

Neural Signatures of Autism Spectrum Disorders: Insights into Brain Network Dynamics

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Neuroimaging investigations of autism spectrum disorders (ASDs) have advanced our understanding of atypical brain function and structure, and have recently converged on a model of altered network-level connectivity. Traditional task-based functional magnetic resonance imaging (fMRI) and volume-based structural MRI studies have identified widespread atypicalities in brain regions involved in social behavior and other core ASD-related behavioral deficits. More recent advances in MR-neuroimaging methods allow for quantification of brain connectivity using diffusion tensor imaging, functional connectivity, and graph theoretic methods. These newer techniques have moved the field toward a systems-level understanding of ASD etiology, integrating functional and structural measures across distal brain regions. Neuroimaging findings in ASD as a whole have been mixed and at times contradictory, likely due to the vast genetic and phenotypic heterogeneity characteristic of the disorder. Future longitudinal studies of brain development will be crucial to yield insights into mechanisms of disease etiology in ASD sub-populations. Advances in neuroimaging methods and large-scale collaborations will also allow for an integrated approach linking neuroimaging, genetics, and phenotypic data.

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INTRODUCTION

Autism spectrum disorders (ASDs) are heritable neurodevelopmental disorders (eg, Bailey *et al*, 1995; Nordenbæk *et al*, 2014) in which manifestations of behavioral symptomology vary widely in severity. Core behavioral deficits associated with the disorder include impairments in social communication and social interactions, along with the presence of repetitive patterns of behavior, restricted interests, and/or altered sensory responsivity to external stimuli (American Psychiatric Association, 2013). Although these deficits serve as defining criteria on which diagnoses are currently based, not all individuals on the ASD spectrum display each symptom, and there is a broad spectrum of social, emotional, and cognitive impairment among diagnosed individuals.

The last decade has seen the rate of ASD diagnosis rise to an estimated 1 in every 68 children (Center for Disease Control, 2014), making early diagnosis and effective treat-

ment a critical public health concern. However, the heterogeneity present in individuals with ASD makes discerning a singular neuropathological cause and developing effective treatments very challenging. Thus, a major goal of ASD research is to understand the neurobiological underpinnings of ASD from a multidimensional perspective—investigating how brain anatomy, function, and connectivity are altered in ASD and how they vary among affected individuals.

Over the past two decades, major advances in magnetic resonance (MR)-based structural and functional neuroimaging have greatly enhanced our understanding of brain differences in ASD. In structural brain imaging, newer analysis approaches including cortical thickness mapping, voxel-based morphometry (VBM), diffusion tensor imaging (DTI), and the application of these methods in younger subject populations or in longitudinal studies have led to more specific and dynamic models of abnormal brain development in autism. In functional neuroimaging, the field has moved beyond task-based functional activation studies, which were typically limited to high-functioning children and adults. New acquisition methods, such as resting state functional MR imaging (fMRI), and novel data—analytic approaches now allow for the study of large-scale functional brain networks and connectivity in much

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younger populations including toddlers and infants at high risk for developing autism. Finally, the integration of both structural and functional imaging with genetic risk and behavioral data has driven the field toward a better understanding of gene–brain–behavior pathways in autism. Together, the corpus of imaging studies in autism have led to an emerging model of abnormal developmental connectivity, a dynamic model that accounts for both genetic liability and environmental influences that shape early brain development. In this review, we will present data from these major new domains of MR imaging work—structural MRI (sMRI), functional MRI, imaging-genetics, and connectivity studies, focusing on developmental trajectories and ultimately converging on a model of abnormal brain development in autism.

STRUCTURAL NEUROIMAGING (sMRI) STUDIES

Structural Volume Assessment (Volumetry)

Historically, some of the first efforts to characterize the neural correlates of ASD investigated differences in large-scale brain structures between affected individuals and neurotypical controls. Initial evidence for altered brain structure and enlarged brain volume in ASD came from postmortem investigations (eg, Bailey *et al*, 1998). The development of non-invasive MRI techniques subsequently allowed for more detailed study of brain volumes in specific brain regions across the lifespan in otherwise healthy individuals. The primary underlying hypothesis driving such studies has been that abnormalities in specific brain structures early in development, often assumed to be decreased gray matter volume, may pinpoint a causal neuroanatomical basis for behavioral features in autism.

Traditional methods for assessing volume rely on manual tracing of regions of interest (ROIs), often defined by macro-structural features (ie, hemispheres, lobes, subcortical areas, major gyri, and sulci) easily visible on high-resolution sMRI images. In toddlers with ASD, one of the most consistently reported global-level findings in sMRI is an increase in total brain volume of 5–10% compared with locally recruited neurotypical children (eg, Carper *et al*, 2002; Courchesne *et al*, 2001; Hazlett *et al*, 2005; Sparks *et al*, 2002; for a review, see Amaral *et al*, 2008 and Stanfield *et al*, 2008). Analyses of brain development suggest that brain volume is normal at birth, diverging from typical trajectories during early childhood when children with ASD experience a period of brain overgrowth (reflected by enlarged total brain volume); this period is then followed by a plateau in volumetric changes during adolescence, ultimately leading to adult brain volumes that fall within range of typically developing controls (Courchesne *et al*, 2001, 2007). However, there is also some evidence for enlarged total brain volume in adolescence and adulthood (Freitag *et al*, 2009; Hazlett *et al*, 2006).

In addition to enlarged total cerebral volume, ASD is characterized by atypical gray and white matter (WM)

volume in discrete brain structures (see recent reviews by Amaral *et al*, 2008; Chen *et al*, 2011; Stanfield *et al*, 2008; Steigler *et al*, 2011). The nature of these differences, unfortunately, has varied substantially across studies. An early finding in children, adolescents, and adults with autism reported marked decrease in volume of the cerebellar vermis (Courchesne *et al*, 1988, 1994); however, many of these subjects were low functioning. Several studies subsequently found that after controlling for or matching IQ cerebellar differences were no longer apparent (Levitt *et al*, 1999; Manes *et al*, 1999; Piven *et al*, 1992), suggesting that reduced cerebellar vermis may relate to intellectual dysfunction but not necessarily core features of autism. In other brain areas, both increases and decreases in volumes have been reported in many regions including the frontal cortex (eg, Hyde *et al*, 2010; McAlonan *et al*, 2005), superior temporal sulcus (eg, Boddeart *et al*, 2004), inferior parietal lobule (eg, Hadjikhani *et al*, 2006), cingulate, and fusiform gyrus (eg, Bonilha *et al*, 2008)—many areas known to have a role in social cognition.

Voxel-Based Morphometry

Recent advances in postimaging processing methods allow for comparisons of gray and WM density and volume on a voxel-by-voxel basis, referred to as VBM. Unlike traditional ROI-based volume analyses, VBM allows for whole-brain comparisons of gray and WM volume between two groups. Results of these studies comparing individuals with ASD to neurotypical individuals have been extremely mixed, often reporting heterogeneous and at times contradictory results (for a review, see Chen *et al*, 2011). In a recent meta-analysis of VBM studies covering a wide age range of individuals with ASD, Nickl-Jockschat *et al* (2012) found converging evidence for alterations in the lateral occipital lobe, postcentral gyrus, medial temporal lobe, basal ganglia (right caudate and left putamen), and a region in the right hemisphere near the parietal operculum. The authors also suggested that puberty had an impact on the findings reported in VBM studies, namely that brain areas reported as having reduced gray matter in childhood were likely to be reported as having increased gray matter in adulthood, and similarly, brain areas reported as showing increased gray matter in childhood were likely to be reported as having decreased gray matter in adulthood. Thus, discrepancies in VBM findings in ASD may also be related to differences in sample characteristics across studies, particularly age, which impacts developmental trajectories of gray and WM growth (Lenroot *et al*, 2007).

Importantly, in some cases the nature of the reported volumetric differences (increases, decreases, or no change from neurotypical individuals) seems to be impacted by the age of the cohort under investigation. For example, in the amygdala, Schumann *et al* (2004) investigated regional volume in a cross-sectional cohort of males with ASD, finding enlarged amygdala volumes in the 8- to 12-year-old group, but no differences from control subjects in the 13- to 18-year-old group. Degree of amygdala enlargement has also been associated with more severe social and communication

impairment in children aged 3–4 years (Munson *et al*, 2006) and with anxiety symptoms in children aged 7–14 years (Juraneck *et al*, 2006). Furthermore, in a recent meta-analysis, Stanfield *et al* (2008) found that amygdala volumes were increased in young children with ASD, but decreased with age, eventually falling to neurotypical volume levels. Even reports of head circumference changes across development, which have been consistently reported in ASD, have tended to suggest an age-specific pattern of initial overgrowth followed by reduced development in ASD (Courchesne *et al*, 2001).

WM Structure and DTI

Structural brain imaging studies in autism have increasingly moved from an early focus on gray matter volume to the structure and organization of WM. WM can be measured using MRI in several ways: by measuring the WM volume globally or regionally, the integrity of WM by diffusion tensor imaging (DTI), or the density of specific tracks using tractography, a DTI analytic technique. Atypical WM volume and other measures of WM integrity indicate a structural cause of disruptions in how different brain regions communicate with each other. This research has contributed to an emerging understanding of autism as a disorder of developmental connectivity.

Early studies focused on WM volume in key regions associated with ASD. For instance, regional differences in WM volume have been reported in individuals ranging from toddlerhood to middle age in the cerebellum and in multiple regions of the corpus callosum (eg, Egaas *et al*, 1995; Hardan *et al*, 2009; Keary *et al*, 2009; Piven *et al*, 1997), a WM tract connecting the left and right hemispheres that is critical for integration of neural information across distant brain regions. Indeed, there is evidence that global brain enlargement in many individuals with autism is due primarily to increased WM but decreased gray matter volume. In one seminal study, Herbert *et al* (2003) divided the WM in local ‘radiate’ compartments composed largely of short, locally connecting circuits, and long tracts. They found that in children with ASD there was increased WM volume in more surface cortical regions, while the deep, long pathway structures including the corpus callosum either exhibited lower or unchanged WM volume. The WM differences showing overgrowth in cortical regions are later to myelinate, and suggest a very specific developmental pattern of abnormal WM overgrowth. In contrast, Hardan *et al* (2009) found that children with ASD had reduced corpus callosum volumes, and that regional reductions in corpus callosum subdivisions were associated with greater reciprocal social interaction impairments, atypical speech, and sensory abnormalities. Together, these brain-based volume differences suggest altered development of brain structures implicated in high-level sociocognitive processes in individuals with ASD.

Diffusion MRI (dMRI; see Box 1; Figure 1) provides a measure of structural connectivity by measuring the

BOX 1

Diffusion tensor imaging: DTI (Figure 1) allows for mapping of WM tracts by measuring the diffusion of water molecules in the brain (eg, Basser and Pierpaoli, 1996). When unrestricted by physical boundaries, water diffuses in an isotropic manner (equally in all directions). In the brain, the diffusion of water is restricted by the physical boundaries of axons and myelin. Thus, in the brain the diffusion of water occurs preferentially along the long axis of the axon. DTI measures the principal direction of water diffusion in each brain voxel and models this information in the shape of an ellipsoid whose long axis points in the direction of the mean axonal direction for the voxel—this information can be reconstructed to identify gross trajectories of WM fiber tracts in the whole brain. The most reported measure in DTI neuroimaging studies is FA, which provides a metric of the degree of diffusion for each voxel and is thought to be a reflection of WM integrity. In DTI, the direction in which fiber tracts travel is typically expressed with different colors that correspond to the primary direction at each point. In addition, various mathematic algorithms can approximate the pathway a particular fiber tract takes as it curves and turns to reach its target, thus isolating fiber bundles throughout the brain. This approach is called tractography. Although DTI has greatly improved our understanding of structural brain connectivity at the macroscale, confounds including the inability to distinguish crossing fibers because of spatial resolution limitations imposed by imaging at the voxel level, the limited ability to quantify connection strengths, and the probabilistic nature of DTI tractography (potentially leading to inaccurate models), remain active areas of methodological development (Craddock *et al*, 2013).

diffusion of water molecules in the brain to reconstruct WM tracts. The extent to which water molecules diffuse in a consistent direction along the WM tract provides a proxy measure of WM integrity, the most common of which is fractional anisotropy (FA). Diffusion studies in children, adolescents, and adults with ASD have documented multiple structural connectivity differences, mostly suggesting reduced WM integrity in long-range anterior–posterior and interhemispheric fiber tracts (Alexander *et al*, 2007; Barnea-Goraly *et al*, 2004, 2010; Cheng *et al*, 2010; Shukla *et al*, 2011; Sundaram *et al*, 2008), with few studies reporting heightened WM integrity (Bode *et al*, 2011; Cheng *et al*, 2010; Cheung *et al*, 2009). Notably, many of the specific fiber tracts reported as altered in ASD serve as structural connections between brain regions subserving social cognition. For example, Cheon *et al* (2011) found reduced connectivity in the right anterior thalamic radiation, corpus callosum, and uncinate fasciculus in children with ASD, suggesting disruption of thalamic-to-frontal structural connectivity. In addition, reduced structural integrity of the corpus callosum has been consistently observed from childhood through adulthood (eg, Alexander *et al*, 2007; Keller *et al*, 2007) and may be associated with lower nonverbal IQ in ASD subjects (Alexander *et al*, 2007). However, observed differences in WM structure may not be causative in ASD, as unaffected siblings also show widespread reductions in structural integrity in medial prefrontal WM regions, anterior forceps, in substructures of the corpus callosum (body and splenium), cingulate, superior longitudinal fasciculus, internal and external capsules, superior temporal gyrus, and temporoparietal junction (Barnea-Goraly *et al*, 2010). Thus, it is possible that dMRI measures of structural integrity may be indicative of increased risk for ASD diagnosis only.

Despite these findings, a few critical questions remain unanswered in sMRI research among children with ASD. First, how do these structural abnormalities relate to specific

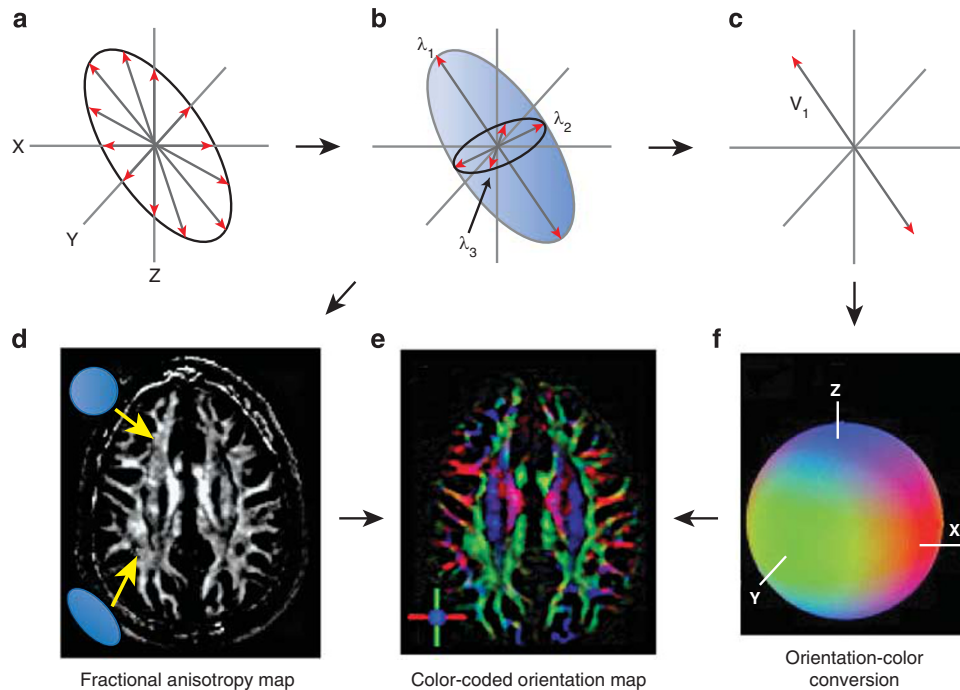


Figure 1. Diffusion tensor imaging. (a) For each voxel, the diffusion of water is measured in multiple directions. (b) The shape of the diffusion ellipsoid is estimated, yielding values for three axes of the ellipse. (c) The primary diffusion direction for a given voxel is taken as the direction of primary fiber orientation. (d) From the diffusion ellipsoid a fractional anisotropy map is created in which isotropic diffusion (spherical—ie, uniform diffusion in all directions) is represented by darker shades, while anisotropic diffusion (directional—ie, with primary diffusion along one axis) is represented by lighter shades. (f) The direction of primary diffusion is color converted and combined with luminosity of the FA map to yield a color-coded fiber orientation map (e). Reprinted from Mori and Zhang (2006), with permission from Elsevier.

autism symptomatology? Few studies have related variations in brain structural abnormalities to specific phenotypes in autism, other than overall severity. In the language domain, Bigler *et al* (2007) found that superior temporal gyrus volume related to receptive language ability among typically developing children and adolescents but not those with autism, suggesting a breakdown in the structure–function relationship. In an early study, Pierce and Courchesne (2001) reported that cerebellar hypoplasia in children with ASD was correlated with the severity of repetitive behaviors. Together, these reports lend further support to the notion that heterogeneity in neuroimaging findings may be related to differences in subject characteristics (age, severity of behavioral symptomatology, and so on) across samples, and highlight the need for longitudinal studies of cortical volume development in ASD. However, without comprehensive, large-scale studies that examine multiple regions and multiple phenotypes in the same samples, we cannot yet conclude that specific regional brain volume differences relate to autism phenotypes.

A second major issue concerns whether structural brain abnormalities are causal for ASD features, or whether early behavioral changes and abnormal interactions with the environment shape the development of brain structure to reveal these patterns of group differences. Longitudinal studies can help address this issue. The recent DTI findings of WM abnormalities found in infants at-risk for autism, in an age range that typically precedes diagnosis, suggests that

such differences precede and thus may be causal for ASD (Elison *et al*, 2013; Wolff *et al*, 2012), although this is not a conclusive evidence. Ongoing studies that combine imaging with intervention may also shed light on causality, however, there are as of yet no published findings of brain changes associated with early intervention.

FUNCTIONAL NEUROIMAGING (fMRI) STUDIES OF CORE ASD DEFICITS

In contrast to sMRI, fMRI measures neural activity in the brain that relates directly to ongoing cognitive functions *in vivo*. Numerous fMRI studies in ASD have examined multiple functions including motor, sensory, and language performance, but many studies have converged on the brain's social networks, reflecting an appreciation that autism is primarily a disorder of social cognition (other recent ASD neuroimaging reviews include Dichter 2012; Pelphrey *et al*, 2011; Verhoeven *et al*, 2010). It is increasingly accepted that the primate brain has developed a series of brain regions constructed into networks collectively called the 'social brain', evolutionarily developed to recognize and infer the intentions of others (Brothers, 1990). Among the fundamental behaviors associated with social cognition are face recognition, perceiving emotions in others, appreciating the meaning of eye gaze, discriminating biological motion, the ability to infer the mental states of

others, and responding to social rewards such as smiling. The biological ability of neurons to respond specifically to social stimuli has been demonstrated in studies of non-human primates, where single-cell recordings have detected neurons that fire selectively to faces in the superior temporal sulcus (Bruce *et al*, 1981; Desimone *et al*, 1984; Perrett *et al*, 1982), in response to a moving biological entity (eg, a person walking; Bruce *et al*, 1981), head orientation, or direction of eye gaze in the temporal cortex (Perrett *et al*, 1985), and when animals perform or watch others perform an action, providing a means of encoding the goals and intentions of others, in the premotor cortex (eg, di Pellegrino *et al*, 1992; Ferrari *et al*, 2005; Fogassi *et al*, 2005). Further, primate studies indicate that social stimuli in themselves are rewarding (eg, Andrews and Rosenblum, 1993, 1994), and that different types of social stimuli provide differential reward value (eg, viewing faces of high-status *vs* low-status conspecifics; Deaner *et al*, 2005). Together, these studies suggest that social stimuli and social interactions have an evolutionarily conserved neurobiological underpinning and provide socially relevant stimuli and brain loci with which to test and generate hypotheses about atypical neural function underlying social behavior in ASD. Current diagnostic criteria for ASD include deficits in social communication (eg, non-verbal communication, reciprocity, and so on) and the presence of restricted or repetitive patterns of behavior (eg, restricted interests, atypical sensitivity or interest in sensory stimuli; American Psychiatric Association, 2013), thus we focus our review on task-based fMRI studies tapping into core behavioral deficits observed in individuals with ASD—responding to biological motion, looking at faces, understanding and interpreting the intentions of others (theory of mind (TOM)), language and reward processing, and sensory processing differences.

Face Processing

Faces convey critical information not only about people's identity, but also about internal states and intentions, as well as about perceptions of the environment (eg, a fearful face in response to a threatening situation). Research in neurotypical infants has shown a preference to attend to the human face over face-like stimuli from very early life (Fantz 1963; Goren *et al* 1975; Legerstee *et al*, 1998; Mondloch *et al*, 1999). Importantly, children with ASD do not show the same attention to faces as neurotypical children. A retrospective study of home videotapes revealed that infants later diagnosed with ASD could be distinguished from neurotypical children based on a lack of attention to other people and faces (Osterling *et al*, 2002; Osterling and Dawson, 1994), and further, toddlers with ASD appear to be less engaged by faces as they are faster to disengage from faces to attend to a peripheral target (Chawarska *et al*, 2003, 2010). Reduced attention to social stimuli very early in life may predispose children with ASD to atypical social cognition resulting in altered neurodevelopmental trajectories and ultimately to atypical social behavior (Pelphrey *et al*, 2011).

Imaging studies suggest that viewing faces is associated with activity in the bilateral fusiform face area (a region of the fusiform gyrus), lateral occipital cortex, posterior superior temporal sulcus (eg, Grill-Spector *et al*, 2004), and amygdala (especially during fearful face processing; eg, Guyer *et al*, 2008). It was originally proposed that children, adolescents, and adults with ASD display reduced activation to faces based on fMRI studies finding reduced activity in the fusiform gyrus (Corbett *et al*, 2009; Critchley *et al*, 2000; Dalton *et al*, 2005; Hubl *et al*, 2003; Kleinhans *et al*, 2011; Piggot *et al*, 2004; Schultz *et al*, 2000; Wang *et al*, 2004), and amygdala (Corbett *et al*, 2009; Kleinhans *et al*, 2011) during face and emotion processing. However, brain activity in these areas may be mediated by extrinsic factors that increase attention. For example, presenting ASD subjects with a cue to direct visual attention to the eye region (ie, a cross hair at eye level before face stimuli presentation; Bookheimer *et al*, 2008; Davies *et al*, 2011; Hadjikhani *et al*, 2004) is associated with increased activity in the fusiform gyrus. Furthermore, in a combined eye-tracking and neuroimaging study, Dalton *et al* (2005) found that the amount of time spent looking at the eyes was associated with greater activity in the fusiform gyrus and amygdala in individuals with ASD. In addition, Pierce *et al* (2004, 2008) found that when participants with ASD viewed faces of personally significant individuals (ie, mother, friend), activity in the fusiform gyrus was comparable to that of controls. Together, these studies suggest that the original findings of hypoactive responses to faces in ASD are due to either avoidance of or lack of attention to the eye area. It appears that 'normative' levels of activity in the fusiform gyrus may be elicited from ASD subjects by explicitly cueing attention to face stimuli, but doing so may also increase anxiety responses; indeed increased anxiety with direct gaze may underlie eye contact avoidance in ASD (Kleinhans *et al*, 2010).

Biological Motion

The ability to detect salient social stimuli depends critically on the ability to detect biological motion, a behavior present in infancy (Hoehl *et al*, 2009; Simion *et al*, 2008). Examples of biological motion include following eye gaze or discerning the patterns of how people walk and move, as opposed to mechanical motion. This skill develops quickly in early infancy, as neurotypical children can detect eye gaze deviations during social interactions at five months of age (Symons *et al*, 1998). Early attention to biological motion likely heightens the amount of exposure infants receive to social stimuli, setting the stage for ongoing cognitive development in neural substrates involved in social and emotional cognition. Importantly, 2-year-old children with autism show an early behavioral deficit in attention to human biological motion visualized in point-light animations (Klin *et al*, 2009), an impairment that persists into late childhood (Blake *et al*, 2003).

Neuroimaging investigations of biological motion have used a variety of stimuli including animated human

characters moving their mouth, hand, or eyes (Morris *et al*, 2008; Pelphrey *et al*, 2005; Pelphrey and Morris, 2006), moving elements designed to display a range of human-like qualities (eg, a human, a robot, a grandfather clock, and a mechanical assembly; Carter and Pelphrey, 2006), and point-light displays of both non-biological (eg, a spinning wheel) and biological (eg, walking) motion (Herrington *et al*, 2011). These studies suggest that in neurotypical individuals, processing biological motion relies on neural activity in the superior temporal sulcus, (Carter and Pelphrey, 2006; Morris *et al*, 2008; Pelphrey *et al*, 2005; Pelphrey and Morris, 2006), inferior frontal gyrus, amygdala, and visual areas including the fusiform gyrus (eg, Herrington *et al*, 2011). In individuals with ASD, perception of biological motion is consistently associated with reduced activity in the superior temporal sulcus compared with controls when viewing point-light displays (Freitag *et al*, 2008; Herrington *et al*, 2007; Koldewyn *et al*, 2011). Individuals with ASD also show hypoactivation of the ventrolateral prefrontal cortex (Davies *et al*, 2011), temporo-parietal junction and superior temporal sulcus (von dem Hagen *et al*, 2013) when viewing direct *vs* averted gaze. Reduced activity in neurotypical correlates of biological motion in individuals with ASD suggests atypical processing of biological motion cues present in everyday social contexts. In neurotypical individuals, detection of biological motion may serve to direct attention to socially relevant stimuli, a behavior that appears to be impaired in ASD.

TOM and Pragmatic Language

Theory of mind (TOM) is described as the ability to understand and infer the actions and intentions of others (Baron-Cohen, 1991; Frith and Frith, 1999). It is well documented that individuals with ASD show deficits in higher-level social information processing, such as recognizing social faux pas (Baron-Cohen *et al*, 1999), and extrapolating the mental state of others based on cues expressed through the eyes and by voice (Baron-Cohen *et al*, 1997, 2001; Baron-Cohen and Hammer, 1997). In neurotypical individuals, TOM skills such as reasoning about the beliefs of others or their state of mind (eg, Saxe *et al*, 2009; Saxe and Kanwisher 2003) elicit neural activity in the superior temporal sulcus, temporo-parietal junction, medial prefrontal cortex (MPFC), and temporal poles (Gallagher *et al*, 2000; Saxe *et al*, 2009; Saxe and Kanwisher, 2003). In ASD, neuroimaging studies of TOM have shown reduced activity in the left inferior frontal gyrus (Harris *et al*, 2006; Just *et al*, 2004), MPFC (Castelli *et al*, 2002; Kana *et al*, 2009, 2014; Nieminen-von Wendt *et al*, 2003; Wang *et al*, 2007), and temporo-parietal junction (Kana *et al*, 2014). Notably, many of these regions overlap with those activated in biological motion, suggesting a potential common network underlying a range of social deficits in ASD.

Paralleling the deficits seen in TOM abilities, individuals with ASD also show deficits in language processing, particularly high-level language processing such as the proper

use and comprehension of pragmatics, or appropriate use of language in a social context (Boucher, 2003; for a review, see Groen *et al*, 2008). Behavioral studies have reported atypical production and comprehension of prosody (the rhythm, stress, or intonation of speech) in children with high-functioning ASD (eg, McCann *et al*, 2007). Deficits in prosodic comprehension have been documented in both children and adults with ASD, who have difficulty inferring the mental state of others when relying on vocal intonation cues (eg, Golan *et al*, 2007; Peppé *et al*, 2007; Rutherford *et al*, 2002). In line with the behavioral deficits observed in ASD, functional neuroimaging studies also report atypical activation of language relevant brain areas. For example, a growing number of fMRI studies have reported more bilateral or right-lateralized activity in adults (Kleinmans, *et al*, 2008a; Mason *et al*, 2008; Tesink *et al*, 2009) and children (Knaus *et al*, 2010; Redcay and Courchesne, 2008) with ASD. Although some studies have shown hyperactivation (Wang *et al*, 2006), others have reported hypoactivation (Gaffrey *et al*, 2007; Wang *et al*, 2007), and a few others have reported simultaneous decreased activity in frontal brain regions and increased activity in posterior temporal areas (Harris *et al*, 2006; Just *et al*, 2004) during basic language processing.

A handful of studies have focused on higher-level language abilities in ASD by assessing the neural correlates of pragmatic or prosodic cues in language comprehension. In one study of pragmatic language, Tesink *et al* (2009) examined neural activity during a task in which adults with ASD made inferences about a speaker's characteristics (ie, gender, age, and social background) using voice-based cues. Although both ASD and neurotypical controls showed equivalent behavioral performance, the ASD group showed greater activity in the right inferior frontal gyrus, suggesting an atypical and potentially compensatory neural mechanism in individuals with ASD. A second study of pragmatic language processing found that adults with ASD showed increased activity in the left supramarginal gyrus compared with controls (Hesling *et al*, 2010). Several other investigations have focused on the neural correlates of prosodic cues in ASD by examining brain activity during processing of ironic *vs* sincere speech. Wang *et al* (2006) used a task in which children and adolescents with ASD listened to short scenarios and made a choice to indicate whether the speaker was sincere or sarcastic. Although both the ASD and neurotypical control groups performed well on the task, the children with ASD showed increased activity in the right inferior frontal gyrus and bilateral temporal pole, suggesting more effortful processing in the ASD group during high-level prosodic language processing. A second study by Wang *et al* (2007) tested whether explicit instructions to attend to facial or tone of voice cues could regulate neural activity in children with ASD during ironic speech processing. Indeed, the authors demonstrated that while the ASD group showed reduced activity in the MPFC during ironic *vs* sincere speech (a region associated with TOM), this activity was modulated by specific instructions to attend to face or voice

cues, and that activity in this region was negatively correlated with social impairment in ASD (ie, less activity in the MPFC was associated with greater social impairment). Finally, a recent study by Colich *et al* (2012) showed that when processing ironic *vs* sincere speech, children with ASD show a more bilateral pattern of activation in right hemisphere language homologues, and in brain areas implicated in TOM processing (such as the MPFC) compared with neurotypical children. Together, these studies suggest that compensatory activity in distributed brain regions in individuals with ASD may allow for normal behavioral performance during high-level language processing, and that atypical neural activity may be modulated by attention to secondary social (ie, face and voice) cues. Further, although language deficits are a common feature of ASD, it is no longer required for an ASD diagnosis (DSM V); thus heterogeneity in the ASD phenotype may help explain the range of findings in language regions among children with ASD.

Reward Processing

In humans, social cues such as smiles are processed early in infancy and appear to be highly rewarding, biasing attention toward these cues. Early attentional biases to social stimuli may be modulated by increased neural mediated reward-value for these stimuli. Evolutionarily, successful social interaction in infancy is critical for survival as it impacts mother-offspring bonding (Lévy *et al*, 1995). One general theory of autism posits that reduced social motivation underlies the development of autism (Chevallier *et al*, 2012); reduced reward responsiveness could provide a potential neural basis of reduced social motivation. Animal studies suggest that reward processing involves activity in the anterior cingulate cortex, orbitofrontal cortex, and ventral striatum (Febo *et al*, 2005; Young *et al*, 2005). Importantly, recent neuroimaging studies have found that the same areas underlie reward processing in humans, including food rewards (O'Doherty *et al*, 2002), monetary rewards (O'Doherty *et al*, 2001; Thut *et al*, 1997), and social rewards such as viewing happy faces (Phillips *et al*, 1998).

Given that children with ASD display reduced attentional biases to social stimuli, recent neuroimaging work has begun to investigate whether decreased activity in social-reward brain regions may have a role in atypical ASD social behavioral and neural phenotypes. These studies have primarily contrasted social reward stimuli (ie, faces) to monetary reward in individuals with ASD and neurotypical controls. Compared with controls, children, adolescents, and adults with ASD show aberrant activity during monetary reward conditions in the anterior cingulate, frontal cortex, and ventral striatum (Dichter *et al*, 2012; Kohls *et al*, 2013; Schmitz *et al*, 2008; Scott-Van Zeeland *et al*, 2010). During positive social reward conditions (ie, smiling faces), ASD participants show reduced striatal activity in comparison with controls (Delmonte *et al*, 2012; Scott-Van Zeeland *et al*, 2010). Recently, Cascio *et al* (2014) investigated brain

activity in children with ASD during exposure to images of participant-specific restricted interest objects, aiming to disentangle whether the observed difference in neural activity during reward processing in ASD may be modulated by the salience of the reward, or instead represent broad functional atypicalities. Although both controls and individuals with ASD showed activity in reward-related circuitry when viewing pictures of their own interests, only the neurotypical group showed similar activity when seeing pictures of another child's interest. Conversely, the ASD group showed reduced activity in reward-related areas including the insula and anterior cingulate cortex when seeing pictures of another child's interest. Thus, similar to results in neuroimaging studies of face processing, extrinsic factors that increase attention to personally relevant rewarding stimuli may be associated with more neurotypical activity in individuals with ASD. As narrow, selective interests are a core feature of children with ASD, reduced neural responses in reward-related brain regions to non-preferred stimuli has face validity; however, these data do not provide a mechanistic causative explanation for these atypical fMRI findings.

Sensory Over-Responsivity

Many children with ASD display over-responsivity to sensory stimuli (eg, scratchy clothing and vacuum cleaners), but others are under-responsive and many are both over- and under-responsive depending on the situation (eg, Liss *et al*, 2006). Sensory processing issues in individuals with ASD have been challenging to study. Physiological studies often fail to find group (ASD *vs* control) differences, likely because they fail to take into account within-ASD heterogeneity (Rogers and Ozonoff, 2005). A recent neuroimaging study of sensory over-responsivity (SOR) found that children with ASD display hyper-reactivity in limbic areas (amygdala and hippocampus) and primary sensory cortices to mildly aversive visual and auditory sensory stimuli (Green *et al*, 2013). Notably, this study took into account individual levels of SOR, and found that activation in these areas was related to parent-reported SOR in both groups of children. Cascio *et al* (2012) compared neural response with pleasant, neutral, and unpleasant tactile stimuli in adults with and without ASD. They found that in general, the ASD group was under-responsive to the stimuli compared with the TD group, with the TD group having greater activation in multiple brain areas including the primary somatosensory cortex, middle frontal gyrus, superior temporal gyrus, and cingulate cortex. However, the ASD group had greater activation in the thalamus (pulvinar) in response to both the pleasant and unpleasant stimuli, and in the posterior cingulate and insula in response to the unpleasant stimulus. Greater insula response was correlated with severity of ASD symptoms. The authors hypothesized that individuals with ASD are hyporesponsive to pleasant tactile stimuli in primary and association somatosensory areas, but are hyperresponsive to unpleasant stimuli in areas associated

with emotional processing of sensory stimuli. Voos *et al* (2013) also found that in neurotypical adults, higher levels of autism traits were associated with diminished response to pleasant touch in the superior temporal sulcus and orbital frontal cortex. Although neither the Cascio *et al* (2012) nor Voos *et al* (2013) study examined individual differences in sensory processing, these studies suggest that social touch is processed differently from unpleasant sensory stimuli in individuals with ASD.

In summary, a broad range of fMRI studies tapping into several aspects of social cognition and other core deficits show abnormal brain activity in ASD. A recent meta-analysis of 39 task-based fMRI studies in children and adults with ASD found that during social neuroimaging experiments, individuals with ASD had reduced probability of activation in the anterior cingulate cortex, right amygdala, and left frontal gyrus, as well as greater probability of activation in somatosensory brain regions (Di Martino *et al*, 2009). In particular, research shows reduced engagement throughout brain networks involved in processing social stimuli and responding to both positive and negative affect, as well as brain systems involved in understanding the emotional states of others (eg, Dapretto *et al*, 2006) and regulating sensory and emotional experience. Interestingly, in some cases there is increased activity in regions not typically associated with task performance, which may suggest engagement of compensatory neural systems. Of note, many regions showing reduced activity under certain conditions can show more normative responses when attention is explicitly directed to the task at hand, when the salience of the stimuli is increased, or when stimuli or tasks are more personally relevant to the individual. This argues in favor of the social motivation hypothesis of ASD, whereby a lack of intrinsic motivation to attend to social stimuli early in life leads to an altered developmental trajectory of neurocognitive development in ASD.

STUDIES OF BRAIN CONNECTIVITY IN ASD

Although functional neuroimaging studies have informed our understanding of the regional neurobiological underpinnings of ASD during social-emotional cognition, recent work has focused on elucidating differences at the network/systems level. Another way to conceptualize functional brain abnormalities in autism is to look at activity not within individual brain regions, but at the way in which regions within social brain networks connect with each other, working in concert to perform complex tasks. It has been hypothesized that very early disruption in both the structural architecture and functional connectivity of local circuits in individuals with ASD may impact maturation of large-scale brain networks required for complex cognitive processing (Belmonte *et al*, 2004; Courchesne and Pierce 2005; Geschwind and Levitt 2007; Just *et al*, 2004; Mundy *et al*, 2009). These structural and functional abnormalities

may thus prevent typical experience-dependent reorganization of neural circuitry into fully integrated networks, which are critical for understanding and initiating complex social behavior.

Connectivity in Task-Related Brain Networks

In ASD, task-based functional connectivity (fcMRI; Figure 2) studies have shown altered connectivity in multiple brain networks underlying complex social and emotional information processing. In an early study, Just *et al* (2004) found that during a sentence comprehension task, individuals with ASD displayed reduced connectivity between multiple high-level association cortical areas. These findings led the authors to suggest that cognitive deficits in ASD may be due to a general underconnectivity of brain regions important for information integration. In support of this hypothesis, many other task-based connectivity studies have reported underconnectivity in individuals with ASD in task-related brain areas including fronto-parietal connections during tasks involving working memory (Koshino *et al*, 2005), visuomotor coordination (Villalobos *et al*, 2005), visual imagery (Kana *et al*, 2006), executive functioning (Just *et al*, 2007), response inhibition (Kana *et al*, 2007), facial processing (Kleinhans *et al*, 2008b; Rudie *et al*, 2012b), theory of mind (Kana *et al*, 2009), and during rest (Kennedy and Courchesne, 2008b). However, others have reported overconnectivity of neural networks in ASD, (eg, Mizuno *et al*, 2006; Noonan *et al*, 2009; Rudie *et al*, 2012b; Shih *et al*, 2010; Turner *et al*, 2006).

Importantly, recent functional and structural neuroimaging studies have demonstrated that altered brain connectivity is related to behavioral phenotypes in ASD. In a recent study, Abrams *et al* (2013) investigated resting state functional connectivity of the bilateral posterior superior temporal sulcus in children with ASD. The posterior superior temporal sulcus is involved in human voice processing in neurotypical individuals (Belin *et al*, 2000), but fails to activate in individuals with ASD (Gervais *et al*, 2004). Children with ASD showed reduced connectivity between the posterior superior temporal sulcus and many reward-related brain regions including the nucleus accumbens, insula, orbitofrontal cortex, and ventromedial prefrontal cortex. Importantly, the authors found that reduced connectivity between the posterior superior temporal sulcus and reward circuitry was associated with greater communication deficits. These findings suggest that the human voice may be less intrinsically rewarding for children with ASD and as a consequence negatively impact language outcomes.

Resting State Connectivity fMRI

One major limitation of task-based functional MRI studies is that they require subject participation and thus are typically limited to older, higher functioning children with autism. Brain changes in later years may be a consequence rather

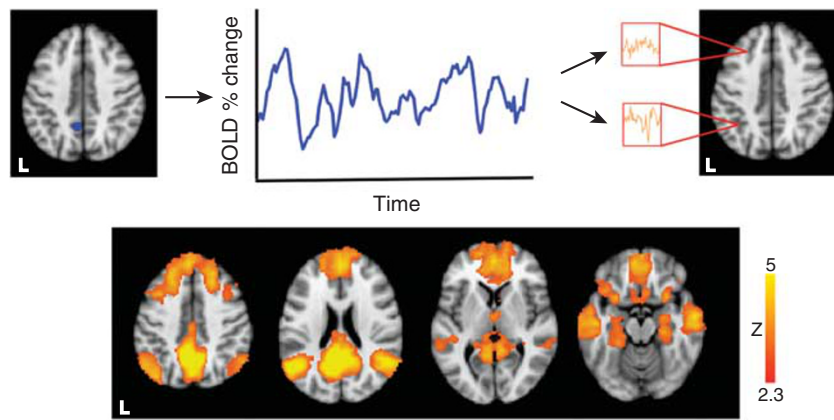


Figure 2. Seed-based functional connectivity. The average BOLD signal time series is extracted from a seed region (eg, the precuneus). The time series of activity from this seed region is then correlated with the time series of activity of all other voxels in the brain, yielding maps of coactivating brain areas. Brain areas represented in these maps are inferred to be part of the same functional brain network, as activity in these regions is highly correlated with one another.

BOX 2

Resting state connectivity: resting state-functional connectivity MRI (rs-fcMRI) refers to a growing body of literature in which imaging is performed in the absence of an overt task to detect brain regions where the BOLD fMRI signal is co-fluctuating; these methods provide a map of intrinsic functional brain networks. There are two main methodological approaches used to identify resting state brain networks. (1) Seed-based methods (Figure 2), in which the average BOLD time course is extracted from a seed region and correlated with every other voxel in the brain, thereby identifying voxels with BOLD signal time series co-fluctuating with that of the seed. (2) Independent component analysis (ICA), in which statistically independent components of the resting state BOLD scan are identified in a data-driven manner, providing the user with all statistically independent time-varying signals within the data. Although a main advantage of ICA is that it provides an unbiased metric of all components in the data (ie, no *a priori* hypotheses related to a seed region of interest are needed), a critical disadvantage is that individual users must decide which components are biologically meaningful (eg, as opposed to noise components) and merit reporting and further investigation. Some of the most common resting state brain networks include, sensory networks such as visual and auditory systems, attentional networks that include regions such as dorsal prefrontal cortex, the default mode network, which is negatively correlated with task performance, and the salience network, which relates to identifying relevant information in one's environment. Critically, these networks persist both during task-based activity and when individuals are at rest, as well as during sleep and sedation. Connectivity-based methods are uniquely suited to inform our understanding of network-level brain activation, providing insight into the history of coactivation between brain regions, and atypicalities indicative of clinical diagnoses. However, interpretation of fcMRI results can be difficult because connectivity measures can be impacted by differences in underlying brain structure, cognitive state, and subject motion during data acquisition (Buckner *et al*, 2013).

than a cause of abnormal social development, and findings may not generalize to lower-functioning or non-verbal children or those with more severe social deficits. Furthermore, traditional fMRI studies comparing neural functioning between ASD and neurotypical populations must control for baseline differences in task performance, and ensure that the task is well designed to address specific questions relating to ASD neurobiology. A relatively new approach that alleviates many of these concerns aims to understand functional brain connectivity by examining the interactions between brain regions not during task performance but while subjects are at rest. Resting state-functional connectivity MRI (rs-fcMRI; see Box 2) is a method in which fMRI is performed in the absence of an overt task in order to detect low-frequency

(<0.1 Hz) fluctuations in neural activity and identify coactivating brain regions (ie, intrinsic functional brain networks) (Biswal *et al*, 1995; for a review, see Fox and Raichle 2007). Findings of synchronized activity across brain regions, both at rest and during task conditions, suggest that functional brain organization consists of multiple interacting large-scale neural networks (eg, Calhoun *et al*, 2008; Smith *et al*, 2009). Neuroimaging studies of ASD have recently begun to characterize functional connections within and between brain networks.

In neurotypical individuals, rs-fcMRI studies have identified multiple, widely replicated brain networks (for a review of resting state networks present in early development, see Hoff *et al*, 2013, and van den Heuvel and Hulshoff Pol, 2010 for a review of findings in adults). Here we will focus on networks implicated in ASD etiology. Perhaps the most widely studied functional connectivity network important for social cognition is the so-called 'default mode network' (DMN), which comprises the posterior cingulate cortex (PCC), MPFC, lateral temporal cortex, inferior parietal lobule, and hippocampal formation (Buckner *et al*, 2008). The DMN has been shown to be involved in internally directed cognition, as it is deactivated during goal-directed behaviors and shows an anticorrelated relationship with the 'attentional control network' (Stevens *et al*, 2009). In children, adolescents, and adults with ASD, reports consistently suggest that connectivity between nodes of the DMN is diminished (Assaf *et al*, 2010; Cherkassky *et al*, 2006; Kennedy and Courchesne, 2008a, b; Monk *et al*, 2009; Rudie *et al*, 2012a; Weng *et al*, 2010). This is consistent with the known role of specific DMN nodes in tasks of social cognition (eg, watching social interactions; Iacoboni *et al*, 2004) and the observed behavioral deficits characteristic of ASD (ie, atypical TOM processing and social interactions). However, the DMN interacts in a dynamic manner with other brain systems and is unlikely to be the only functional network affected in ASD.

Another network that has recently received a substantial amount of attention in the ASD literature is the 'salience

network' (Seeley *et al*, 2007), which is involved in identification of the most relevant information in one's environment, including social stimuli. Primary nodes of the salience network are the anterior cingulate cortex and anterior insula, which neuroimaging studies suggest have a role in perception of social exclusion (Bolling *et al*, 2011; Masten *et al*, 2011) and cognitive control (Agam *et al*, 2010). A recent study (Uddin *et al*, 2013) compared connectivity in large-scale brain networks in children with ASD and matched controls. Hyperconnectivity was observed in a number of brain networks, including the DMN and the salience network. Importantly, salience network connectivity values showed the highest classification accuracy (CA) in parsing neurotypical from ASD individuals, and correlated with severity scores for restricted interests and repetitive behaviors. Another study investigating connectivity of the salience network in adolescents and adults found reduced connections with the medial temporal lobe network, including the amygdala (von dem Hagen *et al*, 2013). Reduced functional connectivity between networks may suggest altered integration of social-emotional information across distributed brain regions in individuals with ASD.

Further evidence for network-level dysfunction in ASD comes from two recent studies by Keown *et al* (2013) and Supekar *et al* (2013), which found increased functional connectivity across multiple brain networks in children with ASD. Both studies also found that increased connectivity was associated with greater severity of ASD impairments. As both under- and over-connectivity have been reported in ASD, a major challenge facing the autism neuroimaging field is to reconcile these seemingly discrepant findings. Findings of hyper- vs hypo-connectivity in ASD may depend on the nature of the task-related demands, the specific brain networks under investigation, study-specific methodological choices, as well the age of the cohort under investigation (Rudie and Dapretto, 2013). For example, Uddin *et al*'s (2013) review of the functional connectivity literature in ASD suggests that studies of adults and adolescents with ASD tend to report hypo-connectivity compared with neurotypical controls, whereas studies of younger children often report hyper-connectivity—indicating that differences in sample characteristics can lead to opposite findings. Taken together, these studies highlight the complexity of brain network organization in ASD and the need for longitudinal investigations in order to elucidate the entire developmental trajectory of altered connectivity in ASD.

Graph Theoretical Methods

As described above, many neuroimaging studies report differences in regional network connectivity in ASD; however, how these findings may be reflective of more complex systems-level dysfunctions across the brain in individuals with ASD remains unclear. Recently, researchers have begun using graph theory methods to address this question by modeling the brain as a network of integrated and segregated systems composed of

hundreds of brain regions or 'nodes'. Graph theoretical approaches depict the brain as a hierarchically organized network comprising large-scale functional systems or modules (for a review, see Wang *et al*, 2010). Each module is made up of discrete brain regions (nodes) and the connections between these nodes (edges). In the brain, functional and structural networks are 'small-world' in nature, meaning that they are efficient at both a local-systems and global-systems level (Watts and Strogatz, 1998). Graph theory measures such as the number of nodes, edges, and small-world characteristics such as modularity can be quantified (Bullmore and Sporns, 2009; Rubinov and Sporns, 2010) and compared across populations during development (eg, Fair *et al*, 2009; Hagmann *et al*, 2010), and in diseases such as schizophrenia (eg, Bassett *et al*, 2008) and Alzheimer's disease (eg, Supekar *et al*, 2008). Graph theoretical metrics are useful in that they go beyond simple connectivity analyses to describe large-scale properties of how brain networks are organized and how they interact.

To date, there have been relatively few graph theory studies of ASD, and reported findings have been mixed. In a whole-brain investigation of network properties across four functional brain networks, Redcay *et al* (2013) found few differences between adolescents with ASD and neurotypical controls, except for greater 'betweenness centrality' (a measure of how often the shortest path goes through a given node, or its centrality to the network) in a parietal region of the DMN in individuals with ASD. In another study of adolescents with ASD, Keown *et al* (2013) found increased local functional connectivity in temporo-occipital regions, which was associated with greater scores of ASD symptom severity. In a third study of children and adolescents with ASD, Rudie *et al* (2013) investigated both functional and structural connectivity using graph theory methods, finding alterations in local and global network measures including modularity and local efficiency of brain networks in children with ASD. Overall, graph theory studies of ASD suggest wide-scale disruptions in how brain networks communicate, suggesting that in autism, critical networks are less modular and less segregated from one another, with abnormalities both within and between networks. Although graph theoretical approaches are in their infancy, further research may elucidate more complex interactions between large-scale brain networks in ASD.

Integrating Imaging and Genetics

The identification of genetic contributions to ASD has progressed rapidly in the last decade (for a review, see Huguet *et al*, 2013 and Persico and Napolioni, 2013). Mirroring the heterogeneity observed in behavioral phenotypes, hundreds of genes have been implicated in conferring increased risk for ASD. Importantly, the biological functions of many ASD-associated genes impact the formation of neural circuits in the developing brain (Won *et al*, 2013), including prenatal transcription regulation and synapse development, and are enriched in outer cortical layers of the brain (Parikshak *et al*, 2013). However, little is known about how

autism risk genes relate to brain structure, function, and behavior. For over a decade, research on a range of common genetic variants related to neurobehavioral disorders has demonstrated differences in brain structure and function in risk gene carriers despite having no overt behavioral symptomatology (for a review, see Hariri and Weinberger 2003). The field of imaging-genetics examines the relationship between risk genes and brain structure and function, conceptualizing neuroimaging metrics as potential endophenotypes. As MRI metrics of brain functional and structural connectivity are both heritable (Chiang *et al*, 2011; Fornito *et al*, 2011; Glahn *et al*, 2010; Kochunov *et al*, 2010; Koten *et al*, 2009) and altered in individuals with ASD, neuroimaging endophenotypes are well suited to inform our

understanding of how genetic risk impacts brain circuitry. A key goal of imaging-genetics research is to elucidate neural mechanisms by which genetic heterogeneity may give rise to phenotypic heterogeneity in ASD (Figure 3). As genetics research suggests that many common single-nucleotide polymorphisms are related to increased risk for autism diagnosis (for a review, see Klei *et al*, 2012), imaging studies have investigated whether stratifying neuroimaging data by common genetic risk factors can inform understanding of ASD neurobiology.

To date, neuroimaging-genetics studies have taken two forms: studies of the effects of ASD-associated risk alleles on brain measures in neurotypical children, adolescents, and adults (eg, Clemm von Hohenberg *et al*, 2013; Dennis *et al*,

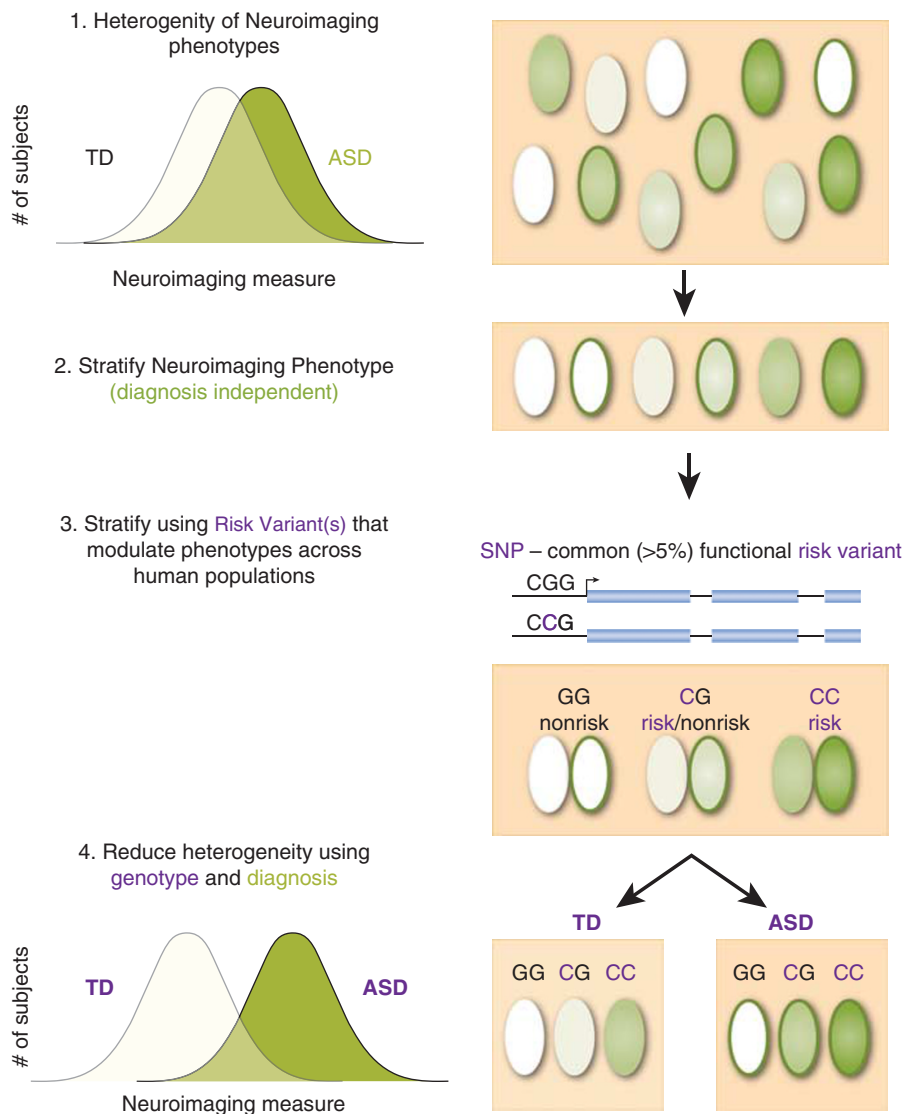


Figure 3. Parsing phenotypic heterogeneity using imaging-genetics. (1) A sample population contains subjects who display a range of ASD-associated neurocognitive phenotypes (shades of green within ovals) and a subset of individuals with a diagnosis of ASD (dark green border outlining ovals). (2) When subjects are stratified by neuroimaging phenotypes, a continuous range of phenotypes is observed across neurotypical subjects and those with ASD. (3) Subjects' neuroimaging data may also be stratified by common genetic risk variants (ie, those that occur in >5% of the population) for a particular neurobiological disorder. (4) Combining these data allow for added stratification of phenotypic heterogeneity by creating subgroups of neurotypical and affected individuals, ultimately elucidating neural mechanisms unique to the diagnosis of ASD vs risk variant status. Reprinted from Rudie *et al* (2012a), with permission from Elsevier.

2011; Hedrick *et al*, 2012; Raznahan *et al*, 2012; Sauer *et al*, 2012; Tan *et al*, 2010; Voineskos *et al*, 2011; Whalley *et al*, 2011) and studies comparing the effects of ASD-associated risk alleles on children and adolescents with ASD compared with neurotypical controls (eg, Rudie *et al*, 2012a; Scott-Van Zeeland *et al*, 2010). Scott-Van Zeeland *et al* (2010) investigated the impact of the contactin-associated protein-like 2 (CNTNAP2) rs2710102, C risk allele on functional connectivity in children and adolescents with ASD. Results suggested that while nonrisk allele carriers (in both neurotypical and ASD groups) displayed connectivity between frontal cortex and language regions in the left hemisphere, risk allele carriers showed a pattern of diffusely increased functional connectivity with frontal cortex and temporal regions. A second study by Rudie *et al* (2012a) found that children and adolescents carrying the met receptor tyrosine kinase (MET) rs1858830, C risk allele had decreased functional connectivity between the PCC and MPFC and reduced WM integrity in the splenium of the corpus callosum, cortical spinal tract, and inferior longitudinal fasciculus. Interestingly, the authors also identified a significant interaction whereby the presence of one or two risk alleles in ASD children had a significantly larger impact on functional connectivity values than in neurotypical children.

Together, these results suggest that these and other ASD liability genes may confer risk through their effects of brain function and structure in regions involved in social and emotional cognition. Although not causal, autism risk genes may bias the brain toward patterns of neural activity and connectivity that are atypical, and in combination with a range of additional genetic and environmental factors may contribute to abnormal brain development that ultimately underlies ASD symptoms. Future neuroimaging studies should continue to use relevant genetics data to help explain variance observed in both behavioral and brain-based phenotypes of ASD, as well as to improve diagnostic tools and treatment strategies for individuals falling throughout the autism spectrum (Fox and Greicius 2010).

Machine Learning

Prediction and classification of diagnostic status based on neuroimaging data represents a powerful tool for improved clinical care in ASD. Machine learning algorithms extract highly relevant components from neuroimaging data to classify an individual's diagnostic status (see Box 3; Figure 4). Machine learning algorithms have been applied to neuroimaging data to identify ASD from neurotypical subjects using MRI measures of gray and WM volume (CA 81% and 68%, respectively, Ecker *et al*, 2010), regional cortical thickness (CA 70–87%; Jiao *et al*, 2010; Zhou *et al*, 2014), VBM (CA 79–92%; Uddin *et al*, 2011), DTI (CA 80%; Ingalhalikar *et al*, 2011), and resting state functional connectivity (CA 71–89%; Anderson *et al*, 2011; Uddin *et al*, 2013). Variations in CA may be attributed to the types of classification systems used, which MRI-based metrics are utilized, and the number of features on which classification is determined

BOX 3

Machine learning. Traditional machine learning methods (Figure 4; also see Klöppel *et al*, 2012) begin by feeding neuroimaging data from labeled cases and controls (the training data set) into a mathematical classifier and identifying relevant components (or features) from the neuroimaging data that contribute to group discrimination. The classifier then uses the training data set to establish a set of rules that allow for optimal discrimination of patient and control groups, converging on an optimal classification algorithm. Finally, this algorithm is applied to a new set of neuroimaging data consisting of non-labeled cases and controls and classification accuracy (CA) is assessed by calculating the number of correct positive (eg, ASD) and negative (eg, neurotypical) classifications for the new data. A major advantage of this approach is that it allows individual subjects to be evaluated for likelihood of ASD diagnosis. An important limitation to the application of this method to the study of autism is the inherent heterogeneity of the ASD subject population, which can decrease overall CA. There is great potential to overcome this limitation by studying circumscribed ASD subgroups (including restrictions based on age, comorbid symptoms, and so on) and collection of larger data sets.

(eg, number of brain areas included in measures of regional cortical thickness). In a recent study, Nielsen *et al* (2013) used machine learning to evaluate whole-brain resting state fMRI data collected from 16 sites in 964 subjects ranging in age from 7 to 64 years from the Autism Brain Imaging Data Exchange (ABIDE). The maximum CA achieved by this study was just 60%, much lower than CAs reported for single site studies. However, the authors note that higher CAs were calculated for sites where longer resting state scans were collected, providing support for longer fMRI imaging times in future machine learning paradigms.

Very recently, machine learning algorithms have been applied to address questions of heterogeneity in ASD—aiming to distinguish between ASD sub-populations. Sato *et al* (2013) used inter-regional whole-brain cortical thickness correlations and machine learning to predict scores on the Autism Diagnostic Observation Scale (Lord *et al*, 1989) in children, adolescents, and adults with ASD, yielding a significant correlation ($r = 0.362$) between predicted and actual values. In another study, Uddin *et al* (2013) classified children with and without ASD using large-scale brain network connectivity measures. Connectivity of the salience network was best able to classify subjects, achieving a CA of 83%, with BOLD signal in this network also predicting restricted and repetitive behaviors in the sample of children with ASD. Although the machine learning literature in ASD is just beginning to emerge, these studies suggest that neuroimaging data evaluated with machine learning may help to identify brain-based biomarkers that correlate with severity of ASD symptomatology. Continued methodological development of this technique will undoubtedly further our understanding of neural signatures of ASD sub-populations.

METHODOLOGICAL CONSIDERATIONS

Despite the growing corpus of brain imaging studies in ASD, many discrepant findings make it difficult to draw broad and definitive conclusions about brain connectivity abnormalities in ASD. As described in detail by Rudie and Dapretto (2013), there are a few major methodological considerations that may help to explain the seemingly discrepant findings between many prior studies of neural

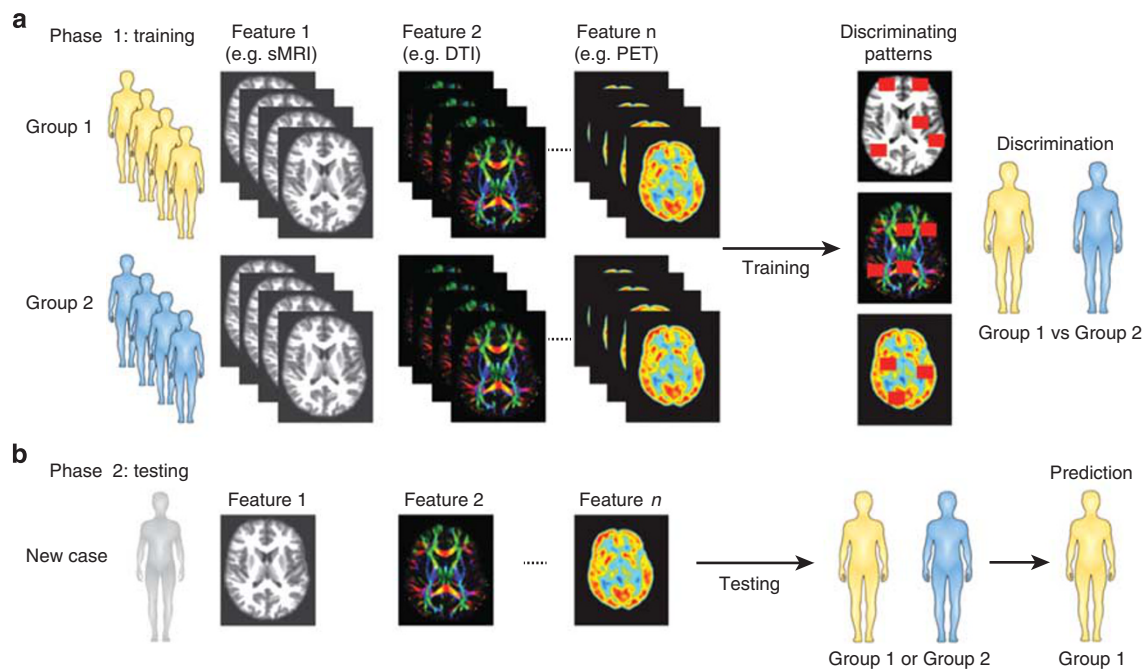


Figure 4. Machine learning. (a) During the first phase, the classifier is trained on neuroimaging data such as sMRI, DTI, or positron emission tomography (PET), from two groups of participants (eg, neurotypical individuals and individuals with ASD). During training, patterns within the neuroimaging data that best discriminate between groups are identified. (b) During the second phase, the classifier is provided with feature data from a new set of subjects and determines to which group each of the subjects belongs. CA is determined based on classifier performance in the testing phase. Reprinted from Ecker and Murphy (2014), with permission from Elsevier.

systems in ASD and more recent studies. First, recent studies have used rigorous motion-correction methods. Recently, it has been reported that even very small amounts of motion in resting state functional connectivity data (eg, Power *et al*, 2012; Van Dijk *et al*, 2012) and in structural dMRI data (Yendiki *et al*, 2013) can bias findings of group differences in connectivity metrics. These findings are crucial to the interpretation of reports of altered brain connectivity in ASD, as ASD cohorts may display increased amounts of motion related artifacts in their MRI data compared with neurotypical controls, and similarly, the degree of motion present in the data is likely to be correlated with subject age (Satterthwaite *et al*, 2013), producing a possible age and diagnostic status confound. A multitude of studies have recently been published speaking to how best to account for motion-related artifacts and aiming to identify the optimal series of processing steps for connectivity data analysis (eg, Carp, 2013; Hallquist *et al*, 2013; Power *et al*, 2012, 2013, 2014; Satterthwaite *et al*, 2013). On the heels of these reports, scientists have begun to revisit published results of connectivity-related findings in ASD, and in more recently published studies to analyze their data using a variety of processing streams. Other method-related choices such as use of low-pass filtering, seed selection, and whether connectivity results are obtained for the whole brain (*vs* within *a priori* ROIs) may also impact findings of over- or under-connectivity in ASD (for a review, see Müller *et al*, 2011). Importantly, when analyzing data using a variety of suggested processing streams, findings of altered connectivity in children and adolescents with ASD appear to hold

(eg, Maximo *et al*, 2013; Nair *et al*, 2014; Starck *et al*, 2013; Uddin *et al*, 2013).

A second cause of discrepant findings are differences in cohort age and severity among different studies. The trajectory of age-related development in both brain structure and function may be complex, not holding to a simple linear increase or decrease with increasing age. For example, Schumann *et al*'s (2004) work showing that the pattern of amygdala brain overgrowth seen early in life in ASD reverses later in development indicates that differences in sampling characteristics can lead to opposite findings. Ultimately, large-scale studies examining developmental trajectories will be essential if we are to understand how brain structure and function differ in ASD.

A third problem in brain imaging studies relates to the heterogeneity of the autism phenotype. The vast heterogeneity present in behavioral symptomatology and genetic liability to ASD likely reflects variation in disease etiology between diagnosed individuals (Geschwind 2009). Dissimilar disease etiology would additionally imply varied neurodevelopmental trajectories in ASD affected individuals. Discrepant findings in the neuroimaging literature may reflect variance in the severity of ASD symptomatology, the constellation of ASD behavioral symptoms represented, or the presence or absence of associated features such as mental retardation and severe language impairment. Furthermore, as described above, evidence suggests that the atypical functional brain responses to task stimuli in ASD may not simply be a result of a fundamental deficit in neural functioning, but rather, that incorporating extrinsic factors that increase attention or interest into neuroimaging task designs are associated with

more normal activity (Hadjikhani *et al*, 2004; Perlman *et al*, 2011; Pierce *et al*, 2004; Pierce and Redcay 2008; Wang *et al*, 2007; Zürcher *et al*, 2013). Thus, discrepant findings in the neuroimaging literature may also be due to variation in sample characteristics or task demands. To address these issues, replication of previous findings will be essential.

FUTURE DIRECTIONS AND CLINICAL IMPLICATIONS

Although neuroimaging techniques allow us to relate behavioral traits and genetic risks to structural and functional brain development, an important question in autism neuroimaging research is whether findings of altered brain activity and connectivity during childhood, adolescence, and adulthood are the *cause of*, or the *result of* ASD behavioral pathology. Experience shapes brain structure, function, and connectivity; reduced social attention will affect a child's social experience, and the brain changes observed in older children may simply reflect this socially deprived experience. Recent advances in neuroimaging methods will allow researchers to begin to address some of these complex interactions by studying very young infants who are at high genetic risk for developing ASD, and by following individuals with ASD over time to map long-term neurodevelopmental trajectories. Our understanding of causality will be further guided by animal models, which can manipulate both genetic risk and experience to understand brain development in ASD, as well as large-scale neuroimaging data sharing projects designed to achieve sufficient power to detect true brain-gene-behavior relationships. Such work will be greatly enhanced by large-scale collaborations such as ABIDE (Di Martino *et al*, 2014) andNDAR (the National Database for Autism Research), combining imaging data from multiple sites and integrating these data with both genetic and behavioral data. Given the correlational nature of imaging and genetic methods, causality can only begin to be addressed in the context of longitudinal studies of both affected and unaffected individuals with different genetic vulnerability for ASD. Recently, neuroimaging studies have begun to assess brain structure and function in unaffected family members of individuals with ASD. By mapping developmental trajectories in unaffected siblings, we may also gain insight into possible genetic and neurodevelopmental protective factors and critical periods during which such factors come on line.

Understanding developmental trajectories will be essential, both for understanding brain development in heterogeneous subgroups of individuals with ASD, as well as for determining the impact of treatment on brain structure and function in these populations. As the infant brain is very plastic and adaptable, early interventions should help to shape the emerging activity and connectivity patterns that experience helps to create. As our technologies improve, brain imaging may allow us to measure the impact of interventions on brain development, as well as to inform the

choice of optimal interventions. With the increasing move toward imaging infants and toddlers at-risk for autism, we should be able to identify abnormal neurodevelopmental trajectories and guide intervention strategies that will be most effective at this stage of greatest brain plasticity.

Any application of neuroimaging data to aid in diagnosis and treatment will ultimately rely on the ability to accurately identify children at-risk for developing ASD. A major question is whether differences in neuroimaging measures (which are typically interpreted at the group level) are robust at the individual subject level, a prerequisite for identifying and developing treatment options for individuals at high risk for ASD. Recent advances in data analytic methods, such as machine learning classification techniques that allow for integration of information across multiple modalities (eg, Ingallhalikar *et al*, 2012) and identification of sub-populations within a heterogeneous population (eg, Filipovich *et al*, 2012), may be able to identify the most relevant signatures of ASD from neuroimaging, genetic, and behavioral data in order to accurately predict diagnostic status, treatment response, and/or developmental outcome at the individual level.

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