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REVIEW

Brain connectivity in autism spectrum disorder

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Purpose of review
Many studies have reported that individuals with autism spectrum disorder (ASD) have different brain connectivity patterns compared with typically developing individuals. However, the results of more recent studies do not unanimously support the traditional view in which individuals with ASD have lower connectivity between distant brain regions and increased connectivity within local brain regions. In this review, we discuss different methods for measuring brain connectivity and how the use of different metrics may contribute to the lack of convergence of investigations of connectivity in ASD.

Recent findings
The discrepancy in brain connectivity results across studies may be due to important methodological factors, such as the connectivity measure applied, the age of patients studied, the brain region(s) examined, and the time interval and frequency band(s) in which connectivity was analyzed.

Summary
We conclude that more sophisticated electroencephalography analytic approaches should be utilized to more accurately infer causation and directionality of information transfer between brain regions, which may show dynamic changes of functional connectivity in the brain. Moreover, further investigations of connectivity with respect to behavior and clinical phenotype are needed to probe underlying brain networks implicated in core deficits of ASD.

Keywords
autism spectrum disorder, brain connectivity, graph theory

INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental disorder featuring deficits in social communication and language acquisition, as well as restricted interests and repetitive behaviors [1]. Much research has attempted to understand the neural underpinnings of ASD by the identification of biomarkers (i.e., objectively measured biological markers that indicate risk for autism [2]) that relate to its core deficits. Measures of brain connectivity are promising ASD biomarkers [3], yet a plethora of methods for extracting and delineating brain networks from recordings of functional brain activity exist.

Why connectivity? Brain connectivity measures infer which brain regions are physically or functionally connected to form brain networks that subserve either cognitive/behavioral task performance or the brain's resting/default state [4]. Although hundreds of genes convey risk for ASD [5], many of these genes notably converge on synaptic pathways [6–9,10▪,11]. On a microscopic level, this convergence underscores synaptic connectivity as a potential neurobiological mechanism of ASD; however, on a macroscopic level, it points towards axonal or functional connectivity patterns as a plausible biomarker for ASD. The number of publications with the keywords 'brain connectivity' has grown exponentially over the past 30 years (1985–2015, Fig. 1) [12], whereas the number of publications for 'brain imaging' has grown almost linearly over the same period. The exponential explosion in brain connectivity publications underscores the importance of this new field in understanding the brain as an integrated system.

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KEY POINTS

- Individuals with ASD have different brain connectivity patterns compared with typically developing individuals.
- There are discrepancies in brain connectivity results across studies that may be due to important methodological factors, such as the type of connectivity measure used, the age of patients studied, the brain region(s) examined, and the time interval and frequency band(s) in which connectivity was analyzed.
- We recommend that future studies compare cross-correlation or coherence to sophisticated measures of connectivity to determine whether the results converge.

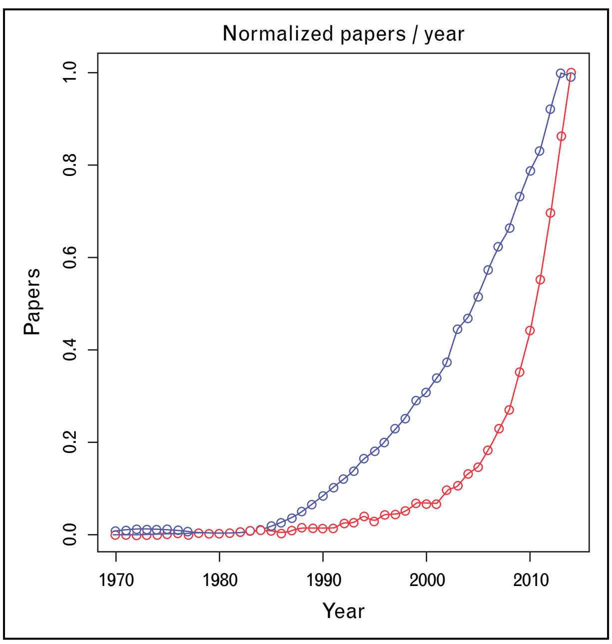

FIGURE 1. Exponential growth of Scopus hits for brain connectivity. Comparison of hits for 'brain connectivity' (gray) and 'brain imaging' (black) by year (abscissa) for 1970–2014 from academic search engine Scopus (date of search 11/06/15). Number of papers (ordinate) is normalized showing both traces on the same scale, thus emphasizing style of growth rather than raw number of papers. Both fields of research show approximately constant publication output until 1985, after which publications for brain connectivity show exponential growth compared with almost linear growth for brain imaging publications. One can attribute the exponential growth in brain connectivity publications as a push against the functional segregation approach of traditional brain imaging, replacing such approaches with an integrated understanding of the brain as a distributed network.

Published studies on brain connectivity in ASD yield inconsistent results, not only because of the use of different imaging modalities and techniques for (re)constructing brain networks but also because of the challenges inherent in the selection of appropriate methods for delineating brain networks to test a given hypothesis. Additionally, choosing a proper neuroimaging technique that suits a clinical cohort may avoid detrimental filtration of the sample, that is, omitting low-functioning individuals with severe cognitive impairments who yield noisy data or outliers for a given brain connectivity technique. For example, in cohorts with ASD, motor stereotypies and cognitive level must be taken into account when considering imaging techniques that are sensitive to motion artifacts or require the participant to lie motionless for a long period of time.

This following is not meant to be an exhaustive review on the literature; rather, we provide a critical review of the specific methods used to capture brain connectivity, methods that quantify the delicate balance between functional segregation and integration of neuronal circuits. We discuss how different brain connectivity approaches can lead to divergent results – even when applied to the same data. We conclude with general recommendations for connectivity measures that are most promising – in terms of feasibility, robustness, and sensitivity – for studying individuals with ASD.

OVERVIEW OF BRAIN CONNECTIVITY APPROACHES

Brain connectivity approaches can be categorized as structural or functional. Within functional connectivity, methods that infer causality and directionality of information transfer are considered effective connectivity.

(1) In structural brain connectivity approaches, regions of the brain are considered to be connected if there are anatomical (white matter) connections between distinct brain regions. Structural connectivity may vary across development and can be used as an index of brain plasticity.
(2) In functional connectivity approaches, the interdependency among activities of different brain areas is measured using statistical methods, such as correlation, covariance, phase coherence, and phase locking. These methods characterize the strength of the relationship (e.g., correlation) but not the direction of information flow or causality. Functional connectivity can illustrate the integration and segregation of brain networks in much finer

temporal resolution than structural connectivity methods.

(3) Effective connectivity examines interactions – inferred to be casual – between nodes of brain networks while showing directionality of information transfer. Common approaches to measure effective connectivity are Granger causality and its derivatives, as well as phase slope index.

Diffusion magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI) represent methods for mapping structural connectivity that characterize anatomical fibers within brain networks. Both methods are sensitive to the diffusion of water molecules along axon fibers [13]. Delineation of functional brain networks is arguably less straightforward than that of structural brain networks, as statistical dependencies are far less concrete than anatomical fibers. Functional networks may be obtained by utilizing hemodynamic imaging techniques such as functional MRI (fMRI) or other measures of brain activity such as electroencephalography (EEG) and magnetoencephalography (MEG). EEG and MEG signals reflect approximate measures of postsynaptic pyramidal cell activity with millisecond temporal resolution ideal for describing brain dynamics. However, the spatial resolution of both methods is poor compared with MRI, even though this limitation can be partially compensated using advanced signal processing analytic techniques. The spatial resolution of MEG exceeds that of EEG owing to the fact that magnetic fields are less distorted by the skull and scalp than electric fields [14].

BRAIN IMAGING TECHNIQUES FOR CONNECTIVITY ANALYSIS

Choice of an appropriate noninvasive in-vivo neuroimaging technique for delineating brain networks depends on the clinical population of interest and the type of connectivity to be analyzed. In the context of neurodevelopmental disorders such as ASD, the developmental level of the individual is also an important consideration.

Although many studies use fMRI to study task-related and resting state functional connectivity, EEG/MEG are preferable for describing functional and effective connectivity due to their rich temporal dynamics. Both fMRI [15] and MEG [16] are highly sensitive to motion artifacts, making both techniques largely impractical for young children and/or children with repetitive, stereotyped behaviors. Other MRI techniques used for mapping structural connectivity, such as diffusion MRI and DTI, share this limitation.

CHARACTERIZING THE BRAIN NETWORK'S NODES AND EDGES

One of the most commonly used approaches for characterizing a network and its components is graph theory. In the parlance of graph theory, brain regions, or recording sensors (e.g., voxels or electrodes) are treated as the network's nodes and the connections between those nodes are the edges of the network. The most straightforward approach to choosing network nodes is to use sensor location as nodes. However, signals in sensor space may exhibit spurious functional and effective connectivity due to volume conduction. Volume conduction is a phenomenon whereby electrical signals are spread out widely as they travel through brain tissue and spatially smeared by the skull, like a narrow point of light viewed through frosted glass. As a result of volume conduction, spatial relationships measured from the scalp may not represent true neural connectivity but rather artifacts of volume conduction. Spatial filters [17] such as current source density – the second spatial derivative (Laplacian transformation) of sensor-space recordings [18▪▪] – have been introduced by researchers to deal with the volume conductance issue (Fig. 2). Alternatively, by using an inverse model approach such as standardized low resolution brain electromagnetic tomography, beamforming, and independent components analysis for dipole localization, spatial locations of 'cortical activity' sources can be estimated and considered as the nodes of the network [19].

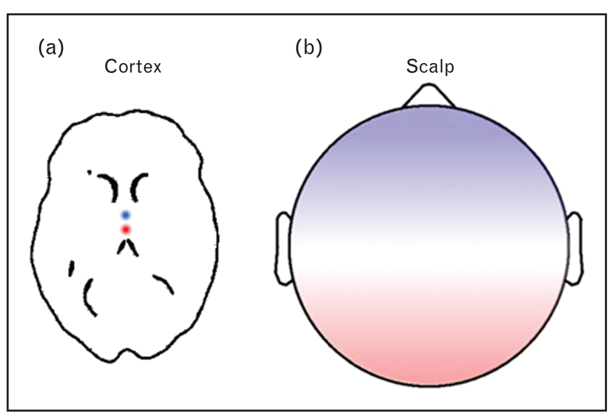

FIGURE 2. Example of volume conductance of a dipolar cortical source. A neural generator modeled as a dipolar source in the cortex (a) and its back projection onto the scalp (b). Because of the volume conductance issue, one may incorrectly conclude that the polarity in the frontal and occipital regions in the scalp map is from different dipolar sources if only the scalp potential map is being used.

Choosing network edges – measures of connectivity

The existence or strength of a network's edges is an important factor when studying brain connectivity. Here, we discuss different methods to quantify edges commonly used in functional and effective connectivity approaches.

(1) Time-lag measures: The simplest time-lagged measure is cross-correlation, which is the degree of similarity between activation of one brain region with a shifted (time-lagged) activation of another region. This measure can estimate the neural processing delay between two regions. For example, when measuring cross-correlation between brain areas A and B, if the time lag is 500 ms, the cross correlation will represent the degree of similarity between activity in area A at 0 ms and activity in area B 500 ms later.
(2) Coherence: This is a measure of synchronization between two signals of the same frequency, and it quantifies the extent to which they share a constant oscillating frequency and phase difference. For instance, two signals that are oscillating at the same frequency f_0 may have a phase difference value ranging anywhere from zero (in-phase) to 180° (antiphase). In this case, they have a magnitude coherence value of 1 because they share the same oscillation frequency f_0; however, their phase coherence value may vary from 0 to 1 for antiphase to in-phase, respectively (Fig. 3). In theory, neuronal ensembles oscillate coherently to share information [20].
(3) Causality: Although true causal relationships cannot be extracted from EEG or MEG recordings without applying electrical or magnetic stimulation [4], Granger causality is a weaker notion of causality: at frequency f_0, if past values of one brain recording 'A' help to predict future values of brain recording 'B' beyond what can be inferred from past values of recording B alone, then (according to Granger causality), 'A' has a Granger causal effect on 'B'. Although not true causality, Granger causality is useful for inferring directionality of neural information transfer [18▪▪].

The methods mentioned above can be applied to data from many neuroimaging modalities including fMRI, MEG, and EEG. However, it should be noted that the accuracy of determining coherence or Granger causality at frequency f_0 depends on the length of data. For example, to investigate low frequencies, longer recording time is required. Therefore, choice of frequency band plays a critical role in the interpretation of connectivity data, as will be discussed in later sections.

Graph theory measures

How does one summarize connectivity in a network with hundreds to thousands of edges? Edges weaker than a certain threshold strength are often eliminated to create a pruned network/graph. Next, the architecture of the network is described using graph theory measures, several of which are described below and illustrated in Fig. 4.

Small worldness

This refers to the property by which any two nodes in a network are connected by a small number of steps or 'hops' (Fig. 4). For instance, consider a global network of airports where any given city can be reached by three or fewer connecting flights. Such a network has small-world properties. As a

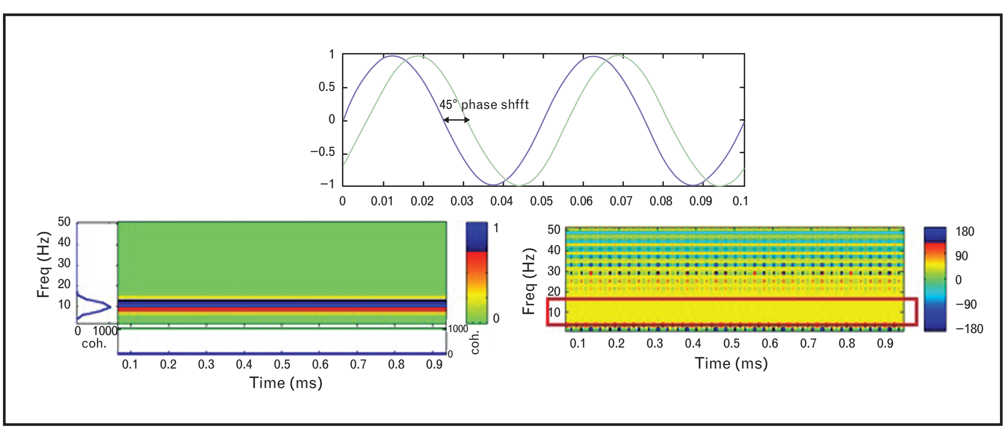

FIGURE 3. Magnitude vs phase coherence. The magnitude (or power) value (bottom left) and phase value (bottom right) of coherence for two artificial signals (top) $x(t) = \sin(\Omega t)$ and $y(t) = \sin(\Omega t + 45^\circ)$ where $\Omega = 2\pi f$ and $f = 10$ Hz. The peak can be seen at 10 Hz for the magnitude values and at 45° for phase value of coherence.

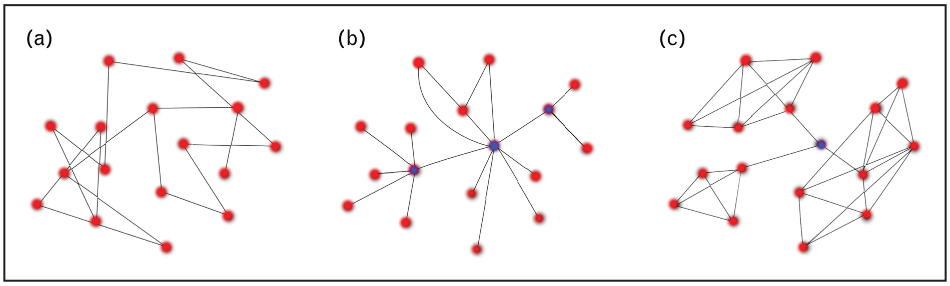

FIGURE 4. Examples of three network architectures described by graph theory. (a) An inefficient network with large path length and small clustering coefficient. Note that a metaphorical walk from one arbitrary node to another will take many more steps than the network in (b) owing to the lack of hub nodes in (a), that is, nodes connected to many neighbors that facilitate quick trips across the network. (b) A small-world network with small path length and small clustering coefficient. Hub nodes (dark gray) greatly reduce the path length and increase the efficiency of the network, such that all nodes are connected by a small number of steps. (c) A highly modular small-world network with small path length and large clustering coefficient. Like (b), this network is highly efficient, but also more integrated owing to the larger proportion of realized edges (i.e., higher clustering coefficient) creating densely interconnected modules or subnetworks linked by a central hub node (dark gray).

result, within the brain's small-world network, the information flow is highly efficient with minimal serial-synaptic conduction delay. Small-world networks are also more robust to deletion of random nodes or damage to the network.

Path length

The efficiency of a network is related to the path length, or the average number of edges between any two nodes, which is minimal for small-world networks (Fig. 4). For instance, social networks are said to have a path length of 6, meaning any two people in the world know each other through six series of acquaintances.

Modularity

Also relevant to efficiency and small-worldness, this term describes the tendency for nodes to form hierarchical and recursive clusters within clusters (Fig. 4). Closely related is the clustering coefficient, a measure of local interconnectedness or 'cliquishness,' which reflects the degree to which clustering occurs around an average node.

BRAIN CONNECTIVITY FINDINGS IN AUTISM SPECTRUM DISORDERS

Considering the growing interest in brain connectivity in ASD (Fig. 1), a reasonable skeptic might ask if many of these studies are largely the product of a bandwagon effect. However, given the growing insights gained from autism genetics, with many pathways converging on synaptic function and structure, efforts to characterize connectivity in ASD hold biological validity. ASD can be better understood through the lens of network science, which may elucidate the role of genetic factors, clinical characteristics, and phenotypic heterogeneity.

Brain connectivity and genetics in autism spectrum disorder

Many potential autism risk genes regulate synaptic connectivity, with mutations leading to microscopic neuronal dysconnectivity [6–9,10▪,11]. The concordance rate for ASD between monozygotic twins is 77% for male twins and 50% for female twins [21], suggesting genetic risk patterns with strong but not absolute penetrance. Intermediate phenotypes of ASD should show similar levels of heritability and genetic influence. An analysis of small-world resting-state EEG functional networks from twins and siblings computed with synchronization likelihood (a method which can deal with nonstationary dynamics of EEG data) has found that 37–62% of differences in path length are heritable [19]. Clustering coefficient showed similar genetic influence, with 46–89% of individual differences found to be heritable. The high heritability of these small-world parameters opens them to future consideration as ASD or ASD-risk endophenotypes. However, it should also be noted that many inherited and *de novo* ASD risk genes converge on synapses [5,9,22–25]. Thus, heritable brain networks – while promising as risk biomarkers – are incomplete endophenotypes of ASD risk and, moreover, agnostic with respect to specific genetic factors.

Long-range vs short-range connectivity in adults with autism spectrum disorder

Results from studies of connectivity in ASD are variable, largely due to discrepancies in the

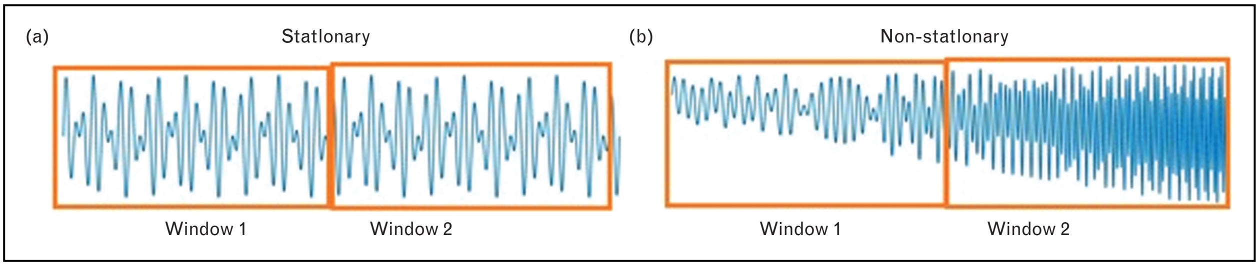

FIGURE 5. Stationarity vs nonstationary EEG signals. A stationary process is one whose statistical properties (such as its average, standard deviation, etc.) do not change over different time windows. For example, in panel (a), the average oscillation frequency and standard deviation values are the same for both time windows 1 and 2. However, it is obvious these values are not the same for panel (b) in time windows 1 and 2.

experiment and its cognitive or behavioral components, the type of functional brain data (e.g., EEG, MEG, or fMRI), the age of patients examined, the anatomical region(s) examined, and the time interval and frequency band(s) in which connectivity was analyzed. Considerable focus has been placed on long vs short-range connectivity patterns. Several fMRI studies support the prevailing notion that individuals with ASD have lower connectivity (or hypoconnectivity) between distant brain regions (such as the frontal and parietal lobes) and increased connectivity (or hyperconnectivity) between local brain regions (such as within the frontal lobe) [26,27▪▪,28▪▪]. Contrary to these findings, recent studies of neural connectivity with higher temporal resolution using EEG/MEG do not support this notion. For example, Khan *et al.* [29] examined event-related MEG recordings from male young adults and adolescents with ASD and an age-matched control group of typically developing (TD) individuals during a face-viewing task. Source-localized signals in fusiform face area (FFA) were used as a seed-region, with local connectivity measured by phase-amplitude coupling – the strength of the relationship between the phase of oscillations in the α band (i.e., 8–12 Hz) and the amplitude of oscillations in the γ band (above 40 Hz) – and long-range connectivity measured as coherence between FFA and other regions. Contrary to prior findings [26,27▪▪,28▪▪], Khan *et al.* [29] found significantly reduced local and long-range connectivity in cohort with ASD compared with controls. For long-range connectivity, this difference was significant in α band coherence. Not only did participants with ASD feature hypoconnectivity rather than hyperconnectivity at the local scale, but moreover, reduced local connectivity correlated with the social component of the autism diagnostic observation schedule (ADOS) in this cohort.

In addition to α band coherence, differences in functional connectivity between ASD and TD controls have been found in other frequency bands. For example, a study by Barttfeld *et al.* [30] supported the traditional view of local hyperconnectivity in ASD during resting-state EEG recordings from high functioning adults with ASD. Specifically, they found enhanced local, lateral frontal connections accompanied by reduced long-range fronto-frontal and fronto-occipital connections as measured with δ (0.5–3.5 Hz) band synchronization likelihood. Furthermore, Barttfeld *et al.* [30] demonstrated that EEG networks from cohort with ASD featured lower clustering coefficient and higher path length compared with an age and gender-matched TD cohort. Although this study only examined the δ band, the functional and/or mechanistic significance of δ oscillations in ASD remains unclear *a priori*, though δ band coherence abnormalities have also been found in REM sleep EEG recordings from young adults with ASD [31].

It is important to note that analyzing low frequency oscillations – such as δ oscillations or default mode network – requires longer temporal segments of EEG recordings (at least twice the duration of the period of the slowest oscillation). This caveat alone may lead to inaccuracy of connectivity estimation due to the nonstationarity, that is, the fact that statistical properties of the signal (such as its mean and variance) change over the temporal interval of one segment (Fig. 5).

Thus, studying connectivity mediated by relatively fast oscillations may be more accurate. For example, α oscillations, which are associated with restful focus and may relate to the ability of an individual to concentrate his or her focus while habituating to distracting stimuli [32,33], may be an ideal frequency band for computing functional connectivity. It has been shown that the coherence at α oscillations measured over right centro-parietal regions is inversely related to the tendency for adults with ASD to notice and process details [34]. Furthermore, in resting-state eyes-closed recordings, adults with ASD also have globally reduced α coherence in frontal networks compared with TD adults [35]. Interestingly, the same study showed that the coherence of θ oscillations –which play a similar role as α in executive function and working memory [33,36] – are locally enhanced in left frontal and temporal regions in adults with ASD [35]. Thus, proper frequency ranges should be chosen while studying short or long-range brain connectivity patterns.

Relating connectivity to clinical phenotypes and circuit dysfunction

Ultimately, future work along these lines relating connectivity differences to clinical phenotypes rather than broad diagnosis may be beneficial for stratifying this very heterogeneous disorder into more homogeneous subpopulations. Very few studies have correlated EEG or MEG connectivity metrics with behavioral symptoms or clinical phenotypes in ASD. In addition to the previously mentioned Khan *et al.* [29] study, which correlated ADOS scores with local connectivity from a face processing task, Grice *et al.* [37] used evoked (for early sensory processing and local feature processing) and induced (for later configurational feature and top-down processing) γ band coherence from EEG recording in adults with ASD to compare frontal connectivity in a face processing paradigm using upright faces and inverted faces as stimuli. No significant change in induced/evoked γ band coherence between frontal electrodes was reported for cohort with ASD, whereas TD adults showed greater induced γ coherence for upright faces. In addition, they found no modulation of the γ response compared with controls when the faces were inverted. This lack of sensitivity to the face inversion in the ASD group may represent deficits in the integration and information binding of local features during face processing. Similar work in the future may be beneficial for probing neural circuits implicated in core behaviors implicated in ASD. Therefore, choice of experimental task, latency of specific sensory/cognitive processes, frequencies of interest, and network features (nodes and edges) are important factors in quantifying and interpreting brain connectivity patterns and, consequently, classifying ASD into biologically relevant subgroups.

Connectivity as an autism spectrum disorder risk marker in early and middle development stages

Brain connectivity may have potential as a risk marker for ASD in early and development stages. Of paramount interest to clinicians are connectivity measures that can identify ASD risk early in development prior to diagnosis or inform prognosis of children with ASD. Given our understanding of the convergence of genetic risk factors on synaptic pathways, one could postulate that aberrant neuronal connectivity should be able to be quantified in early infancy. Recently, Orekhova *et al.* [38▪▪] analyzed functional brain connectivity by phase lag index in 14-month-old infants at high and low risk for ASD using EEG while infants attended to videos. At 36 months, the high-risk infants were assessed for symptoms of ASD. High-risk infants who were later diagnosed with ASD featured higher functional connectivity compared with both low-risk infants and high-risk infants who did not meet criteria for ASD. The degree of hyperconnectivity in frontal regions at 14 months strongly correlated with the severity of restricted and repetitive behaviors in participants later diagnosed with ASD at 3 years. Another large study of sleep EEG recorded from 106 children with ASD and 70 TD controls ages 2–6 years identified distinct differences in coherence across different frequency bands in slow wave sleep [39▪].

A smaller study of 20 older children with ASD (ages 6–11 years) and 20 controls matched for age, IQ, and gender [40] identified distinct patterns of EEG coherence across multiple frequency bands in eyes-closed resting recordings, both within and between hemispheres. Relative to controls, children with ASD exhibited a pattern of hypoconnectivity, which included decreased intrahemispheric δ and θ coherences across short to long interelectrode distances. Additionally, δ and θ coherences in the ASD group were low across the frontal region, interhemispherically.

However, these studies did not explicitly address concerns regarding multiple comparisons, spurious connectivity due to volume conductance, or nonstationarity in long EEG recording segments. Collectively, these studies suggest that brain connectivity may index risk for ASD diagnosis or altered developmental trajectory. However, careful consideration should be given to the selection of the appropriate brain connectivity method and important methodological factors that may confound results.

CONCLUSION

Although many studies have identified differences in functional connectivity with EEG/MEG between individuals with ASD and TD individuals, more studies that investigate and identify such differences in early development as markers of ASD risk are greatly needed. There are few longitudinal studies

Table 1. Summary of functional and effective connectivity measures

Methods	Pros	Cons	Recommended applications	Relevant findings
Cross-correlation	Easy to compute	Only sensitive to linear relationships	Exploratory analysis	Several fMRI studies support the notion that individuals with ASD have lower connectivity between distal brain regions and increased connectivity within proximal brain regions (such as within the frontal lobe) [26,27■■,28■■]
	Time-lags account for volume conduction and neural delay	Difficult to choose appropriate lag	fMRI recordings from young children and/or low-functioning individuals with ASD	
		Does not account for nonstationarity in neuroimaging data		
Coherence	Easy to compute	Only sensitive to linear relationships	Short, approximately stationary segments of EEG recordings	Many findings in EEG and MEG, including relevance to detail processing [34], face processing [29,37], sleep [31,39■], and resting-state [40] connectivity in ASD
	Theoretical basis in neural information transfer [20]	Sensitive to volume conduction	Tests hypotheses of neural communication, between spatially distant regions in children or adults (e.g., lesser communication between frontal and temporal circuits in ASD)	
	Complimentary to Fourier analysis	Works best with signals of narrow bandwidth (e.g., δ, θ, or α oscillations)		
		Nonstationarity limitation for lower frequencies (such as δ) because it needs large data segment (approximately 3 s)		
		Correlational, not causal		
GC and DTF methods	Infers causality	Accuracy of these methods depends on data segment length, model order selection and windowing	Best used in conjunction with source-localization to test circuit-specific hypotheses (e.g., influence of frontal cortex over language areas in ASD)	Replicates findings from structural brain networks in ASD better than coherence [18■■]
	Infers directionality of information transfer	Computationally intensive		87.5% machine learning classification in small sample of young adults with and without ASD [46]
SL	Accounts for nonstationarity	Computationally intensive	Appropriate for long recordings of clean EEG/MEG data from adults, high functioning individuals with ASD	Small-world EEG networks computed from SL are heritable [19]
	Measures nonlinear relationships	Requires long, continuous segments of EEG/MEG recordings; thus low temporal resolution		Long-range hypo-connectivity and short-range hyperconnectivity in resting-state δ band [30]

PAC	Allow measurements of cross-frequency connectivity	Difficult to interpret intraregional connectivity	Tests hypothesis that one region regulates the excitability of another	Reductions of α-γ PAC in FFA of men with ASD during face-processing task correlate with ADOS scores [29]
	Allows measurements of connectivity within a single node	Fundamentally different from undirected measures of connectivity within the same frequency band	Tests hypothesis of intraregional connectivity	
	Directed measure (e.g., thalamic α modulates cortical γ)			
PLI	The PLI is an index of the asymmetry in the distribution of phase differences calculated from the instantaneous phases of two time-series [47]	Sensitive to noisy data and phase estimation method	For EEG it can be used to find bridges between electrodes as well as connectivity between channel pairs	Early hyperconnectivity in the α frequency range has been observed using PLI which can be an important feature of the ASD neurophysiological phenotype [38■■]
	Can differentiate channel pairs with coupling (PLI $>$ 0) and without coupling (PLI $\sim$ 0)	Nonstationarity issue for large data segments		
	Less affected by the influence of common sources and active reference electrode [48]	Not many research studies have been done by implementing this method		
		Sensitive to new data cleaning approaches using blind source separation methods such as independent component analysis		

ADOS, autism diagnostic observation schedule; ASD, autism spectrum disorder; DTF, directed transfer function; EEG, electroencephalography; FFA, fusiform face area; fMRI, functional MRI; MEG, magnetoencephalography; PAC, phase-amplitude coupling; PLI, phase lag index; SL, synchronization likelihood.

of EEG/MEG connectivity in infants or young children with ASD. Moreover, further investigations of connectivity with respect to behavior and clinical phenotype are needed to probe underlying brain networks implicated in core deficits of ASD. Considering that the theoretical basis for studying connectivity in ASD is rooted in ASD risk genes pointing towards synaptic dysfunction [6–9,10▪,11], we recommend investigations of EEG functional connectivity in relation to single nucleotide polymorphisms, copy number variants, or other genotypic measures.

The vast majority of studies reviewed here have relied on coherence to measure EEG functional connectivity. Coherence is a linear measure of connectivity that is based on similarity of activations in different regions while not taking into account nonstationarity or directionality of information transfer. Additionally, volume conductance, especially between spatially adjacent recording electrodes, may lead to spurious connectivity and misinterpretation of results. For these reasons, we recommend that future studies compare cross-correlation or coherence to more sophisticated measures of connectivity, such as synchronization likelihood, which takes into account nonstationarity [41–43], or effective connectivity measures such as Granger causality [44,45], which infers causation and directionality of information transfer. In addition, the above methods can be applied to data obtained from source localization methods rather than channel space data to eliminate the volume conductance problem [19]. In Table 1, we summarize and compare some frequently used functional/effective connectivity methods.

Finally, dynamic changes in functional connectivity patterns have yet to be deeply investigated. The tendency of the brain to become ‘stuck’ (vs flexibly adaptive) in a redundant pattern of functional connectivity may relate to motor and cognitive systems [49] in ASD, which are also ‘stuck’ in a series of repetitive behaviors or restricted interests, respectively. In this way, cortical and subcortical dynamics of coordinated activity lead to generation of inflexible brain connectivity patterns which may relate to core deficits of ASD such as repetitive behaviors [50]. In conclusion, cutting-edge methodologies sensitive to nonlinear and/or causal relationships drawn from multiple recording modalities may be fruitful for discovering risk and outcome markers of ASD.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
▪ of special interest
▪▪ of outstanding interest

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-5®). American Psychiatric Pub; 2013.
2. Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Ther 2001; 69:89–95.
3. Jeste SS, Frohlich J, Loo SK. Electrophysiological biomarkers of diagnosis and outcome in neurodevelopmental disorders. Curr Opin Neurol 2015; 28:110–116.
4. Sporns O. Networks of the brain. MIT Press; 2011.
5. Iossifov I, O’Roak BJ, Sanders SJ, *et al.* The contribution of de novo coding mutations to autism spectrum disorder. Nature 2014; 515:216–221.
6. Durand CM, Betancur C, Boeckers TM, *et al.* Mutations in the gene encoding the synaptic scaffolding protein SHANK3 are associated with autism spectrum disorders. Nat Genet 2007; 39:25–27.
7. Guilmatre A, Dubourg C, Mosca A-L, *et al.* Recurrent rearrangements in synaptic and neurodevelopmental genes and shared biologic pathways in schizophrenia, autism, and mental retardation. Arch Gen Psychiatry 2009; 66:947–956.
8. Berkel S, Marshall CR, Weiss B, *et al.* Mutations in the SHANK2 synaptic scaffolding gene in autism spectrum disorder and mental retardation. Nat Genet 2010; 42:489–491.
9. Gilman SR, Iossifov I, Levy D, *et al.* Rare de novo variants associated with autism implicate a large functional network of genes involved in formation and function of synapses. Neuron 2011; 70:898–907.
10. ▪ Chen JA, Peñagarikano O, Belgard TG, *et al.* The emerging picture of autism spectrum disorder: genetics and pathology. Annu Rev Pathol 2015; 10:111–144.
The study points to etiological mechanisms in ASD.
11. Ebrahimi-Fakhari D, Sahin M. Autism and the synapse: emerging mechanisms and mechanism-based therapies. Curr Opinion Neurol 2015; 28:91–102.
12. Scopus search query ‘‘brain connectivity’’. http://tinyurl.com/zk4hbjc [accessed 9 September 2015]; search query ‘‘brain imaging’’ http://tinyurl.com/jcfvtqy [accessed 9 September 2015]. Elsevier; 2015.
13. Le Bihan D, Mangin JF, Poupon C, *et al.* Diffusion tensor imaging: concepts and applications. J Magn Reson Imaging 2001; 13:534–546.
14. Okada YC, Lahteenmäki A, Xu C. Experimental analysis of distortion of magnetoencephalography signals by the skull. Clin Neurophysiol 1999; 110: 230–238.
15. Byars AW, Holland SK, Strawsburg RH, *et al.* Practical aspects of conducting large-scale functional magnetic resonance imaging studies in children. J Child Neurol 2002; 17:885–889.
16. Marinkovic K, Cox B, Reid K, Halgren E. Head position in the MEG helmet affects the sensitivity to anterior sources. Neurol Clin Neurophysiol 2004; 2004:30.
17. Srinivasan R, Winter WR, Ding J, Nunez PL. EEG and MEG coherence: measures of functional connectivity at distinct spatial scales of neocortical dynamics. J Neurosci Methods 2007; 166:41–52.
18. ▪▪ Coben R, Mohammad-Rezazadeh I, Cannon RL. Using quantitative and analytic EEG methods in the understanding of connectivity in autism spectrum disorders: a theory of mixed over-and under-connectivity. Front Hum Neurosci 2014; 8:45.
The study compares the findings from MR-DTI, pairwise coherence, and Grancer causality using electroencehalography data on a patient with ASD.
19. Smit DJ, Stam CJ, Posthuma D, *et al.* Heritability of ‘small-world’ networks in the brain: a graph theoretical analysis of resting-state EEG functional connectivity. Hum Brain Mapp 2008; 29:1368–1378.
20. Fries P. A mechanism for cognitive dynamics: neuronal communication through neuronal coherence. Trends Cogn Sci 2005; 9:474–480.
21. Hallmayer J, Cleveland S, Torres A, *et al.* Genetic heritability and shared environmental factors among twin pairs with autism. Arch Gen Psychiatry 2011; 68:1095–1102.
22. Sebat J, Lakshmi B, Malhotra D, *et al.* Strong association of de novo copy number mutations with autism. Science 2007; 316:445–449.
23. Neale BM, Kou Y, Liu L, *et al.* Patterns and rates of exonic de novo mutations in autism spectrum disorders. Nature 2012; 485:242–245.

24. O'Roak BJ, Vives L, Girirajan S, *et al.* Sporadic autism exomes reveal a highly interconnected protein network of de novo mutations. Nature 2012; 485: 246–250.
25. Sanders SJ, Murtha MT, Gupta AR, *et al.* De novo mutations revealed by whole-exome sequencing are strongly associated with autism. Nature 2012; 485:237–241.
26. Vissers ME, Cohen MX, Geurts HM. Brain connectivity and high functioning autism: a promising path of research that needs refined models, methodological convergence, and stronger behavioral links. Neurosci Biobehav Rev 2012; 36:604–625.
27. Maximo JO, Cadena EJ, Kana RK. The implications of brain connectivity in the ■■ neuropsychology of autism. Neuropsychol Rev 2014; 24:16–31.

The study shows how a multimodal brain connectivity approach may help to characterize the complex neurobiology of autism and lead to identification of biomarkers for autism.

28. Rane P, Cochran D, Hodge SM, *et al.* Connectivity in autism: a review of MRI ■■ connectivity studies. Harv Rev Psychiatry 2015; 23:223–244.

Very insightful review of the application of MRI in brain connectivity and autism.

29. Khan S, Gramfort A, Shetty NR, *et al.* Local and long-range functional connectivity is reduced in concert in autism spectrum disorders. Proc Natl Acad Sci 2013; 110:3107–3112.
30. Barttfeld P, Wicker B, Cukier S, *et al.* 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; 49:254–263.
31. Léveillé C, Barbeau EB, Bolduc C, *et al.* Enhanced connectivity between visual cortex and other regions of the brain in autism: a REM sleep EEG coherence study. Autism Res 2010; 3:280–285.
32. Klimesch W, Sauseng P, Hanslmayr S. EEG alpha oscillations: the inhibition-timing hypothesis. Brain Res Rev 2007; 53:63–88.
33. Sauseng P, Klimesch W, Schabus M, Doppelmayr M. Fronto-parietal EEG coherence in theta and upper alpha reflect central executive functions of working memory. Int J Psychophysiol 2005; 57:97–103.
34. Mathewson KJ, Jetha MK, Drmic IE, *et al.* Regional EEG alpha power, coherence, and behavioral symptomatology in autism spectrum disorder. Clin Neurophysiol 2012; 123:1798–1809.
35. Murias M, Webb SJ, Greenson J, Dawson G. Resting state cortical connectivity reflected in EEG coherence in individuals with autism. Biol Psychiatry 2007; 62:270–273.
36. Schack B, Klimesch W, Sauseng P. Phase synchronization between theta and upper alpha oscillations in a working memory task. Int J Psychophysiol 2005; 57:105–114.
37. Grice SJ, Spratling MW, Karmiloff-Smith A, *et al.* Disordered visual processing and oscillatory brain activity in autism and Williams syndrome. Neuroreport 2001; 12:2697–2700.
38. Orekhova EV, Elsabbagh M, Jones E, *et al.* EEG hyper-connectivity in ■■ high-risk infants is associated with later autism. J Neurodev Disord 2014; 6:40.

In this study, functional brain connectivity in 14-month-old infants at high and low familial risk for ASD was analyzed using electroencephalography. The results show hyperconnectivity patterns in the α frequency range which can be an important feature of ASD phenotype.

39. Buckley AW, Scott R, Tyler A, *et al.* State-dependent differences in functional ■ connectivity in young children with autism spectrum disorder. EBioMedicine 2015; 2:1905–1915.

In this study, the importance of brain states (during sleep) when analyzing brain connectivity as a potential biomaker is investigated.

40. Coben R, Clarke AR, Hudspeth W, Barry RJ. EEG power and coherence in autistic spectrum disorder. Clin Neurophysiol 2008; 119: 1002–1009.
41. Stam C, Van Dijk B. Synchronization likelihood: an unbiased measure of generalized synchronization in multivariate data sets. Phys D Nonlinear Phenom 2002; 163:236–251.
42. Stam CJ. Functional connectivity patterns of human magnetoencephalographic recordings: a 'small-world' network? Neurosci Lett 2004; 355:25–28.
43. Montez T, Linkenkaer-Hansen K, Van Dijk B, Stam C. Synchronization likelihood with explicit time-frequency priors. Neuroimage 2006; 33:1117–1125.
44. Granger CW. Some recent development in a concept of causality. J Econom 1988; 39:199–211.
45. Blinowska KJ, Kuś R, Kamiński M. Granger causality and information flow in multivariate processes. Physical Rev E Stat Nonlin Soft Matter Phys 2004; 70:050902.
46. Pollonini L, Patidar U, Situ N, *et al.* Functional connectivity networks in the autistic and healthy brain assessed using Granger causality. In Engineering in Medicine and Biology Society (EMBC), 2010 Annual International Conference of the IEEE: IEEE: 2010:1730–1733.
47. Hardmeier M, Hatz F, Bousleiman H, *et al.* Reproducibility of functional connectivity and graph measures based on the phase lag index (PLI) and weighted phase lag index (wPLI) derived from high resolution EEG. PLoS One 2014; 9:e108648.
48. Stam CJ, Nolte G, Daffertshofer A. Phase lag index: assessment of functional connectivity from multi channel EEG and MEG with diminished bias from common sources. Hum Brain Mapp 2007; 28:1178–1193.
49. Rabinovich MI, Simmons AN, Varona P. Dynamical bridge between brain and mind. Trends Cogn Sci 2015; 19:453–461.
50. Frohlich J, Irimia A, Jeste SS. Trajectory of frequency stability in typical development. Brain Imaging Behav 2015; 9:5–18.

