REVIEW

The Implications of Brain Connectivity in the Neuropsychology of Autism

Jose O. Maximo · Elyse J. Cadena · Rajesh K. Kana

Abstract Autism is a neurodevelopmental disorder that has been associated with atypical brain functioning. Functional connectivity MRI (fcMRI) studies examining neural networks in autism have seen an exponential rise over the last decade. Such investigations have led to the characterization of autism as a distributed neural systems disorder. Studies have found widespread cortical underconnectivity, local overconnectivity, and mixed results suggesting disrupted brain connectivity as a potential neural signature of autism. In this review, we summarize the findings of previous fcMRI studies in autism with a detailed examination of their methodology, in order to better understand its potential and to delineate the pitfalls. We also address how a multimodal neuroimaging approach (incorporating different measures of brain connectivity) may help characterize the complex neurobiology of autism at a global level. Finally, we also address the potential of neuroimaging-based markers in assisting neuropsychological assessment of autism. The quest for a neural marker for autism is still ongoing, yet new findings suggest that aberrant brain connectivity may be a promising candidate.

Keywords Autism · fMRI · Functional connectivity · Underconnectivity · Effective connectivity · White matter integrity

J. O. Maximo · E. J. Cadena · R. K. Kana (✉)
Department of Psychology, University of Alabama, Birmingham, CIRC 235G, 1719 6th Avenue South, Birmingham, AL 35294, USA
e-mail: rkana@uab.edu

Background

Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder characterized by social, communication, and behavioral disturbances (American Psychiatric Association 2013). Today, ASD is regarded as a pediatric health issue of growing urgency given that 1 in 88 children are being diagnosed with this disorder (Centers for Control Disease 2012). While there has not been a definitively accepted etiology for ASD in the scientific community, research has become increasingly focused on understanding the neurobiological mechanisms underlying this disorder. A biological origin for ASD was proposed even in the first scientific account of autism (Kanner 1943), which was followed by the first neurobiological account (Rimland 1964) that dispelled some myths about autism. In 1978, Damasio and Maurer (1978) observed similar behaviors in autism and in frontal lobe damaged patients. They found an impaired dentato-thalamo-cortical pathway, which plays a critical role in language and higher cognitive functions in autism. A decade later, Horwitz et al. (1988), using positron emission tomography (PET), found a global increase in resting glucose metabolism in adults with autism, which provided indirect support for autism being linked to abnormal brain activity. These early studies were critical in providing valuable information about the alterations in brain responses and its role in the pathobiology of autism. Furthermore, genetic studies starting from the 1980s have also helped emphasize the biological origin of autism by providing strong evidence of heritability (Freitag 2007; Geschwind and Levitt 2007; Gillberg and Wahlstrom 1985; Wahlstrom et al. 1986).

With the advent of modern neuroimaging techniques, the last two decades have witnessed an exponential rise in the number of studies examining the brain in autism using a wide variety of techniques, such as functional magnetic resonance imaging (fMRI), electroencephalography

(EEG), magnetoencephalography (MEG), diffusion tensor imaging (DTI), and proton magnetic resonance spectroscopy (1H-MRS). The majority of the first generation fMRI studies reported altered levels of brain activity in people with autism, relative to typically developing individuals. Although such studies have illuminated our understanding of regional brain function and dysfunction in autism, inconsistent findings and the limited potential of such findings to explain a distributed disorder like autism at the global level has remained a topic of debate. Given its complex nature and the heterogeneity in symptoms, attempts to explain autism from the perspective of a focal brain region abnormality have repeatedly fallen short. Considering this void, examining the brain at the network level is a promising new avenue in characterizing the neurobiology of complex syndromes like autism. In these lines, there has been an extensive array of publications, especially in the last decade regarding brain connectivity in autism. In this paper, we will review the connectivity-based fMRI studies of autism by taking into account the following: conceptual origins of brain connectivity, empirical findings, methodological sophistication and concerns, the impact of brain connectivity findings in autism, and the future of this line of research. First, we discuss the conceptual bases of brain connectivity.

Functional Specialization and Integration

Cognitive processes are computationally demanding, and hence require effective allocation of the brain's resources. This would entail optimal functioning of different brain areas, which in turn may be guided by two fundamental principles of brain organization: *functional specialization* and *functional integration*. Functional specialization suggests that different areas in the brain are specialized for different cognitive functions, while functional integration involves the coordination among brain areas to accomplish a task. Integration implies that a cortical area is specialized for some aspects of perceptual or motor processing, and that this specialization is anatomically segregated within the cortex (Friston 2011). Regardless of whether the brain responds to extrinsic or intrinsic stimuli, we experience a unified, integrated conscious experience. This balance between segregation and integration is essential for the operation of distributed networks underlying cognitive functions (Tononi et al. 1998). Early brain development involves a delicate balance between the functional specialization of specific regions as well as the formation of connections across these regions through integration. Autism is a neurodevelopmental disorder with alterations found in brain developmental trajectory (Courchesne 2002), which may point to disrupted functional specialization and integration.

Neuroimaging techniques, like fMRI, have shown altered patterns of functional specialization in several domains of thinking, such as social, cognitive, linguistic, and visuospatial processing in children and adults with ASD. Findings from these studies point to several foci in the brain that had atypical response in individuals with ASD, compared with typically developing individuals (Anagnostou and Taylor 2011; Dichter and Belger 2008; Minshew and Keller 2010). Despite an abundance of such findings, there are also inconsistencies in focal brain area response to different tasks in autism (Müller 2007). Therefore, just as it is important to understand specialized functioning of a region, it is imperative to understand the integration among different brain regions. Conceptualizing autism as a network level disorder involves examining functional integration. One way to quantify functional integration among different brain areas is to examine interregional neural interactions by correlating the timing of brain activity. This measure, commonly known as *functional connectivity* (See Fig. 1a), refers to the temporal correlation between spatially remote neurophysiological events (Friston et al. 1993). Functional connectivity provides an index of the "cross-talk" among brain areas, and hence its application to study brain disorders at a systems-level is quite compelling. In the last decade, the number of functional connectivity studies in autism has increased significantly with findings cutting across different tasks, brain areas, and approaches. Other measures of connectivity, such as effective connectivity (See Fig. 1b), which addresses the directionality of information transfer, and white matter integrity from axonal connections (anatomical connectivity; See Fig. 1c) assessed through diffusion tensor imaging (DTI), have provided a multilevel characterization of neural communication in autism.

Functional Connectivity MRI (fcMRI) Studies in ASD

Findings of Cortical Underconnectivity

The first empirical finding of fMRI-based functional connectivity in autism was reported by Just and colleagues in 2004 using a sentence comprehension task (Just et al. 2004). They found reduced functional connectivity across different regions of the brain in adults with autism. Weaker functional connectivity, also referred to as cortical underconnectivity, in autism was reported by several fMRI studies that followed using different tasks, such as visual imagery and language (Kana et al. 2006), working memory (Koshino et al. 2008); social and emotional tasks (Rudie et al. 2012b; Schipul et al. 2012), problem-solving (Just et al. 2007), response inhibition (Kana et al. 2007), Theory-of-Mind (Kana et al. 2009; Mason et al. 2008; Washington et al. 2013), visuospatial attention (Agam et al. 2010; Damarla et al. 2010), global processing (Liu et al. 2011), global and biological motion (Brieber et al. 2010;

a) Functional connectivity

b) Effective connectivity

c) Structural/anatomical connectivity
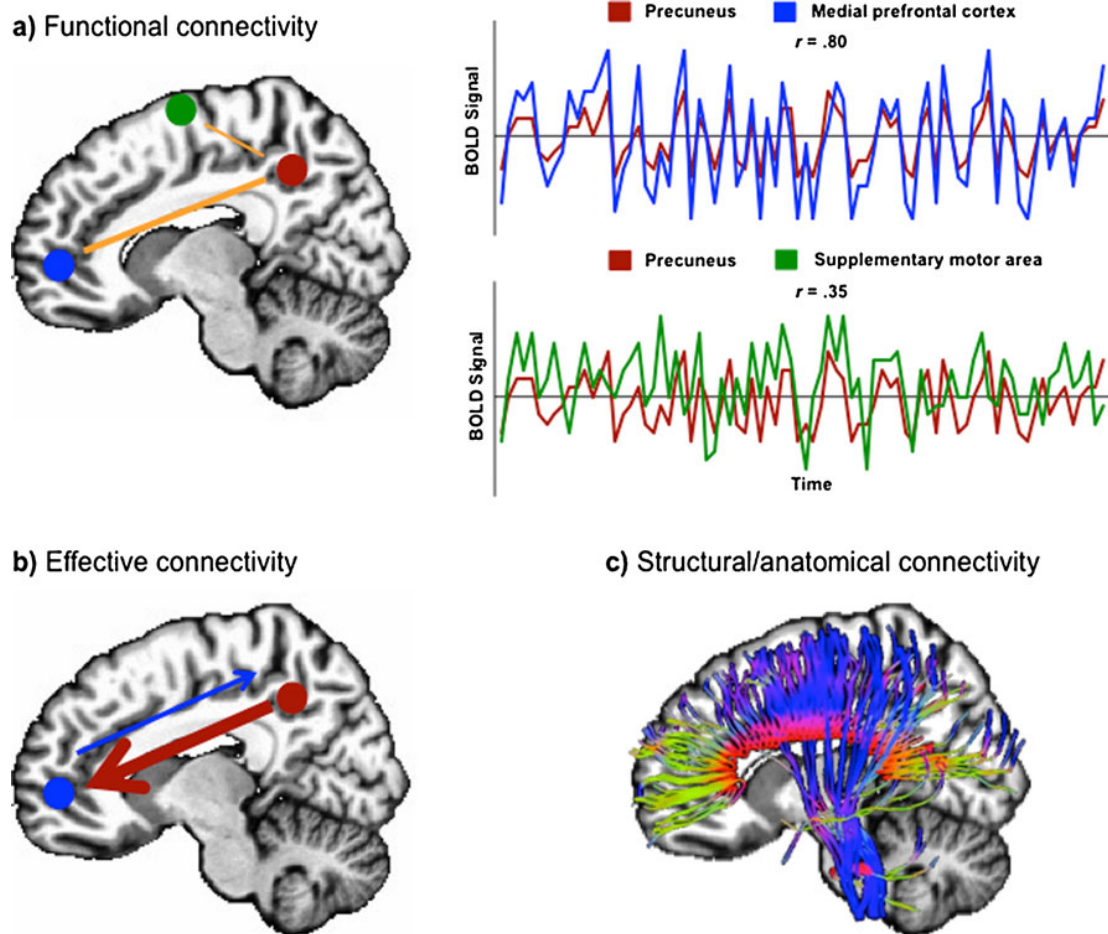
Fig. 1 Models of brain connectivity. Sketches illustrate: **a** functional connectivity between two sets of brain areas. *Top panel graph*: high correlation between precuneus and medial prefrontal cortex; and *bottom panel graph*: weaker correlation between precuneus and supplementary motor area; **b** effective connectivity (information flow) between two regions; and **c** structural/anatomical connectivity depicted by white matter fiber tracts

Freitag et al. 2008), and cognitive control (Solomon et al. 2009) (See supplementary table S1 for a detailed list of connectivity studies). Evidence of underconnectivity in ASD has also been reported in the absence of an active cognitive task [task-free resting state, (Abrams et al. 2013; Assaf et al. 2010; Cherkassky et al. 2006; Di Martino et al. 2013; Kennedy and Courchesne 2008; Kennedy et al. 2006; Lombardo et al. 2010; Weng et al. 2010; Wiggins et al. 2011)]. The weaker connectivity reported in most of these studies was primarily between the prefrontal cortex and relatively posterior brain areas. Poor prefrontal-posterior coordination can affect higher-level processing, and may underlie the difficulty in cognitive, social and language processing witnessed in ASD. For example, social processing involves the coordinated functioning of the medial prefrontal cortex (MPFC) and the temporoparietal junction (TPJ, associated with ToM), the superior temporal sulcus (STS, associated with biological motion), and the fusiform gyrus (FG, associated with face processing) (Schipul et al. 2011).

Other studies have reported underconnectivity in ASD in regions outside the frontal-posterior network, such as the amygdala, temporal and frontal regions (Monk et al. 2010), anterior cingulate and frontal eye fields (Agam et al. 2010), insula with brain regions involved in emotional and sensory processing (Ebisch et al. 2011), within a motor network consisting of primary and supplementary motor areas, anterior cerebellum, and the thalamus (Mostofsky et al. 2009), prefrontal cortex and premotor and somatosensory cortices (Lombardo et al. 2010), fusiform gyrus and the amygdala, the posterior cingulate and the cuneus (Kleinhans et al. 2008), visual cortex and the thalamus and cerebellum (Villalobos et al. 2005), and between the superior frontal gyrus and the caudate nucleus (Turner et al. 2006). While these studies have found functional underconnectivity in ASD outside the frontal posterior network, the findings vary across a wide variety of pairs of regions and across a large range of tasks, making it difficult to isolate a specific pattern of connectivity disturbances.

Establishing a relationship between the severity of the disorder, assessed by various autism diagnostic instruments, and the brain connectivity measures, has been deemed as the link to connect the behavioral symptoms and the underlying neuropathology. An interesting question in this context is whether the severity of the disorder could give some insights about the degree of alterations in functional connectivity. The Autism Diagnostic Observation Schedule (ADOS) and the Autism Diagnostic Interview-Revised (ADI-R), considered as the gold standard in ASD diagnosis, have shown negative relationships with functional connectivity in different networks, such as the frontal–parietal (Just et al. 2007), and inferior frontal cortex and pre-supplementary motor area (Lee et al. 2009). Other studies have also shown that individuals with ASD with poorer social functioning (high ADI-R social score) had weaker functional connectivity between the superior frontal gyrus and posterior cingulate cortex (Monk et al. 2009; Weng et al. 2010). These findings, albeit correlational, provide some valuable insights into brain-behavior relationships in autism.

An important question is about the nature of an underconnected brain and how it functions. Cortical underconnectivity may reflect an inefficiency in optimizing network connections to achieve task performance (e.g., increasing the communication between task-relevant brain regions). A weak coherence among key areas of a network could mean less coordination and hence less than optimal output. Such lack of coherence may be due to several factors, such as the use of an alternative cortical route, dysfunction of key brain areas, or structural anomalies in certain areas. Subtle anatomical abnormalities, such as aberrant white matter growth early in life (Courchesne et al. 2001), atypical white matter maturation in infants and toddlers (Weinstein et al. 2011; Wolff et al. 2012), alterations in white matter volume (Herbert et al. 2004) and white matter integrity (Shukla et al. 2011) in children have been reported in ASD. Such axonal abnormalities, in some way, limit the transfer of information or "bandwidth" (the maximal rate of data transfer supported by a communication channel, taking into account the impact of noise) across different brain regions, given that cognitive functioning involves co-activation of a network of cortical areas whose activity is coordinated (synchronized), and the coordination is based on inter-regional communication using the white matter tracts that provide the anatomical connectivity (Just et al. 2012).

Thus, cortical underconnectivity may be an important aspect of brain functioning and information transfer in autism, which may explain several behavioral symptoms in individuals with autism. The social and communication impairments, which define the triad of symptoms, in autism could be explained by poor connectivity among brain areas underlying social cognition, language, and executive functions. The underconnectivity accounts have also helped develop a new way of thinking, a network-based approach to brain

functioning, in understanding the neurobiology of autism spectrum disorders. However, there have been several studies of autism where underconnectivity has not been found; instead, an overconnectivity among specific brain areas has been reported. Below we discuss such findings and their implications in understanding autism.

Findings of Cortical Overconnectivity

While the preponderance of underconnectivity findings in ASD literature has been noteworthy, there have also been several reports of enhanced cortical connectivity in ASD. For example, overconnectivity has been reported in the extrastriate cortex, frontal and temporal regions, amygdala, and parahippocampal gyri (Murphy et al. 2012; Noonan et al. 2009; Shih et al. 2010, 2011; Uddin et al. 2013a; Welchew et al. 2005). Similarly, Monk et al. (2009) reported higher functional connectivity among posterior cingulate cortex, temporal lobe, and parahippocampal gyrus using resting state fcMRI. In another study, Nair and colleagues (2013) found overconnectivity in temporo-thalamic regions in individuals with ASD, which partially supports some previous findings of overconnected cortical-subcortical networks in ASD (Mizuno et al. 2006). The overconnectivity in thalamocortical projections, which is part of the cerebello-thalamo-cortical pathway may be related to an early reduction in the number and density of Purkinje cells in ASD (Bailey et al. 1998). In other words, the reduction in the number and density of Purkinje cells, which are inhibitory neurons, can affect the inhibition-excitation balance and hence the connectivity. However, other studies have found contradicting results revealing decreased connectivity in cortical-subcortical pathways (Cheon et al. 2011).

Overall, the findings of overconnectivity (See supplementary table S1 for a detailed list of studies) have been interpreted to reflect hyperspecialized, rather than more efficient connectivity. Thus, inefficient connectivity may be the hallmark of ASD, with possibly overabundant connectivity between 'non-essential' regions, allowing for low-level cross talk resulting in increased noise in the system (Noonan et al. 2009). This may also relate to findings of early brain overgrowth in children with ASD. Impaired synaptic pruning, important for brain organization and network specialization in typical development may also play a role in creating enhanced connections (overconnectivity) in the ASD brain (Shih et al. 2011). It should be noted that, in addition to findings of exclusively overconnected regions in ASD, studies have also reported mixed patterns of both under- and overconnectivity [(Di Martino et al. 2011; Lynch et al. 2013; Mizuno et al. 2006; Turner et al. 2006), see supplementary table S1 for more studies].

Most of these studies of overconnectivity, like the underconnectivity studies, also have reported a relationship

between enhanced connectivity and behavioral symptoms in ASD. For example, adolescents with ASD who had higher functional connectivity within the default mode network (DMN: the posterior cingulate cortex, retrosplenial cortex, lateral parietal cortex/angular gyrus, medial prefrontal cortex, superior frontal gyrus, and parahippocampal gyrus (Gusnard et al. 2001; Raichle et al. 2001), also had lower abilities in both verbal and non-verbal communication (Weng et al. 2010), measured by ADI and ADOS. Higher functional connectivity between the posterior cingulate cortex (PCC) and the parahippocampal gyrus (PHG) was associated with more severe repetitive behaviors (Monk et al. 2009), and higher functional connectivity between the anterior cingulate and the frontal eye fields was positively associated with restricted, repetitive behaviors (Agam et al. 2010). It was also suggested that enhanced connectivity between PCC and PHG may either be the cause or consequence of the repetitive and restrictive behaviors in ASD (Monk et al. 2009).

Overconnectivity, based on radial cytoarchitecture abnormalities has been typically seen within the frontal lobes (Courchesne et al. 2011; Courchesne and Pierce 2005), in the lateral occipital complex in the posterior region (Pierce et al. 2001) and superior temporal gyrus (Mottron et al. 2006). An overconnected local network can be compared to a peninsula, separated from and with limited access to the rest of the brain, thereby creating long-distance underconnectivity. This may imply that the brain compensates for abnormal connectivity by incorporating areas that it has easier access to, such as the neighboring regions (Belmonte et al. 2004). An overconnected peninsula may not be confined to prefrontal cortex as an enhanced connectivity in parietal lobe in autism may result in parietal autonomy (Just et al. 2012). An interesting question in this regard is that whether frontal and parietal overconnectivity are the consequence of frontal-parietal underconnectivity or the cause of it. Considering the findings of overconnectivity and underconnectivity in ASD, perhaps a better way to characterize connection abnormalities in autism may be in terms of *disrupted connectivity*, which would encompass the wide array of findings involving increased and decreased connectivity.

Factors Affecting Connectivity

As brain connectivity research in autism is growing, so is the use of wide variety of techniques, measuring different indices of connectivity, different levels of examination, and different topographic parameters. Thus, it is important to understand subtleties of the findings reported by different studies, as it will help in drawing common consensus as well as making better sense of inconsistent findings. In the following sections, we examine these factors and their impact on brain connectivity findings in autism.

Spatial Distance: Short-Distance vs. Long-Distance Connectivity

One of the factors that may influence the behavior of a network is how proximal or distal the nodes of that network are located. Thus, the spatial distance between two brain areas may prove critical in understanding the functional interaction between them. Long distance connectivity represents interactions between distant brain regions that are likely to play a large role in perception and information processing (Sporns et al. 2000). For example, executive functioning, especially problem-solving, may involve the coordination between dorsolateral prefrontal cortex (DLPFC) and inferior parietal lobule (IPL), two regions that are spatially distant (Newman et al. 2003). Interestingly, such connections have been found to be disrupted in individuals with ASD (Just et al. 2007). Conversely, studying short-distance connections may reflect neural communication between adjacent populations of neurons (Fries 2005). In the fcMRI literature of autism, it has been suggested that behavioral symptoms observed in ASD may relate to findings of increased *short-distance* and decreased *long-distance* connections in the brain (Courchesne and Pierce 2005). However, no generic definition exists as to what really constitutes "*short*" and "*long*" distance in terms of path length. Short-distance connectivity is often synonymously used with local connectivity. Local or short-distance connectivity can encompass different spatial scales from a few microns to millimeters and even centimeters; whether a neuron transferring information to a neighboring one through an action potential, the study of minicolumnar organization of a brain region or lobe, or simply examining time series correlations of a voxel's time-course with its closest neighbors. Long-distance connectivity, loosely, can be labeled as the connectivity among brain regions across different lobes.

At the cellular level, postmortem studies have introduced a model where the abnormal cytoarchitecture in ASD is thought to be responsible for abnormal local or short-distance connectivity. Vargas et al. (2005) reported the first microscopic evidence of maldevelopment in the frontal lobe and cerebellum, with the presence of activated astroglia with enlarged cell bodies, and panlaminar microglial activation in the dorsal and mesial regions of frontal cortex. In the cerebellum, glial activation was associated with degenerating Purkinje neurons, granule cells and axons. Glial activation persists into postnatal life in autism, and may cause the brain in the infant and toddler with autism to grow larger than normal (Courchesne and Pierce 2005). This enlargement in brain volume due to neuroinflammation may result in excessive neuronal production causing cortical minicolumns to be numerous (Casanova et al. 2002). Since minicolumns are excitatory vertical circuits, their relative density in the autistic brain would be associated with atypically enhanced excitatory cortical function, thus affecting inhibitory systems. This will result in reduced network

differentiation, i.e., "muffled" communication between regions within a functional network, and "noisy" crosstalk within non-involved regions. Thus, increased excitation/inhibition ratio might result in altered local functional differentiation (Rubenstein and Merzenich 2003), which may point out to islets of sparing in ASD, such as the visual cortex, where minicolumns are thought to be more abundant (Keehn et al. 2013).

Local connectivity in ASD has been examined by correlating fMRI BOLD time series from a given voxel with the vicinity of its immediate neighbors (6, 18, and 26 voxels respectively) (Zang et al. 2004). This index of local connectivity has been labeled as the regional homogeneity (ReHo), which has been shown to be sensitive to regional abnormalities (Dai et al. 2012; Farb et al. 2013; Weaver et al. 2013; Yin et al. 2012; Zalesky et al. 2012). In the first ReHo study in ASD, Paakki and colleagues (2010) examined resting-state fMRI BOLD time series correlations of one voxel with its 26 nearest neighbors. They reported mixed findings, with increased ReHo in adolescents with ASD (compared to matched TD participants) in the right thalamus and left occipital regions and decreased ReHo in the right temporal, frontal, and insular sites. Similarly, Shukla et al. (2010), in a ReHo analysis of a voxel with its six immediate neighbors, reported increased ReHo in children and adolescents with ASD in right temporal regions, and decreased ReHo in numerous bilateral fronto-parietal sites. These studies provide evidence of reduced cortical functional differentiation in ASD, yet, decreased ReHo was also reported in both studies, which may be due to difference in scanner strength, nature of the tasks used, and cluster size and voxel dimension used. Thus, synchronizing the methods across studies may be a topic that future studies should pay attention to (Maximo et al. 2013). Despite the methodological differences in ReHo studies, the findings in local functional connectivity may suggest altered functional differentiation in ASD.

Contrary to the limited number of local connectivity studies, reports of long-distance connectivity are more predominant in the ASD literature. In typically developing individuals, long-distance connectivity is prominent across association areas in parietal, lateral temporal, and frontal cortices as well as paralimbic cortex including posterior cingulate (Schipul et al. 2011; Vissers et al. 2012). These regions have been previously described as important for higher-order cognitive processes, such as attention, memory, and language (Sepulcre et al. 2010), where people with autism have difficulty. In ASD fcMRI studies, disturbances in long-distance connectivity (under- and overconnectivity) have been reported in several networks as previously alluded, such as the fronto-parietal (Just et al. 2007; Kana et al. 2006), fronto-striatal (Silk et al. 2006), frontal-fusiform (Koshino et al. 2008), frontal inhibition network and the inferior parietal lobe (Kana et al. 2007), visual cortex and frontal (Villalobos et al. 2005), anterior

cerebellum and thalamus (Mostofsky et al. 2009), thalamo-cortical (Mizuno et al. 2006; Nair et al. 2013), the prefrontal-premotor-somatosensory (Lombardo et al. 2010), areas involved in language (Dinstein et al. 2011), the fusiform-amygdala, the posterior cingulate and the cuneus (Kleinhans et al. 2008), and superior frontal-caudate (Turner et al. 2006). These findings point to ASD as a disorder of aberrant cortical connectivity involving multiple brain networks. The long-distance connectivity impairment is supported by anatomical MRI findings of aberrant white matter growth patterns in the first few years in ASD (Courchesne et al. 2001; Hazlett et al. 2005; Sparks et al. 2002) and diffusion tensor imaging (DTI) findings of reduced white matter integrity later in life (Alexander et al. 2007; Cheung et al. 2009; Fletcher et al. 2010; Shukla et al. 2011).

Cognitive Demand: Task-Based vs. Resting State Functional Connectivity

Traditionally, fMRI studies have relied on cognitive tasks to elicit hemodynamic changes in the brain, which represent an indirect measure of neuronal activity. In ASD research, many earlier fMRI studies reported reduced activation in brain areas associated with functions like face-processing, ToM, and visual processing. Such studies served the primary purpose of understanding specialized function or dysfunction of a single region. However, studies in the last decade have begun examining the activation-driven interregional BOLD correlations in ASD (Muller et al. 2011). Thus, synchronized patterns of activation induced by a task would entail high correlation, which in turn would imply the functioning of the brain as a coordinated, coherent unit. The tasks used for task-induced fcMRI studies in ASD include, but not limited to, cognitive (working memory, problem-solving, response inhibition), social (ToM, biological motion, face processing), language (discourse processing, prosody, pun, irony, sentence comprehension, semantic processing), visuospatial (visual imagery, visual search, embedded figures task, block design task, mental rotation), and motor (finger tapping). It should be noted that these task domains would loosely represent and elicit the symptoms that underlie the triad of impairments in autism. Most of these studies have reported alterations in brain activity and/or connectivity, possibly reflecting ineffective use of neural resources and impaired coordination in the modulation of psychologically-driven activation among brain regions.

Task-based functional connectivity studies have provided great insight into understanding the pathophysiology of autism and its relationship with behavioral symptoms. Nevertheless, there are points to ponder while considering their broader implications. For instance, compensatory neural routes used by individuals with ASD may result in reduced time series correlations in "typical" networks and can trigger a difference in connectivity when compared to TD participants.

In addition, task-based functional connectivity studies assume the baseline connectivity in ASD and TD individuals to be equal, which may not be the case. Therefore, examining spontaneous low-frequency BOLD fluctuations is critical in order to determine whether the task-based alterations in connectivity in ASD is a by-product of their baseline brain functioning. The implementation of a temporal (low-pass) filter serves the purpose of isolating these spontaneous low-frequency BOLD fluctuations ($0.008 < f < 0.08$), which are considered to reflect network-specific intrinsic functional connectivity most robustly, even in the absence of a cognitively demanding task (Biswal et al. 1995; Cordes et al. 2001; Fox and Raichle 2007). An alternative to assess connectivity without relying on task-based fMRI is to compute the correlation between residual fluctuations in task activation datasets after task effects have been regressed out, i.e., the removal of task-related effects via nuisance regression and usage of a low-pass filter (Fair et al. 2007; Villalobos et al. 2005). While some of these studies found underconnectivity in autism (Jones et al. 2010), others did not (Mizuno et al. 2006; Noonan et al. 2009; Shih et al. 2010, 2011; Turner et al. 2006).

Yet another approach to study baseline connectivity is by using task-free resting state (continuous resting state) fcMRI. Based on the observation that the spontaneous BOLD fluctuations during resting state are not random noise, but specifically organized pattern of signal change, resting state has opened a new avenue for investigating functional connectivity (Fox and Raichle 2007). Resting state fcMRI may also be more feasible and appealing to study ASD individuals of low cognitive ability given that they may perform relatively poorly in demanding cognitive tasks. The emergence of resting state fcMRI has also facilitated data collection from younger children with ASD. Resting state fcMRI is usually studied in the absence of externally stimulated demanding cognitive tasks, where participants are typically instructed to close their eyes and think of nothing in particular or gaze at a fixation cross for a period between 5 and 10 min. While resting state requires no active cognitive response from participants, mind wandering and/or other variants still represent a task, though less constrained. Most of these studies (See Supplementary table S1) have had similar findings of underconnectivity in regions of the DMN, but also in other social processing-related brain circuits, such as the MPFC, the amygdala, insula, and hippocampus (Gotts et al. 2012; von dem Hagen et al. 2013). Overconnectivity has also been reported in some studies of resting state in autism between striatum with insula and STG (Di Martino et al. 2011), in the salience, default mode, frontotemporal, motor, and visual networks (Uddin et al. 2013a), and even in the DMN (Lynch et al. 2013). Interestingly, the findings of overconnectivity came from studies that examined fcMRI in children with ASD, while the underconnectivity was mainly seen in young adolescents and adults. Only one study did not find any significant

evidence for altered resting state connectivity in their participants with autism (Tyszka et al. 2013).

While the impact of task-based fcMRI in understanding the brain functioning in autism cannot be ignored, resting state fMRI provides a unique opportunity to learn about autism at a level which was previously considered non-existent. It should be noted that resting state fcMRI is not a substitute for task-based fcMRI; instead it should supplement the findings of task-based fcMRI. While each approach has its advantages and disadvantages, all three (task-based functional connectivity, task-removed baseline connectivity, and task-free resting state functional connectivity) provide a new perspective to our understanding of brain connectivity in ASD given that each one explores a different aspect of cognitive states.

Method of Data Analyses: ROI-Based vs. Whole Brain Analyses

An important factor that needs close examination in brain connectivity is the specific search space used for connectivity analysis, and how it differs across studies. In other words, in connectivity *where you search* and *the way you search* can have an impact on *what you find*. Most fcMRI studies of ASD use anatomical or functional regions of interest (ROI) to correlate signal time-courses. If the ROIs defined do not accurately represent participants with ASD and TD controls, it can create a bias, especially when ASD participants may not activate typical networks (Muller et al. 2011). Nevertheless, some studies have attempted to circumvent this by defining ROIs that are representative of both ASD and TD groups by examining activation sites shared by both groups from within-group analyses, or by combining activation clusters seen either in one or the other group (Just et al. 2007; Kana et al. 2012). Studies that report connectivity results across a selected few ROIs and not at the whole brain level need to be interpreted as specific to those ROIs. While the focus on specific ROIs may be justified by a priori hypotheses, failure to examine whole-brain effects may impede a comprehensive understanding of connectivity.

One technique that has been utilized to examine whole-brain functional connectivity is the independent component analysis (ICA). ICA identifies temporally coherent networks by selecting spatially independent brain areas or components whose hemodynamic time courses closely co-vary. ICA uses algorithmic constraints so that each voxel in a component that has the same time-course can be considered a functionally connected network without being limited to a priori regions. In ASD, ICA has been used to assess functional connectivity during resting state and it has revealed a pattern of underconnected regions between the precuneus, the anterior cingulate cortex and the DMN (Assaf et al. 2010); however, other studies have reported opposite findings using the same technique (Uddin et al. 2013a; Washington et al. 2013). Using

ICA, Cardinale et al. (2013) examined asymmetry of functional networks, where hemispheric asymmetries were detected in ASD in components thought to be implicated in auditory, visual, sensorimotor, executive, attentional, and visuospatial processing. More recently, ICA has been used in classification analyses, where the components from functionally connected networks were used as features for predicting the group membership of a subject [ASD or TD, (Uddin et al. 2013a)].

While whole brain functional connectivity methods have several advantages, such analyses must use stringent statistical corrections to account for multiple comparison issues given the large voxel number. Thus, the statistical threshold at which these studies report their results can have a huge impact on the replicability of the findings. In addition, connectivity results reported at different levels (whole brain and a priori ROIs) can not only help conceptualizing the findings better but also in improving the replicability of findings. Thus, future studies should take the aforementioned factors into account in order to improve the reliability and replicability of connectivity studies.

Is Heterogeneity of ASD Reflected in Brain Connectivity Findings?

Heterogeneity in the manifestation of autism has been an inherent challenge not only to researchers attempting to scientifically explain the disorder, but also to clinicians working towards designing appropriate intervention plans for affected individuals. Such differences have also affected the investigations to understand the neurobiological basis of ASD (Rudie et al. 2012a). The wide range of abilities and levels of functioning in ASD encompass severe cognitive impairment, no functional language skills, engagement in self-injurious behavior, poor adaptive living skills, and high intelligence with poor social skills. According to Geschwind and Levitt (2007), the neurobiological heterogeneity of ASD points to the likelihood that ASD may not be one disorder but many, both in the sense that it has myriad manifestations and because numerous etiological factors may converge on a similar outcome.

Numerous genetic studies have further supported the complex genetic model in that there is no one gene that explains at least 50 % of the cases of ASD and that the most frequently occurring genes appear at most 2 % of cases diagnosed with autism (Abrahams and Geschwind 2008). This implies that ASD is heterogenetic, with the located genes reflecting various mechanisms (Geschwind 2011; Happe et al. 2006). The variation of cellular mechanisms of possible ASD-linked genes reflects the multiple pathways affected and diverse traits in autism (Geschwind 2008; Losh et al. 2009). If the multiple pathways converged in certain brain regions, this may implicate that ASD is an integrative disorder. Thus, it is unlikely that the behavioral aspect of ASD can be equated to a single pathological entity on the neurobiological level.

Most of the empirical findings suggest that ASD is a disorder in which multiple networks are altered (not well connected or overconnected) compared to typically developing individuals, yet, most of these findings originate from only examining high-functioning individuals in the autism spectrum, which may make it problematic to generalize to the entire spectrum. There is hardly any functional imaging study involving low-functioning samples of ASD, perhaps due to obvious reasons, such as stereotypies (repetitive or ritualistic movement, posture, or utterance), thus potentially not being able to remain steady in the MRI scanner. This may also result in increased head motion, which represents a serious confound to fcMRI studies (Satterthwaite et al. 2013; Van Dijk et al. 2012). Nevertheless, some neuroimaging studies have addressed the heterogeneity in autism by examining intrasubject variability in their data by reporting spatial variability in activation (Muller et al. 2001) and volumetric differences in structures like amygdala (Sparks et al. 2002). Attempts to examine individuals at the lower end of the spectrum can provide valuable insights into understanding the nature and extent of neuropathology at different levels of intellectual functioning. One possible direction for this line of research, despite the challenges, is to acquire fMRI data using resting state since low-functioning individuals may not be able to fully understand or successfully complete a demanding cognitive task. Another approach to examine low-functioning individuals with autism would be to induce light sleep during the fMRI scan. Some studies have found that connectivity in the DMN does not significantly change during light sleep (Horovitz et al. 2008; Larson-Prior et al. 2009). However, there is always the risk of participants falling into deep sleep, which might increase modularity, hindering the brain to integrate information and therefore might account for decreased consciousness during dreamless sleep (Boly et al. 2012).

Developmental Trajectory of Brain Connectivity in Autism

Since ASD is a pervasive developmental disorder, the alterations in connectivity observed may reflect delayed and/or disrupted developmental maturation of the brain. However, the dearth of longitudinal neuroimaging studies has limited our knowledge of the developmental trajectory of brain connectivity in ASD. Most of the studies of functional connectivity in ASD in children under the age of 12 years have reported increased functional connectivity, while studies involving adolescents and adults have reported reduced functional connectivity (Uddin et al. 2013b). Such findings point to differences in critical developmental delay and/or deficits that can impact brain connectivity.

A growing body of studies has documented age-related increases in white matter volume in typical individuals (Lenroot and Giedd 2006), which may be related to increases in long-range functional connectivity from childhood through

adolescence and into adulthood (Fair et al. 2008; Kelly et al. 2009). Recent reports also suggest strengthening of structural and functional connectivity with age (Hagmann et al. 2010; Supekar et al. 2010; Uddin et al. 2011). Structural MRI studies have reported evidence of larger brains in younger children with autism (2–4 years old) compared to older children (10-year old) who had a significantly smaller brain (Courchesne et al. 2001). In addition, early overgrowth of white matter among young children with autism, followed by reduced white matter in adolescence and adulthood could underlie the reported findings of overconnectivity in children and underconnectivity in adolescents and adults (Courchesne et al. 2001, 2003; Waiter et al. 2005). This is parallel to DTI findings of increased fractional anisotropy (FA) in children with ASD (Ben Bashat et al. 2007; Cheng et al. 2010; Cheung et al. 2009; Ke et al. 2009), and reduced FA in young adolescents and adults with ASD (Barnea-Goraly et al. 2004; Fletcher et al. 2010; Sahyoun et al. 2010; Sundaram et al. 2008).

Other Indices of Brain Connectivity: Effective Connectivity & White Matter Integrity

For most part of this review, we have focused on fcMRI studies as the neural connectivity models of ASD are primarily based on functional connectivity. However, a holistic understanding of the brain would also entail gathering information about the nature and route of information transfer, and axonal integrity. The number of published studies on these topics, especially effective connectivity (causal influence of one brain area on another) in autism, is relatively small compared to fcMRI studies. However, the variation in methodology and inconsistencies in fcMRI findings cannot be ignored and would suggest the need for understanding more indices of brain functioning in autism. Thus, we have included a limited discussion on structural and effective connectivity and white matter integrity.

Effective and Anatomical Connectivity

Functional connectivity is a method for assessing observed correlation between active brain areas, but does not provide insight into the time-lagged causality and directionality of such correlations. Effective connectivity, on the other hand, provides information about the influence one system exerts over another with respect to a given experimental context (Buchel and Friston 2000; Friston 2011). Only a handful of studies have examined effective connectivity in ASD. In one study, Wicker and colleagues (2008) reported abnormal patterns of effective connectivity in ASD during explicit emotion processing with the prefrontal cortex as a key site of dysfunction. In another study, Bird and colleagues (2006) found atypical flow of information between extrastriate cortex and V1 in autism during attentional modulation of social information. Yet another study revealed atypical connectivity of the

imitation network (IFG, IPL, and STS) with an enhanced role of the dPFC (Shih et al. 2010). Similarly, Shen et al. (2012) found an atypically enhanced network participation of extrastriate cortex via a direct path connecting it with the IFG. More recently, Deshpande et al. (2013) found reduced effective connectivity in participants with ASD during a theory-of-mind task. These studies suggest differences in information transfer among brain areas in autism. Further studies are needed that examine both functional and effective connectivity in order to better understand the functioning of different networks in autism.

One of the obvious questions emerging from functional connectivity alterations in autism is about the quality and integrity of axonal fibers that connect different brain areas. Anatomical connectivity can be measured using DTI, which examines the water diffusion along white matter fibers in the brain. Since cooperation between distal nodes in functional brain networks rely on axonal connections, the integrity of these physical connections can prove vital. DTI studies in ASD have consistently reported abnormal FA in several white matter fiber bundles (Alexander et al. 2007; Keller et al. 2007; Lee et al. 2007) reflecting white matter damage or reduced axonal integrity. Other DTI studies, conducted on participants who are 8 years or older, have detected increased mean diffusivity and/or radial diffusivity in regions such as the corpus callosum, and arcuate fasciculus in autism (Fletcher et al. 2010; Shukla et al. 2011). Studies examining younger populations report partially divergent results. For example, Ben Bashat and colleagues (2007) found increased FA for a number of tracts (including corpus callosum) in a small sample of toddlers with ASD (Ages 1–3 years old), and in frontal lobe tracts in short-range fibers in children around 5 years old (Sundaram et al. 2008) and others (Cheng et al. 2010; Ke et al. 2009). Such heterogeneity of results may arise from the rapid developmental changes in white matter in children with ASD. Establishing anatomical connectivity bases to alterations in functional connectivity in autism has been less explored (Just et al. 2007; Kana et al. 2006), although such relationships have been reported in typical population (Greicius et al. 2009).

A few recent studies have examined connectivity in ASD using simultaneous DTI and fcMRI (Delmonte et al. 2013; Deshpande et al. 2013; Kana et al. 2012; Mueller et al. 2013; Nair et al. 2013). These studies provide two levels of investigation, although sometimes finding no significant direct relationship between the two. Another technique that can supplement functional and anatomical connectivity is proton magnetic resonance spectroscopy (1H-MRS), which detects the concentration of brain metabolites based on chemical resonance shift. Such studies, if used in conjunction with fMRI and DTI can provide yet another layer of information on the neurobiology of autism.

Other non-invasive neuroimaging methods that could complement future connectivity studies in autism are EEG and

MEG. While fMRI can measure the blood flow in the brain in a matter of seconds, EEG and MEG can measure electrical and magnetic signals of neuron firing on the order of milliseconds and, therefore, may reflect properties of brain function that are distinct from fMRI. Previous EEG/MEG studies in autism have reported abnormal synchronization of brain activity in different band frequencies during cognitive tasks where abnormal fcMRI has also been observed, such as sentence processing (Braeutigam et al. 2008), executive function (Perez Velazquez et al. 2009), and resting state (Murias et al. 2007). More recently an MEG study, (Buard et al. 2013) found reduced evoked high-gamma activity in the ASD group in the right superior temporal gyrus (STG) and reduced high-beta/low-gamma evoked power in the left inferior frontal gyrus (IFG) during a picture-naming task. It is important to note that with the better temporal resolution of EEG and MEG, the findings of these studies support disrupted connectivity reported by fcMRI studies.

Brain Connectivity Research in Autism: Implications and Future Directions

One of the primary goals of neurobiological investigations of ASD is to understand its etiology. A clear delineation of a neural marker for autism can potentially lead to aiding the diagnostic process, which currently is only behavior-based. One aspect of concern in connectivity studies in ASD is the relatively medium-to-small sample sizes. Considering the high cost involved in neuroimaging, data sharing and/or multicenter projects would be quite effective (Di Martino et al. 2013); however precautions need to be taken considering the differences in protocols across sites. Despite these shortcomings, neuroimaging based brain connectivity assessment provides a promising window in identifying a neural signature of autism. While most of the studies discussed in this paper are fMRI-based assessment of functional connectivity, such measures can be complemented by other modalities of imaging, such as DTI for anatomical connectivity, EEG and MEG for connectivity with better temporal resolution, and proton magnetic spectroscopy (1H-MRS) to assess neuronal health. Each index of brain connectivity (functional, anatomical, effective) in conjunction provides a great deal of information about the nature of the neural mechanisms underlying autism. Such an approach will provide a multi-level characterization of the neurobiology of ASD.

In addition, complex network analyses such as graph theory can be used to examine both anatomical and functional connectivity, and describe complex systems as a set of nodes (i.e., brain regions) and edges (i.e., connections between nodes), and characterize the brain as a complex network with a hierarchical modular organization consisting of several major functional communities (Wang et al. 2010). Graph theory

can examine functional specialization (connectivity *within* major networks) and functional integration (connectivity *between* different networks) in a sense that it can be viewed from at least two different perspectives, one based on the efficiency of global communication and the other on the ability of the network to integrate distributed information (Sporns 2013). Recent functional connectivity studies using graph theory in ASD have found reduced modularity (a network organized into densely connected modules that are segregated from each other), global efficiency (which describes the average number of connections to be crossed to go from each voxel to every other voxel in the brain), increased betweenness centrality, (which indicates the degree to which a seed or node functions as a hub within and between networks), and altered local connection density (the number of connections of one voxel in proportion to the total number of possible connections) in several functioning networks (Maximo et al. 2013; Redcay et al. 2013; Rudie et al. 2013; You et al. 2013). This entails that functional differentiation may play a factor in reduced modularity and global efficiency and altered density of connections which may be reflected in brain connectivity.

Another important factor related to information processing is segregation and integration across time and task. Most fcMRI studies provide a summary of the brain dynamics over a long period of time (5 to 10 min). Functional connections are in constant flux and vary across time, which can be described as fluctuations in brain networks across time. These network dynamic approaches can be useful in ASD research, given that attentional deficits have been reported in ASD. Such deficits can affect in switching from one brain network to another in a fast manner (Kana et al. 2011). The integration of different modalities of neuroimaging in ASD and in other complex developmental disorders will certainly bring us a step closer to a better understanding of such disorders.

Perhaps a major outcome of neuroimaging research in neurodevelopmental disorders would be the implementation of neuroimaging-based inference to complement behavioral assessment in diagnosis. The emergence of complex computer algorithms has enabled researchers to build classifiers that are capable of predicting group membership based on neural brain connectivity features. Only a handful of studies have relied on this technique in classifying ASD individuals from healthy controls based on their functional connectivity patterns (Anderson et al. 2011; Deshpande et al. 2013; Murdaugh et al. 2012; Nielsen et al. 2013; Uddin et al. 2013a). These studies have found reliable classification results with relatively high accuracy, and provide a promising starting point for brain-based classification and identification of neurodevelopmental disorders. Future studies should test the accuracy, sensitivity, and specificity of classification with larger and varied samples.

While neuroimaging-based markers can aid the diagnosis of autism, such markers can also be influential in designing interventions. In the last decade, advances in cognitive

neuroscience research have led to the development of intervention and treatments that rely on neurobiological principles. For example, neurofeedback (NF) training has emerged as an intervention based on operant conditioning that results in self-regulation of brain's electrical oscillations, and it is believed that NF produces positive behavioral changes in ASD children by normalizing the aberrant connections within and between neural circuits, although its precise mechanisms are not well understood (Pineda et al. 2012). By grounding in known anatomical (e.g., mirror neuron system) and functional markers (e.g., mu rhythms) of ASD, NF training holds promise to support current treatments for this complex disorder. Some studies have also used repetitive transcranial magnetic stimulation (rTMS), a non-invasive technique for manipulating cortical activity, in individuals with ASD as an intervention (Baruth et al. 2010; Sokhadze et al. 2009). Following post-rTMS sessions, individuals with ASD showed significant improvement in discriminatory gamma activity (30–80 Hz) between visual stimuli and also showed improvement in responses on behavioral assessment. Both NF training and rTMS, in a not-so distant future, could be used as intervention tools in order to ameliorate not only behavioral deficiencies observed in ASD, but also improve aberrant connections in the brain.

Conclusions

Aberrant brain connectivity has been a relatively stable finding in neuroimaging studies of autism spectrum disorders. Despite some pitfalls, our review of such findings suggests a great deal of promise in this line of research in understanding the pathobiology of autism. Attempts to establish alterations in connectivity as potential neural signature of autism, and to target faulty neural circuitry through intervention are significant from clinical and public health perspectives. Nevertheless, lots need to be done in fine-tuning the methods before even considering to adapt neurological findings to clinical world. Future studies of autism using neuroimaging should consider data sharing to improve sample size, implement multisite studies, and examine under-studied areas, such as developmental trajectory and females with autism. Also, with the recent advances in imaging techniques, the implementation of multiband sequencing in fMRI studies can be extremely useful for improving the statistical definition of brain networks, and diffusion based fiber tractography to visualize structural connections in the autistic brain (Feinberg and Setsompop 2013). The use of multimodal imaging seems another promising direction as it can uncover the complex neurobiology of autism by proving insights into multiple layers of brain organization and brain functioning.

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