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The Disrupted Connectivity Hypothesis of Autism Spectrum Disorders: Time for the Next Phase in Research

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Abstract

During the past decade, the disrupted connectivity theory has generated considerable interest as a pathophysiological model for autism spectrum disorders (ASD). This theory postulates that deficiencies in the way the brain coordinates and synchronizes activity amongst different regions may account for the clinical symptoms of ASD. This review critically examines the current structural and functional connectivity data in ASD and evaluates unresolved assumptions and gaps in knowledge that limit the interpretation of these data. Collectively, studies very often show group alterations in what are thought of as measures of cerebral connectivity, though the patterns of findings vary considerably. We argue that there are three principle needs in this research agenda. First, further basic research is needed to understand the links between measures commonly used (DTI, fMRI, EEG) and other (histological, computational) levels of analysis. Second, speculated causes of inconsistencies in the literature (age, clinical heterogeneity) demand studies that directly evaluate these interpretations. Finally, the field needs well-specified mechanistic models of altered cerebral communication in ASD whose predictions can be tested on multiple levels of analyses.

Keywords

autism; disrupted connectivity; functional; structural; review; future research

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INTRODUCTION

The disrupted cerebral connectivity hypothesis is currently a leading pathophysiological model for autism spectrum disorders (ASD). The most common version of this hypothesis proposes that individuals with ASD have weak connections between distant brain regions and increased connections within local regions; these abnormalities contribute to the social, cognitive and behavioral phenotype (1). Indeed, there are many data consistent with this view. Close examination of this body of work, however, reveals conflicting findings, untested assumptions and gaps in knowledge that leave the validity of this hypothesis open to question.

ASD is a chronic neurodevelopmental disorder affecting approximately 2.25% of children (2,3). Recognition of the high prevalence has accelerated research to identify causes, mechanisms and treatments. Thus far, a primary and unitary etiology for ASD, however, remains elusive.

This review critically evaluates the connectivity literature in ASD. We assert that several confounds of this work temper firm conclusions supporting the disrupted connectivity hypothesis, and we present approaches to transcend current limitations.

1. History of the disrupted connectivity hypothesis

The disrupted connectivity hypothesis had its origins in 1988 when Horwitz *et al* (4) found reduced correlation in PET signals among frontal, parietal, subcortical regions in adults with ASD. This initial finding was pursued almost 15 years later when Just *et al* found that individuals with ASD exhibit reduced frontal-posterior fMRI connectivity when performing a sentence comprehension task (5). The hypothesis that children with ASD have local overconnectivity originated separately, with the discovery that young children with ASD have increased head circumference (6–8). Subsequent investigations found that the increased white matter volume was specifically located in superficial (“radiate”) white matter, the fibers connecting neighboring regions, which suggests local overconnectivity (9). Also suggestive of local overconnectivity was the finding of tightly packed minicolumns (which alternatively may result from local inhibitory underconnectivity) (10, 11). This reduction may contribute to the higher risk for seizures and “sub-clinical” epileptiform EEG discharges (12). Belmonte *et al* (1) integrated accounts of global under- and local overconnectivity and posited that, together, they may together “reinforce each other by failing to differentiate signal from noise.”

Currently, there is modest evidence in support of this hypothesis. Many task-based fMRI studies show that individuals with ASD exhibit reduced functional connectivity between multiple cortical regions or between cortical and subcortical regions (13–15). Further, data from resting state studies indicate reduced connectivity within the default mode network (16–19) and other relevant brain networks (20, 21). There are, however, substantial data challenging the finding of long range underconnectivity in ASD. For example, several studies examining intrinsic connectivity reveal long range overconnectivity or mixed patterns of long range under- and overconnectivity (22–25). The resting state results also show long range overconnectivity or mixed patterns of connectivity (26–28). Similarly,

when considering the hypothesis of local overconnectivity in ASD, fMRI data indicate a pattern of widespread local overconnectivity (28), but also a mixed picture of local over- and underconnectivity (29–32). A review of the DTI literature suggests that many studies demonstrate reduced fractional anisotropy (FA) in individuals with ASD although a handful of studies indicate an increase in FA or a combination of reduced and increased FA (33–39). These conflicting findings were usually present in younger children with ASD.

Collectively, the existing connectivity data in ASD are inconsistent. One possible explanation for the variability is that, while altered connectivity is in fact a pathogenic mechanism, we have insufficient specificity in our hypotheses, insufficient precision in our techniques, excessive sensitivity to confounds and/or insufficient power in our studies to correctly identify the supporting evidence. The other possibility is that alterations in connectivity are not relevant to ASD, and positive findings in so-called connectivity measures result from bias or variance for many of the same reasons.

2. What do we mean by “brain connectivity”?

Our notion of connectivity may be defined, somewhat circularly, by whatever is measured by so-called “connectivity metrics,” including anatomical (DTI) and physiological functional/effective (fMRI/MEG/EEG/TMS) connectivity analyses. Better yet, our conceptual notion of connectivity could be based on cellular (e.g., intact *vs.* broken axons; effective *vs.* impaired synapses), computational or information transmission characteristics (certain bandwidth and signal-to-noise ratio) (40). Optimally, we should be able to relate micro-scale phenomena to our meso- and macro-scale measures. However, the study of brain connectivity in ASD is inherently limited by gaps in basic knowledge linking the two scales and is influenced by the current state of connectomics (the “wiring diagram of the brain” and the techniques used to map it), and by theoretical models that relate network properties of the brain to behavior (41,42).

EEG and MEG measure electromagnetic activity, but local field potentials rather than action potentials. Each modality records only a very small percentage of total neural activity. Functional MRI measures neuronally-coupled metabolic activity at slow frequencies and is perhaps less directly reflective of neural computation than EEG/MEG (43). Basic science is only beginning to understand what information is coded in each form and how it is captured by EEG. Our connectivity metrics may not *necessarily* mean what we assume they do. For example, functional connectivity in EEG is typically operationalized as a statistical time-series correlation between the read-out of two macroscopic brain regions. EEG signals are generated by post-synaptic potentials (44), and it is possible that altered dendritic processing, rather than impaired axonal/synaptic transmission could influence so-called connectivity measures. Considerable effort is underway to understand how signals from these modalities can speak to information theoretical parameters, such as bandwidth and signal-to-noise ratio (45).

DTI is a macroscopic anatomical technique that examines the orientation and organization of white matter based on characteristics of water diffusion within an axon (46). Fractional anisotropy (FA), a DTI metric, represents the average direction of water diffusion in a given voxel. Higher FA values may reflect greater organization and orientation of fibers, which is

hypothesized to reflect greater connectivity. Multiple factors can affect FA, one being that axons may have different orientations (i.e., crossing fibers), which when averaged can lower the FA value. As such, there is always some ambiguity as to whether low FA represents a true biological finding or a methodological artifact. Some have argued that there is no direct quantitative relationship between FA and connectivity (47). Newer methods, including diffusion spectrum imaging and multi-shell high angular resolution diffusion imaging (HARDI), are currently being used to enhance the resolution and quantification of axonal fibers (48).

As an imperfect proxy to understanding precisely what these macro-level measures mean on a micro-scale, we can assess convergence, in health and disease, among the various techniques. Although substantial evidence is not yet available, preliminary reports demonstrate that some EEG connectivity measurements may correlate with fMRI and with anatomic measurements (49). Divergence of results, as discussed below, is useful when the mechanisms driving the results of different analyses are sufficiently well-understood and when a model is sufficiently nuanced to predict different results from different techniques.

Conversely, measures not typically labeled as “connectivity measures” may, in fact, have the potential to provide strong evidence for altered connectivity. For example, latencies of event-related potentials/fields (ERP/ERFs via EEG/MEG) can shed light on the speed of neural transmission. Roberts *et al* (50) found that children with ASD exhibit, on average, an 11ms latency increase in cortical auditory-evoked fields, which may speak to slowed conduction in the auditory system. Even behavioral results may have a role. Reaction time and error rate results from multi-sensory integration (MSI) paradigms could be altered as a result of disordered connectivity, as abnormal synchronization/binding of inputs from spatially distant brain regions could contribute to performance deficits (51, 52). Further, TMS is perhaps underutilized as a physiological measure of connectivity and is able to interrogate networks by perturbing the system (53).

LIKELY CONFOUNDS IN THE ASD CONNECTIVITY LITERATURE

1. Systematic artifacts may account for group differences within studies

Multiple types of artifacts could affect conclusions drawn from each connectivity measure. In fMRI, foremost is head motion, which has been shown to result in a pattern of long range underconnectivity and short range overconnectivity, analogous to that seen in ASD (54–56). In DTI, Koldewyn *et al* (57) demonstrated greater head motion in the ASD group than the typically developing group. Widespread reductions in FA were present in the ASD group when head motion was unaccounted for, however, only one tract exhibited reduced FA when the groups were stringently matched on head motion. Proposed strategies to reduce motion artifacts include specific preprocessing techniques (e.g., scrubbing) and precise group matching on motion measures (58).

In addition to technical factors, systematic differences in participant performance may artifactually affect group results. Group attentional differences can affect the magnitude of activation and therefore measures of connectivity (59). Discarding incorrect trials, using eye tracking methods, and adding a secondary task to assess attention to the primary task may

control for group differences in attention (60). These “task-related” concerns are not absent in resting state studies. There is growing awareness that the resting state in fMRI studies is an active cognitive state. ASD and typically developing individuals may differ systematically in response to resting state instructions and environments (61).

Working memory and instruction comprehension may also be compromised in ASD (62). Tasks should be developed so as to minimize taxing of capacities that are known to differ between groups, except when these domains are the focus of study (63). Lastly, group differences in behavioral performance may create results that are more reflective of performance rather than the underlying disorder. Since the tasks used are typically relevant to the diagnosis, some performance differences are inevitable. Administering tasks with varying difficulty levels can facilitate comparison of physiological results while controlling for performance (64).

2. Methodological heterogeneity can lead to inconsistent findings across studies

When the theoretical basis of a series of studies has sufficient nuance to predict that some analytical methods will show positive results and others will show negative results, then “inconsistency” arising from multiple methods is expected and informative. For example, fMRI may register the same BOLD increases for both excitatory and inhibitory increases, whereas EEG and MEG are able to discern the two (65). If, however, choices about technique or processing parameters are irrelevant to a model, then inconsistency in results is reflective of noise. Replicability may be in question. In ASD, significant efforts have been made to disentangle the various processing parameters that may account for discrepant connectivity findings. Muller *et al* (66) reviewed 32 fMRI studies and found that several data analytic approaches, including pursuing a region of interest (versus whole brain) analysis and not removing task effects or using a low pass filter, increased the likelihood of finding reduced connectivity in the ASD group, whereas regressing task effects and using a low pass filter may eliminate findings of reduced connectivity. A subsequent study found similar results, indicating that task regression and applying a low pass filter were more likely to result in findings of overconnectivity whereas not performing these analyses resulted in underconnectivity (67).

Spatial scale is a specific analysis parameter that is critical to interpretation yet whose definitions vary greatly among studies. As many researchers have pointed out, there are no objective definitions for what constitutes “local” and what constitutes “global” and Studies often fail to define these terms explicitly (68). In general, “long range connectivity” has referred to connections across different lobes (69) or regions of the brain, usually between different cortical regions (e.g., Brodmann areas or other well-delineated regions) but also between cortical and subcortical regions (70). One study explicitly defined long range connectivity as any distance greater than one cubic centimeter irrespective of whether brain regions were spatially separate (68). Definitions of local connectivity, however, are more vague and can refer to spatial scales ranging from microns (e.g., the distance between minicolumns or about 50µm) to millimeters (71). Examples of the latter include approximately 3–5mm distances between neighboring voxels when using regional homogeneity methods (72), 14mm between nodes when using graph theoretical methods

(29), and up to 35mm when using tract based analysis (73). Moving forward, it will be critical for investigators either to clearly express spatial scale in absolute terms or specify neuroanatomic structures under examination to facilitate more valid comparisons across studies.

3. Subject heterogeneity may contribute to inconsistent connectivity patterns across studies

Within ASD, there is great variability within both clinical phenotype and etiology. Clinical heterogeneity is present with respect to symptom severity, language ability, cognitive functioning, co-occurring diagnoses, and functional outcome. On the other end of the scale, hundreds of candidate genes/loci have been implicated in ASD, suggesting substantial etiological heterogeneity. Beyond that, connectivity findings could be influenced by the possibility that children with ASD may exhibit greater variability, one to another, than neurotypical children (74). To avoid averaging fallacies and increase specificity in our models, we can and likely should group/stratify by etiological or clinical factors.

Several groups are examining how specific ASD risk genes (e.g., MET variants, CNTNAP2 polymorphisms) affect brain connectivity patterns, particularly in social cognitive networks (75, 76). In some cases, mouse models have been developed for specific etiologies, and research with these models can provide invasive information that complements data obtained in humans. For example, preliminary evidence from mouse models of Fragile X suggests a pattern of increased structural connectivity in the visual cortex with reduced structural connectivity between the visual cortex and other cortical regions; these regions are hypothesized to play a role in sensory processing (77). By examining multiple genetic etiologies, we will likely find mechanisms and biological therapies specific to each genotype. By looking across genotypes that share an ASD phenotype, we may find mechanisms responsible for the cardinal symptoms of ASD.

We can overcome heterogeneity from the other side, by stratifying by clinical factors. This tactic is consistent with the RDoC (Research Domain Criteria) approach, in which behavioral dimensions (e.g., social communication) serve as the independent variables, rather than DSM diagnoses (78). Even within ASD-diagnostic research, however, subject heterogeneity needs to be assessed and controlled for.

Age is a critical demographic factor that may affect results. There is evidence that brain network connectivity evolves over ontogeny. It is therefore plausible that the role of network connectivity alterations in ASD may also evolve over the lifespan. As a consequence, age and pubertal stage should be considered with both theoretical accounts and with data (79–81). To date, much of the data comes from adolescents and adults with ASD who are male, limiting generalizability of conclusions to females and younger children. Additionally, many studies include broad age ranges, sometimes spanning over 10 years, which can obscure important developmental patterns.

On the positive side, some groups have begun to address developmental factors explicitly. For example, Uddin *et al* recently suggested that younger children with ASD exhibit patterns of overconnectivity whereas adolescents with ASD show underconnectivity (82).

Preliminary evidence in support for this hypothesis is emerging (30, 83) and appears consistent with earlier findings suggesting early brain overgrowth in young children with ASD that appears to normalize by adulthood (8, 84).

The data on developmental trajectories have thus far been principally derived from cross-sectional samples. The most conclusive studies addressing connectivity changes during development will be longitudinal. Testing change over time, within subjects, eliminates aspects of inter-individual variability and allows for explicit determination of the contribution of development. One important area of longitudinal work focuses on identifying early markers of ASD in high risk infant siblings. Thus far, several potential biomarkers have emerged, including atypical trajectories of change in spectral power in high risk infants and reduced functional connectivity in high risk infants who go on to develop ASD compared to those who do not (85, 86).

Whereas *confounds of heterogeneity* refer to disparate connectivity findings within patients taken to be similar, *poor discriminant validity* refers conversely to similar connectivity findings in groups or diagnoses that may be different. The finding of reduced long range connectivity has been reported in other psychiatric and learning disorders, including ADHD (87), schizophrenia (88), depression (89) and dyslexia (90). The question arises as to why this pathophysiological finding seems prevalent across and how it could explain ASD if it manifests in other, clinically dissimilar disorders. It could be that these different disorders stem from unique etiological mechanisms that converge into common neural signatures, but these signatures represent epiphenomena to the causal stream that connects genetic/cellular mechanisms to behavioral symptoms. Alternatively, each of these disorders could be characterized by its own connectivity signature, which our techniques do not adequately differentiate. Examining connectivity patterns across different disorders might delineate which connectivity findings are unique to ASD and which may result from the impact of comorbid diagnosis.

4. Publication bias and lack of reproducibility can skew interpretations of the data

The scientific community is beginning to understand the importance of publishing negative findings. Sharing negative results is critical for several reasons. If we were to conduct a meta-analysis, we would need to know not only how many studies showed overconnectivity and how many showed underconnectivity, but also how many failed to reject the null hypothesis. Publishing null findings from high quality studies also prevents replication and allows for refining of hypotheses and methods. Well-substantiated negative findings may be more useful to validate an alternative hypothesis than positive studies that are merely “consistent with” the tested hypothesis (91). It should be kept in mind that statistically proving equivalence is a higher bar than merely failing to show a difference (i.e., failure to reject the null hypothesis) (92). As sharing of imaging datasets becomes more common, reanalysis of unpublished connectivity data could also allow for a less biased approach toward capturing negative findings.

Another “endemic problem” in neuroscience research is the low power and lack of reproducibility of studies (93, 94). Underpowered studies could play a significant role in the variability of findings and lack of reproducibility in ASD connectivity research. As a field,

we will have to consider what constitutes adequate group sizes, the patterns of funding reproducible research, and the respect we give to replications of previous work.

FUTURE RESEARCH DIRECTIONS

1. The field needs testable models that make specific predictions across levels of analysis

In mature sciences relating to complex phenomena, theoretical models are generated from reasoning and from preliminary observations, and the specific predictions of those models are tested. Competing models are tested explicitly against one another. In a very simple case, one could propose that for some particular reason, intrahemispheric connectivity should be affected in ASD, whereas interhemispheric connectivity is preserved (13). Using various modalities, one would then predict that measures of intrahemispheric connectivity would show group differences, and equivalent measures of interhemispheric connectivity would not. Another group could propose that, for other reasons, the reverse would be true. A single set of data could help validate one model and reject the other.

Better, models that cross levels of analysis allow for *explanation* rather than merely *description*. To date, most studies of altered connectivity in ASD have been descriptive rather than explanatory. Further, many studies have established links between genetic alteration and behavioral phenotypes, although the full causal stream of cellular mechanisms and computational processing in between has not been clearly demonstrated. What is needed in this next phase of research is the development of well-specified models that make predictions on multiple levels of analysis, from genetic mutations to altered cellular processes that affect anatomical and physiological connectivity mechanisms, which affect the nature of information transfer and ultimately behavioral processes. This work is only just beginning. Just *et al* serves as an example. This group has made clinical observations in the Tower of London test and has then constructed computational models that are sensitive to altered connectivity parameters (specifically bandwidth) (45). This model then makes behavioral and physiological (fMRI) predictions that can be tested with human data. Other groups have produced alternative models. Gepner and Feron (95) posit altered timing and synchronicity of downstream information flows from various sensory inputs. Uhlhaas and Singer (96) have similar notions. To date, these models perhaps occupy too broad a domain to come into direct competition with each other, but future work will necessarily move in this direction.

2. The disrupted connectivity hypothesis needs to be linked to other hypothesized mechanisms of ASD

Many “psychological” hypotheses have been proposed to explain the pathogenesis of ASD, including Theory of Mind (97), extreme male brain (98), executive dysfunction (99), weak central coherence (100), mnesic imbalance (101), altered complex information processing (102), intense world (103), and temporal binding window (104). There are also many other “biological” hypotheses beyond disrupted connectivity (GABAergic dysfunction/altered excitatory:inhibitory balance (11, 105), cerebellar (106, 107), minicolumnopathy (71)). For some of these hypotheses, particularly those in the psychological domain, physiological measures of connectivity can and are used in a task-related fashion, targeting networks

known from basic science to be involved in the performance of the relevant task. These studies have targeted psychological domains that are theoretically linked to core ASD domains (i.e., language, social processing) (108). For example, executive function and cognitive control tasks and networks are well-described and have a theoretical relationship to ASD (109). Data are being collected to assess the relationship between executive function, repetitive behaviors and perseveration in ASD on one hand (110), and abnormalities in circuits involving the dorsolateral prefrontal cortex on the other (111–113).

In order to understand connectivity abnormalities in the context of other *neurobiological* frameworks, collaborative or competitive studies of the connectivity hypothesis will be necessary using a broader range of methods. For example, D'Mello and Stoodley (114) have mapped a specific and plausible role of the cerebellum in molding cortical network development, and how alterations of such development could lead to ASD symptoms. A test of this hypothesis might involve genetic along with longitudinal anatomical, physiological and behavioral/clinical testing of high-risk infants over the course of infancy and beyond, specifically relating morphology and physiology of the cerebellum and cerebellar-cerebral tracts to subsequent development of cortical regions and clinical symptoms.

Separately, the altered excitatory:inhibitory hypothesis can be seen as being in competition with the connectivity account, or as a mechanism for it, in the sense of altered synaptic function leading to impaired information transfer (40). In the former case, researchers might examine the relative contribution of inhibitory measures (e.g., EEG/MEG oscillations) *vs.* functional connectivity measures in explaining clinical features in ASD. In the latter case, it is likely that progress at the current time will be made in computational models, mouse models and cellular work.

SUMMARY

Disrupted connectivity has been a popular pathophysiological hypothesis of ASD, however, conflicting results abound. Future work will need to continue to directly assess experimental and analytical confounds. As the science matures, models that cross levels of analysis will be developed and either validated or rejected in favor of better models. These models will subsequently interact with other hypotheses to ultimately uncover the mechanisms responsible for the clinical features of ASD.

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