. Executive functioning theory and autism. Handb. Exec. Funct., Springer; 2014, p. 121–41.

[57]. Baum SH, Stevenson RA, Wallace MT. Behavioral, perceptual, and neural alterations in sensory and multisensory function in autism spectrum disorder. Prog Neurobiol 2015;134:140–60. doi: 10.1016/j.pneurobio.2015.09.007. [PubMed: 26455789]

[58]. Brandwein AB, Foxe JJ, Butler JS, Russo NN, Altschuler TS, Gomes H, et al. The development of multisensory integration in high-functioning autism: High-density electrical mapping and psychophysical measures reveal impairments in the processing of audiovisual inputs. Cereb Cortex 2013;23:1329–41. doi:10.1093/cercor/bhs109. [PubMed: 22628458]

[59]. Jaime M, McMahon CM, Davidson BC, Newell LC, Mundy PC, Henderson HA. Brief Report: Reduced Temporal-Central EEG Alpha Coherence During Joint Attention Perception in Adolescents with Autism Spectrum Disorder. J Autism Dev Disord 2015. doi: 10.1007/s10803-015-2667-3.

[60]. Chan AS, Han YMY, Sze SL, Cheung M, Leung WW, Chan RCK, et al. Disordered connectivity associated with memory deficits in children with autism spectrum disorders. Res Autism Spectr Disord 2011;5:237–45. doi:10.1016/j.rasd.2010.04.005.

[61]. Lazarev VV, Pontes A, deAzevedo LC. EEG photic driving: Right-hemisphere reactivity deficit in childhood autism. A pilot study. Int J Psychophysiol 2009;71:177–83. doi:10.1016/j.ijpsycho.2008.08.008. [PubMed: 18809441]

[62]. Lazarev VV, Pontes A, Mitrofanov AA, deAzevedo LC. Interhemispheric asymmetry in EEG photic driving coherence in childhood autism. Clin Neurophysiol 2010;121:145–52. doi:10.1016/j.clinph.2009.10.010. [PubMed: 19951847]

[63]. Saunders A, Kirk I, Waldie K. Hemispheric coherence in ASD with and without comorbid ADHD and anxiety. Biomed Res Int 2016;2016:1–12. doi:10.1155/2016/4267842.

[64]. Maquet P The Role of Sleep in Learning and Memory. Science (80-) 2001;294:1048 LP–1052. [PubMed: 11691982]

[65]. Lázár AS, Lázár ZI, Bíró A, Győri M, Tárnok Z, Prekop C, et al. Reduced fronto-cortical brain connectivity during NREM sleep in Asperger syndrome: An EEG spectral and phase coherence study. Clin Neurophysiol 2010;121:1844–54. doi:10.1016/j.clinph.2010.03.054. [PubMed: 20434395]

[66]. Barry RJ, Clarke AR, Johnstone SJ, Brown CR. EEG differences in children between eyes-closed and eyes-open resting conditions. Clin Neurophysiol 2007;118. doi:10.1016/j.clinph.2009.08.006.

[67]. Murias M, Webb SJ, Greenson J, Dawson G. Resting state cortical connectivity reflected in EEG coherence in individuals with autism. Biol Psychiatry 2007;62:270–3. doi:10.1016/j.biopsych.2006.11.012. [PubMed: 17336944]

[68]. Mathewson KJ, Jetha MK, Drmic IE, Bryson SE, Goldberg JO, Schmidt L a. Regional EEG alpha power, coherence, and behavioral symptomatology in autism spectrum disorder. Clin Neurophysiol 2012;123:1798–809. doi:10.1016/j.clinph.2012.02.061. [PubMed: 22405935]

[69]. Tseng Y-L, Yang HH, Savostyanov AN, Chien VSC, Liou M. Voluntary attention in Asperger's syndrome: Brain electrical oscillation and phase-synchronization during facial emotion recognition. Res Autism Spectr Disord 2015;13–14:32–51. doi:10.1016/j.rasd.2015.01.003.

[70]. Baron-Cohen S, Wheelwright S, Skinner R, Martin J, Clubley E. The Autism-Spectrum Quotient (AQ): Evidence from Asperger Syndrome/High-Functioning Autism, Malesand Females, Scientists and Mathematicians. J Autism Dev Disord 2001;31:5–17. doi: 10.1023/A:1005653411471. [PubMed: 11439754]

[71]. Catarino A, Andrade A, Churches O, Wagner AP, Baron-Cohen S, Ring H. Task-related functional connectivity in autism spectrum conditions: an EEG study using wavelet transform coherence. Mol Autism 2013;4:1. doi:10.1186/2040-2392-4-1. [PubMed: 23311570]

[72]. Léveillé C, Barbeau EB, Bolduc C, Limoges É, Berthiaume C, Chevrier É, et al. Enhanced connectivity between visual cortex and other regions of the brain in autism: A REM sleep EEG coherence study. Autism Res 2010;3:280–5. doi:10.1002/aur.155. [PubMed: 20717953]

[73]. Happé F The Weak Central Coherence Account of Autism. Handb. Autism Pervasive Dev. Disord., John Wiley & Sons, Inc; 2005, p. 640–9. doi: 10.1002/9780470939345.ch24.

[74]. Chaby L, Chetouani M, Plaza M, Cohen D. Exploring multimodal social-emotional behaviors in autism spectrum disorders: An interface between social signal processing and psychopathology.

Proc - 2012 ASE/IEEE Int Conf Privacy, Secur Risk Trust 2012 ASE/IEEE Int Conf Soc Comput Soc 2012 2012:950–4. doi:10.1109/SocialCom-PASSAT.2012.111.

[75]. Ray WJ, Cole HW. EEG alpha activity reflects attentional demands, and beta activity reflects emotional and cognitive processes. Science 1985;228:750–2. doi: 10.1126/science.3992243. [PubMed: 3992243]

[76]. Buckner RL, Andrews-Hanna JR, Schacter DL. The brain's default network: Anatomy, function, and relevance to disease. Ann N Y Acad Sci 2008;1124:1–38. doi:10.1196/annals.1440.011. [PubMed: 18400922]

[77]. Uhlhaas PJ, Roux F, Rodriguez E, Rotarska-Jagiela A, Singer W. Neural synchrony and the development of cortical networks. Trends Cogn Sci 2010;14:72–80. doi:10.1016/j.tics.2009.12.002. [PubMed: 20080054]

[78]. Gasser T, Jennen-Steinmetz C, Sroka L, Verleger R, Mocks J. Development of the EEG of school-age children and adolescents II. Topography. Electroencephalogr Clin Neurophysiol 1988;69:100–9. doi:10.1016/0013-4694(88)90205-2. [PubMed: 2446829]

[79]. Mohammad-rezazadeh I, Frohlich J, Loo SK, Jeste SS, Behavior H, Angeles L. Brain Connectivity in Autism Spectrum Disorder. Curr Opin Neurobiol 2016;29:137–47. doi: 10.1097/WC0.0000000000000301.Brain.

[80]. Jeste SS. Electrophysiological biomarkers of diagnosis and outcome in neurodevelopmental disorders. Curr Opin Neurobiol 2015;28:110–6. doi:10.1007/3-540-35375-5.

[81]. Tamas G, Buhl EH, Lorincz A, Somogyi P. Proximally targeted GABAergic synapses and gap junctions synchronize cortical interneurons. Nat Neurosci 2000;3:366–71. [PubMed: 10725926]

[82]. Levin AR, Nelson C a. Inhibition-Based Biomarkers for Autism Spectrum Disorder. Neurotherapeutics 2015;12:546–52. doi:10.1007/s13311-015-0350-1. [PubMed: 25813603]

[83]. Glickman ME, Rao SR, Schultz MR. False discovery rate control is a recommended alternative to Bonferroni-type adjustments in health studies. J Clin Epidemiol 2014;67:850–7. doi:10.1016/j.jclinepi.2014.03.012. [PubMed: 24831050]

[84]. Robbie JC, Clarke AR, Barry Rj, Dupuy FE, McCarthy R, Selikowitz M. Coherence in children with AD/HD and excess alpha power in their EEG. Clin Neurophysiol 2016;127:2161–6. doi:10.1016/j.clinph.2016.02.008. [PubMed: 27072085]

[85]. Putman P Resting state EEG delta-beta coherence in relation to anxiety, behavioral inhibition, and selective attentional processing of threatening stimuli. Int J Psychophysiol 2011;80:63–8. doi:10.1016/j.ijpsycho.2011.01.011. [PubMed: 21277914]

Table 1.

Infants and Toddlers

Infants Studies: Task-based				
Keehn (2015)	49 HRA (6-12 months, IQ 102±15 at 12 months, 11 HRA+, 30 HRA−) 46 LRC (6-12 months, IQ 110±12 at 12 months, 37 LRC−)	64 or 128 electrodes	View images of neutral expression on familiar (mother's face) or unfamiliar face	HRA have ↑ L lateralization of intrahemispheric γ coherence at 12 months; HRA+ had ↑ L lateralization of intrahemispheric γ coherence than both HRA− and LRC− at 12 months; No differences between groups at 6 months; No difference between groups in intrahemispheric γ coherence lateralization during nonfamiliar condition at 6 or 12 months;
Righi (2014)	26 LRC (6-12 months, normal IQ, 16 LRC−) 28 HRA (6-12 months, normal IQ, 5 HRA+, 17 HRA−)	64 or 128 electrodes	Listen to speech sounds (/da/, /ta/, /dha/)	↓ average γ coherence at 12 months; No differences present at 6 months in γ; No differences in lateralization between groups in γ
Orekhova (2014)	26 LRC (12-17 months, IQ 104±17) 28 HRA (12-17 months: 18 HRA−, IQ 100±12, 10 HRA+, IQ 86±15)	128 electrodes	Watch social (video of woman singing or playing peek-a-boo) and non-social (moving mechanical toys) videos	↑ α coherence over the F and C areas, particularly in the LF region, regardless of video condition
Toddlers: Resting				
Buckley (2015)	87 ASD (4.4±1.3 years, NVDQ 60.3±16.8) 21 non-ASD DD (4.2±1.1 years, NVDQ 57.8±15.5) 29 TD (4.3±1.7 years, NVDQ 107.3±15.4)	22 electrodes	Eyes-open resting	no differences in coherence compared to TYP and few differences compared to DD; no differences in phase lag compared to TYP and ↓ phase lag compared to DD (across bands and distances)
Toddler Studies: Task-based				
Dominguez (2013)	72 ASD (2-4.9 years, IQ NR) 31 TD (2-5 years, IQ NR)	128 electrodes	View emotional faces (happy and fearful)	↑ coherence over P region in δ and θ and in short-range connections in L hemisphere in δ and θ, α
Boersma (2013)	12 ASD (3.35±0.8 years, IQ 85±17.2), 19 TD (3.53±1.19 years, IQ 108±12.4)	32 electrodes	Eyes-open, passively viewing pictures of cars and faces	↓ global phase lag in high α-β during both tasks, No differences in θ-low α
Toddler Studies: Sleep				
Buckley (2015)	87 ASD (4.4±1.3 years, NVDQ 60.3±16.8) 21 non-ASD DD (4.2±1.1 years, NVDQ 57.8±15.5) 29 TD (4.3±1.7 years, NVDQ 107.3±15.4)	22 electrodes	REM and SWS sleep	↑ δ, θ, α a, and β coherence compared to TD, particularly in F-P pairs, during SWS sleep and REM Few differences between ASD and DD in coherence during both REM and SWS ↓ phase lag, compared to TD (particularly in F-P pairs during SWS) and DD (both REM and SWS across bands and distances)

Main coherence findings are based on ASD compared to TD, unless otherwise specified. ASD=Autism spectrum disorder, TD=Typically developing, DD=Developmentally Delayed, HRA=High risk for autism, HRA+=High Risk for autism with later diagnosis of autism, HRA−=High Risk for autism with no later diagnosis of autism, LRC=Low risk for autism, LRC−=Low Risk for autism with no later diagnosis of autism, IQ=Intelligence Quotient, DQ=Developmental Quotient, NVIQ=Nonverbal IQ, NVDQ= Nonverbal DQ, δ=Delta, θ=Theta, α=Alpha, β=Beta, γ=Gamma, B=Bilateral, L=Left, R=Right, F=Frontal, T=Temporal, C=Central, P=Posterior (Parietal+Occipital), NR=Not Reported, All parameters in standard deviations.

Table 2.

School-Children

School-aged Child Studies: Resting				
Lushchekina (2016)	27 ASD (5.79±1.42 years, IQ NR), 24 TD (6.05±0.86 years, IQ NR)	16 electrodes	Eyes-closed	↓ δ interhemispheric coherence across F and P, ↓, θ interhemispheric coherence across F-T and P, ↓, α intra- and interhemispheric F-T coherence. ↑ inter- and intrahemispheric coherence in β and γ, primarily medium-long-range
Elhabashy (2015)	21 ASD (4-12 years, IQ NR), 21 TD (4-12 years, IQ NR)	19 electrodes	Eyes-open	↓ intrahemispheric coherence in δ, θ, and α; ↓, interhemispheric coherence in δ over C/P/O regions; ↑ interhemispheric coherence in δ band over T
Coben (2008)	20 ASD (8.9±2.3 years, IQ 93±16.8) 20 TD (9.2±1.5 years, IQ 98±15.4)	19 electrodes	Eyes-closed	δ and θ decrease long-range from F-P and globally at short-range, both intra- and interhemispherically
Clarke (2015)	20 HFA (7-12 years, IQ 91.50±14.35), 20 TD (7-12 years, IQ, 107.06±9.86)	19 electrodes	Eyes-closed	↓ α and β coherence in F short/medium inter-hemispheric coherence
Lazarev (2015)	14 ASD (6-14 years, IQ 91±22.8) 19 TD (6-16 years, normal academic achievement)	14 electrodes	Eyes-closed	No difference in inter- or intrahemispheric δ, θ, α, or β, nor in β laterality
Carson (2014)	19 HFA (9.95±1.61 years, IQ 102±17.92) 13 TD (10±1.63 years, IQ 104.15±20.69)	64 electrodes	Eyes-open, watch blank screen	↓ interhemispheric coherence in T-P and F regions in α
Sheikhani (2012)	17 ASD (9.2±1.6 years, IQ>85) 11 TD (9.5±2.8 years, IQ>85)	19 electrodes	Eyes-open	↑ γ coherence primarily between T and other brain regions; ↓, β coherence over L T-P
Machado (2015)	11 ASD (5.9±2.4 years, IQ>85) 14 TD (5.6±2.5 years, normal academic achievement)	19 electrodes	Eyes-open, fixate on green dot on screen	↑ L intrahemispheric short- range δ coherence; ↑ B intrahemispheric medium/long-range δ, β, and γ coherence and L only in α and θ ↑ interhemispheric short- and medium-range in P region in all frequency bands
School-aged Child Studies: Discriminating between Subtypes of ASD				
Duffy (2012; 2013)	430 ASD (2-12 years, IQ NR) 26 HFA (2-12 years, IQ NR) 554 TD (2-12 years, IQ NR)	32 electrodes	Eyes-open	ASD-TD comparison: ↓, short- range coherences (θ, α, β); majority of ↑ coherences found in δ and β medium/longdistance connection factors. ASD-HFA: ASD-HFA: ↑ θ in B P region & ↑ β in L F-T, ↓ β in L T-C. ASD-HFA-TD: HFA classified as ASD in an ASD vs. TD paradigm; HFA classified as distinct from ASD in an HFA vs. ASD paradigm
Peters (2013)	16 ASD (2–5 years, IQ NR), 14 ASD+TSC (1-25 years, IQ NR), 29 non-ASD+TSC (0-23 years, IQ NR), 46 TD (0-17 years, IQ NR)	128 or 19 electrodes	Eyes-open	ASD-TD & ASD/ASD+TSC- TD/non-ASD+TSC comparison: No difference in mean θ or α; ↓, long:short-range θ or α coherence
Han (2013)	17 HFA (11.7±3.1 years, IQ 106±20), 17 LFA (12.2±2.1 years, IQ 56±12)	19 electrodes	Eyes-open, focus on image of car	↑ θ coherence in LFA across short-range in F region and long-range intrahemispheric LF-LP and long-range interhemispheric RF-LP
Barttfeld (2011)	10 ASD (23.8±7.6 years, IQ 101.7±14.97) 10 TD (25.3±6.54 years, IQ NR)	128 electrodes	Eyes-closed	↑ short-range δ coherences in lateral F; ↓, medium/ long-range δ coherences in F-F and F-P connections
School-aged Child Studies: Task-based				

Lushchekina (2016)	27 ASD (5.79±1.42 years, IQ NR), 24 TD (6.05±0.86 years, IQ NR)	16 electrodes	Mental calculation task, Eyes-closed	TD show minor changes in δ between conditions: ASD show interhemispheric F-T and T-P δ ↑; TD show ↓ θ in RF-T and RF-C. ASD show ↓ θ in LF-P; Neither group shows change in α during task; Widespread long-range ↑ β & γ coherence in LF and LC during task relative to baseline in TD group: ASD show comparably minor changes in β & γ
Chan (2011)	21 ASD (5-14 years; NVIQ 101.86±16.09) 21 TD (5-14 years, NVIQ 106.0±14.59)	19 electrodes	Visual encoding object recognition task	↑ long-range coherence in θ both L intra- and interhemispheric. Significant negative correlation between long- range interhemispheric coherence and complex memory performance in ASD subjects
Jaime (2015)	16 ASD (16.2±2.29 years; NVIQ 106±13.2) 17 TD (16.5±1.94 years, NVIQ 103±16.8)	128 electrodes	Combination of Eyes-open baseline (fixate on circle image), incongruent, and congruent joint attention task	↓, α coherence in short-range bilateral intrahemispheric T-C region. No difference in β.
Lazarev (2015)	14 ASD (6-14 years, IQ 91±22.8) 19 TD (6-16 years, normal academic achievement)	14 electrodes	Intermittent photic stimulation (3-24 Hz)	↓, interhemispheric coherence in α, θ, and most prominently β; ↑ L lateralization in β
Carson (2014)	19 HFA (9.95±1.61 years, IQ 102±17.92) 13 TD (10±1.63 years, IQ 104.15±20.69)	64 electrodes	Watch video of familiar or unfamiliar person reading a story	↑ α interhemispheric coherence relative to TD between L and R T-P regions during both task conditions; ↑ α interhemispheric coherence in F regions during social tasks compared to baseline only in TD group, ASD group shows no change across conditions
Machado (2015)	11 ASD (5.86±2.44 years, IQ>85) 14 TD (5.56±2.47 years, normal academic achievement)	19 electrodes	Watch cartoons with (V-A) and without (VwA) sound	Generally ↑ across both tasks; ↓ coherence in R hemisphere during without audio condition compared to with audio, while TD show no difference between conditions; ↓ R short-range α coherence; ↑ B intrahemispheric medium/long-range δ, β, and γ coherence. No differences in α and θ; ↑ interhemispheric short- and medium-range in P region in all frequencies, group differences more prominent in V-A condition
School-aged Child Studies: Sleep				
Lázár(2010)	18 HFA (13.12±4 years, NVIQ Raw Score 51±8.8) 14 TD (14.75±3.41 years, NVIQ Raw Score 49.9±6.5)	10 electrodes	NREM	↑ coherence intrahemispherically within F region (δ, θ, α, β) and within R hemisphere(δ, α)

Main coherence findings are based on ASD compared to TD, unless otherwise specified. ASD=Autism spectrum disorder, TD=Typically developing, HFA=High-functioning autism, LFA=Low-functioning autism, TSC=Tuberous Sclerosis, IQ=lntelligence Quotient, NVIQ=Nonverbal IQ, δ=Delta, θ=Theta, α=Alpha, β=Beta, γ=Gamma, B=Bilateral, L=Left, R=Right, F=Frontal, T=Temporal, C=Central, P=Posterior (Parietal +Occipital), NR=Not Reported, All parameters in standard deviations.

Table 3.

Adults

Adult Studies: Resting				
Murias (2007)	18 ASD (22.7±4.4 years, IQ 107.3±13.96) 18 TD (24.9±6.82 years, IQ 106.1±13.56)	124 electrodes	Eyes-closed	↑ θ coherences in LF and LT regions; ↓, α coherences in F region; ↓, α coherences between F and other brain regions
Mathewson (2012)	15 ASD (18.8-51.6 years, IQ 100.9±18.6) 16 TD (22.6-47.8 years, IQ 107±11.9)	128 electrodes	Eyes-open and eyes-closed	no difference between groups in α coherences in either condition
Saunders (2016)	13 ASD (25.88±8.78 years, IQ 108±13.18) 13 TD (26.68±7.62 years, IQ 108±13.52) 11 ADHD (23.36±3.93 years, IQ 116.6±8.46) 10 Anxiety (25.82±8.50 years, IQ 116.56±8.62)	128 electrodes	Eyes-open (fixate on black cross) and eyes-closed	↑ α coherence over LC-RC region during eyes-closed; approached significance in eyes-open condition NS differences in θ between groups during eyes-closed, approached significance in intrahemispheric frontal-frontal coherence in eyes-open condition
Barttfeld (2011)	10 ASD (23.8±7.6 years, IQ 101.7±14.97) 10 TD (25.3±6.54 years, IQ NR)	128 electrodes	Eyes-closed	↑ short-range δ coherences in lateral F; ↓, long-range δ coherences in F-P and medium-range δ interhemispheric F-F connections
Tseng (2015)	10 HFA (19.6±1.96 years, VIQ 108.0±16.68 NVIQ 107±16.6) 10 TD (24.4±3.24 years, VIQ 113.8±5.79, NVIQ 117.7±12.00)	132 electrodes	Eyes-open, fixate on cross	No difference between groups in δ-θ
Adult Studies: Task-based				
Catarino (2013)	15 ASD (23–42 years, IQ 119±13) 15 TD (21-37 years IQ 119±14)	28 electrodes	Faces and chairs categorization task	↓, α and θ interhemispheric coherence across the brain, however corrected correlations support only reduced coherence in α at one long-range electrode pair (T interhemispheric) during face processing.
Tseng (2015)	10 HFA (19.6±1.96 years, VIQ 108.0±16.68 NVIQ 107±16.6) 10 TD (24.4±3.24 years, VIQ 113.8±5.79, NVIQ 117.7±12.00)	132 electrodes	Facial emotion recognition task (photographs and line drawings conditions)	↓ δ-θ in P and nearby regions in photograph task; No δ-θ differences in line task; No differences in α or β between groups in either condition
Adult Studies: Sleep				
Léveillé (2010)	9 ASD (21.1±4.0 years, IQ 101.3) 13 TD (21.5±4.3 years, IQ 115.7)	22 electrodes	REM	↑ short- and long-range δ and θ coherence between L O-F and L O-P; ↓, θ short-range coherence in RF lobe; No significant interhemispheric differences or differences between groups based on α or β

Main coherence findings are based on ASD compared to TD, unless otherwise specified. ASD=Autism spectrum disorder, TD=Typically developing, HFA=High-functioning autism, LFA=Low-functioning autism, IQ=Intelligence Quotient, VIQ=Verbal IQ, NVIQ=Nonverbal IQ, δ=Delta, θ=Theta, α=Alpha, β=Beta, γ=Gamma, B=Bilateral, L=Left, R=Right, F=Frontal, T=Temporal, C=Central, P=Posterior (Parietal +OccipitaI), NR=Not Reported, All parameters in standard deviations.