Neuroimaging-Based Phenotyping of the Autism Spectrum

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Abstract Recent advances in neuroimaging have offered a rich array of structural and functional markers to probe the organization of regional and large-scale brain networks. The current chapter provides a brief introduction into these techniques and overviews their contribution to the understanding of autism spectrum disorder (ASD), a neurodevelopmental condition associated with atypical social cognition, language function, and repetitive behaviors/interests. While it is generally recognized that ASD relates to structural and functional network anomalies, the extent and overall pattern of reported findings have been rather heterogeneous. Indeed, while several attempts have been made to label the main neuroimaging phenotype of ASD (e.g., 'early brain overgrowth hypothesis', 'amygdala theory', 'disconnectivity hypothesis'), none of these frameworks has been without controversy. Methodological sources of inconsistent results may include differences in subject inclusion criteria, variability in image processing, and analysis methodology. However, inconsistencies may also relate to high heterogeneity across the autism spectrum itself. It, therefore, remains to be investigated whether a consistent imaging phenotype that adequately describes the entire autism spectrum can, in fact, be established. On the other hand, as previous

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findings clearly emphasize the value of neuroimaging in identifying atypical brain morphology, function, and connectivity, they ultimately support its high potential to identify biologically and clinically relevant endophenotypes.

Keywords Autism · ASD · MRI · Connectome · Biomarkers
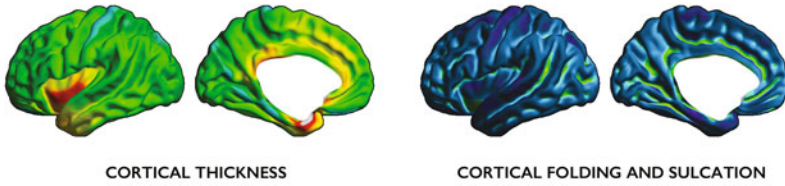
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1   Introduction

Autism spectrum disorder (ASD) encompasses a group of early-onset, lifelong, neurodevelopmental conditions currently diagnosed in >1 % of children (CDC 2014). Core behavioral impairments include atypical social cognition, language function, and sensory abnormalities, often together with narrow and repetitive behaviors and interests.
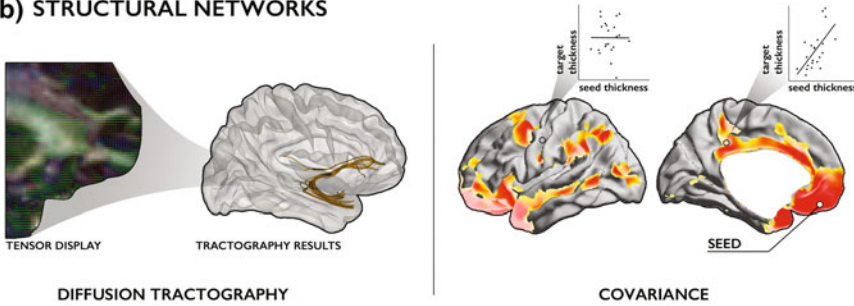
ASD is highly heterogeneous, with significant phenotypic variations across affected individuals. Individuals with ASD show an elevated risk for psychiatric comorbidities and neurological disorders. For example, around 30 % of children with ASD also meet criteria for attention-deficit/hyperactivity disorder (ADHD) (Simonoff et al. 2008); similarly, prevalent subgroups of individuals with ASD present with epileptic seizures (Bolton et al. 2011) or anxiety (van Steensel et al. 2011). Although comorbid conditions often co-occur (Simonoff et al. 2008), the extent to which they cluster in specific patterns is to date unknown. The etiology of ASD is complex and likely not uniform. To that end, an increasing catalog of genetic and developmental risk factors has been identified (De Rubeis and Buxbaum 2015). This remarkable neurobiological variability has challenged the development of novel diagnostic procedures and targeted therapies (Ecker et al. 2015).

Quantitative neuroimaging, particularly magnetic resonance imaging (MRI), offers a rich array of markers that describe the structural and functional organization of the human brain with increasing spatial resolution and validity (Fig. 1). These metrics promise to capture important anatomical aspects in both the typical and atypical brain, and have the potential to be translated into powerful tools that are able to stratify the affected individuals into biological subtypes. This chapter aims to overview the current state of neuroimaging data in ASD. Generally, findings have shown diverse brain anomalies in ASD, ranging from atypical brain growth

NEUROIMAGING MARKERS
(a) REGIONAL MORPHOLOGY

CORTICAL THICKNESS

CORTICAL FOLDING AND SULCATION

(b) STRUCTURAL NETWORKS

TENSOR DISPLAY   TRACTOGRAPHY RESULTS

DIFFUSION TRACTOGRAPHY

target thickness

seed thickness

target thickness

seed thickness

SEED

COVARIANCE

(c) FUNCTIONAL NETWORKS

target time course, r=0.20
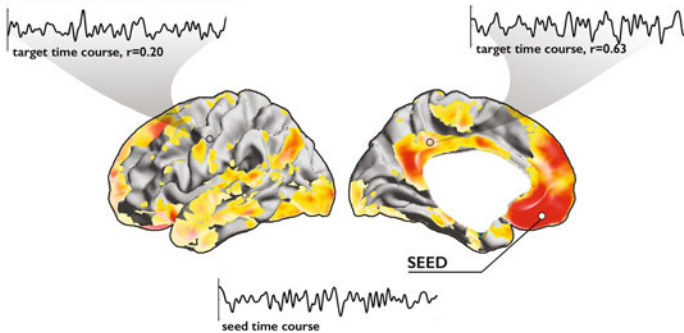
target time course, r=0.63

SEED

seed time course

Fig. 1 Neuroimaging approaches previously applied to study ASD. **a** Markers of regional morphology: surface-based cortical thickness and cortical folding indices; **b** Neuroimaging-based structural networks have been derived mainly from diffusion MRI tractography and structural covariance analysis. Diffusion MRI tractography approximates plausible white matter pathways by following the directionality of water diffusion; covariance analysis infers inter-regional networks through the analysis of across-subjects correlations in morphological quantities. **c** Functional networks can be derived from inter-regional time series correlations

patterns, morphological anomalies in both cortical and subcortical regions, and inter-regional structural as well as functional network alterations. However, a consistent, universally accepted imaging phenotype that adequately describes all facets of the disorder (and reliably characterizes all individuals with ASD) is lacking. While outlining major findings in ASD, we will specifically attempt to

emphasize methodological sources contributing to the somewhat low repro-
ducibility of findings in ASD.

2 Probing Regional Morphology

Among the earliest and most extensively examined structural findings in ASD are
those suggesting *brain overgrowth*. Assessing global brain volume based on MRI,
Piven, and colleagues noted increased brain volumes in males with ASD relative to
controls. These findings were complemented by cross-sectional assessments of head
circumference (a proxy for overall brain growth) by Courchesne et al. (2001), who
reported increased head size in up to 90 % of 2–4-year-old boys. As circumference
was relatively normal in separate cohorts assessed shortly after birth and during
adolescence, the authors suggested that ASD might relate to an atypical develop-
mental trajectory characterized by early overgrowth, followed by normalization in
later childhood and adolescence. In a follow-up study, the same group provided
more direct evidence for this claim by using longitudinal analyses and pinpointed
increases in head size to an interval between 1 and 14 months after birth
(Courchesne et al. 2003). Notably, findings indicative of brain overgrowth were
subsequently confirmed by several groups (Palmen et al. 2004). Nevertheless, a
recent systematic review highlighted potential biases, when comparing head cir-
cumference measures in ASD relative to normative data (an approach chosen by
some previous studies), in contrast to assessing locally recruited controls (Raznahan
et al. 2013). Noteworthy, a recent longitudinal MRI study in newborns with ASD
has demonstrated that increases in brain volume may co-occur with excessive
cerebrospinal fluid (CSF), particularly in the frontal lobes, from 6 months onward
(Shen et al. 2013). On the one hand, these findings suggest that CSF concentrations
may confound findings based on global measures of head size. On the other hand,
they point to the potential role of CSF circulation in the pathogenesis of ASD and
may impact neurogenesis and neuronal migration patterns, eventually contributing
to atypical cortical morphology in the disorder. Despite the support for brain
overgrowth in ASD, remaining inconsistencies emphasize the need for future
studies to prospectively enroll both individuals with ASD and controls, ideally from
fetal stages onward to clarify trajectories of early brain development. To identify
possible mechanisms that relate to overgrowth in subgroups with ASD, these
studies would provide not only head circumference metrics, but also regionally
specific measures of brain morphology and connectivity (see below), and are
complemented by genetic assessments and monitoring of environmental factors.

Several quantitative neuroimaging analysis approaches have been brought for-
ward to provide a more precise window into the morphology of individual brain
regions. Common techniques include volumetry (the manual or automated tracing of
a structure of interest to estimate its volume), voxel-based morphometry (*VBM*, an
automated technique that statistically compares spatially normalized estimates of
gray matter across subjects), together with surface-based measures of cortical

thickness and surface area (the two components of gray matter volume), and gyrification as well as subcortical shape analysis. Using such regionally specific approaches, several studies have suggested gray matter increases in ASD compared to controls, particularly in frontal and temporal lobes in both children (Raznahan et al. 2010) and adults (Ecker et al. 2012). Given the putative functional roles of these areas, fronto-temporal anomalies might be compatible with marked impairments in social cognition and with atypical language often seen in autism (Rojas et al. 2006). Several assessments have indeed suggested a potential link between brain structure and atypical behavior in ASD. For example, fronto-temporal structural changes have been shown to correlate with abnormal sociocognitive and language function (Lai et al. 2014). Moreover, structural imaging studies in healthy populations have reported associations between the structure of similar regions known to play an important role in social cognition, such as the temporoparietal junction (TPJ) and superior temporal sulcus, and autistic traits both cross-sectionally (von dem Hagen et al. 2011) and longitudinally (Wallace et al. 2012)

Despite the frequency of fronto-temporal anomalies being reported in ASD at the group level, they may not be present in all affected individuals. A VBM study in adults and adolescents, for example, has suggested rather diffuse ASD-specific gray matter increases in all but the frontal lobes (Piven et al. 1996). Similarly, a study in children has reported temporal and parietal cortical thickening, while frontal and occipital regions appeared morphologically unaffected (Hardan et al. 2006). The difficulty in synthesizing a consistent pattern of findings is further increased by several studies reporting rather less and not more gray matter in ASD, both in children (Hardan et al. 2006) and in adult samples (Wallace et al. 2010). This high degree of divergence was also revealed in previous meta-analyses, suggesting a rather complex pattern of ASD-related regional anomalies with only modest convergence across studies (Duerden et al. 2012).

It has frequently been suggested that inconsistent findings might have arisen as a function of age of the included cohorts. In other words, individuals with ASD may show a different pattern of changes relative to typical controls when tested at different neurodevelopmental stages and throughout aging. This hypothesis would be compatible with findings suggestive of altered developmental and age-related trajectories in ASD. Indeed, several studies have suggested divergent age effects on brain morphology changes in ASD relative to controls (Raznahan et al. 2010; Wallace et al. 2010; Duerden et al. 2012). Studying a cross-sectional sample of adolescents and young adults with ASD and controls, for example, Wallace and colleagues observed more rapid age-related cortical thinning in temporal and parietal regions compared to controls (Wallace et al. 2010). In two separate longitudinal studies, one including individuals aged 3–39 years (Zielinski et al. 2014) and the other including individuals aged 14–24 years (Wallace et al. 2015), researchers have also demonstrated accelerated thinning in ASD in adolescence. Overall, these data indicate that a comprehensive understanding of ASD may likely require accounting for its impact on dynamic brain changes from childhood into adulthood, in which complex morphological anomalies may vary over time throughout the life span.

NEUROIMAGING-BASED PHENOTYPING IN AUTISM

(a) CORTICAL THICKNESS INCREASES

LEFT   RIGHT
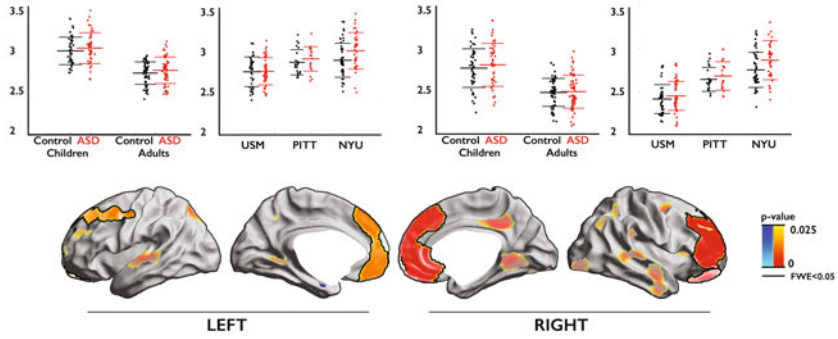
(b) STRUCTURAL COVARIANCE DECREASES

COVARIANCE IN CONTROLS   ASD<CONTROLS
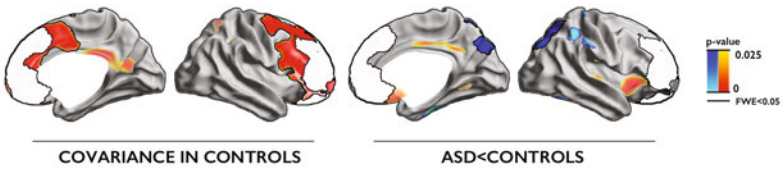
(c) FUNCTIONAL CONNECTIVITY DISRUPTIONS

CONNECTIVITY   ASD<CONTROLS GROUP DIFFERENCES
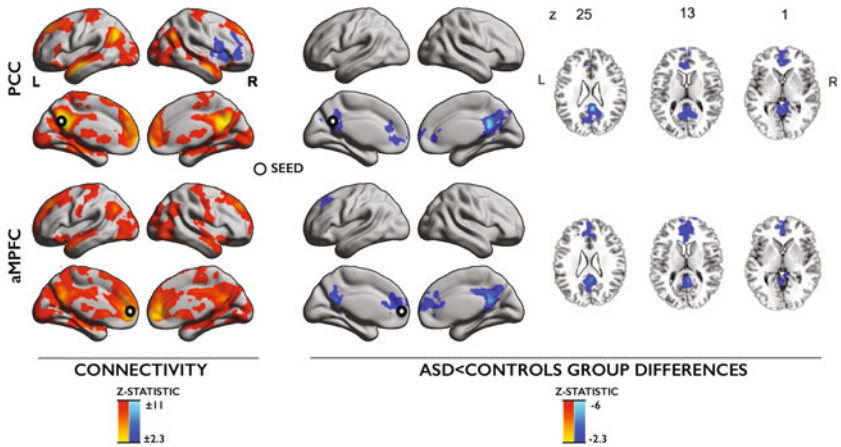
◀ **Fig. 2** Recent findings in ASD based on the autism brain imaging data exchange (ABIDE) repository. **a** Cortical thickness increases in 107 ASD relative to 113 controls, based on the three sites that included children and adult data in both groups. Findings were consistent across all sites studied and measurable in children as well as adults, yet of variable effect size. **b** Structural covariance alterations in ASD, showing largely decreased covariance in ASD between medial/lateral prefrontal seed regions and posterior midline targets corresponding to the larger precuneus area. Similar to the thickness findings (*panel A*), findings were consistent across the three sites but of variable effect size. **c** Functional connectivity alterations showing primarily decreased connectivity between medial frontal and posterior midline regions in ASD relative to controls. Adapted from Valk et al. (2015) and Di Martino et al. (2014) with permission

A further example of heterogeneity of findings in morphological investigations of ASD comes from the study of the amygdala, a structure with a key role in emotional processing. A careful review of the initial inconsistent volumetric findings of amygdala suggested that age of the sample examined may affect the results (Haar et al. 2014). This notion was supported by the reports of increased amygdala volume in toddlers and preschoolers which were related to later measures of joint attention (Mosconi et al. 2009). Beyond age, other potential sources of variability on volumetric findings of the amygdala, such as the role of comorbidity with anxiety disorders or alexithymia (Bird et al. 2010), have been suggested but have not been fully clarified.

A generally limiting factor of reproducibility of findings relates to low statistical power resulting from relatively small samples studied, a condition often imposed by high costs and challenges associated with recruitment and scanning of individuals with ASD. Recently, the Autism Brain Imaging Data Exchange (ABIDE) initiative made a multicenter repository containing neuroimaging data from 539 individuals with ASD and 573 controls, together with standardized behavioral phenotypic information, freely available (Di Martino et al. 2014). Based on data from three independent ABIDE sites, Valk and colleagues performed a surface-based cortical thickness analysis and assessed overall patterns of findings as well as across-site reproducibility (Valk et al. 2015). Assessing data from more than 200 male participants that passed quality control and surface correction procedures, the authors observed cortical thickness increases in ASD relative to controls, particularly in medial and lateral prefrontal cortices, when pooling data across all imaging sites (Fig. 2a). While the authors reported a generally consistent direction of effects across each of the analysis sites, they emphasized variability in effects sizes across the sites (that may be due to variability in scanning parameters and inclusion criteria), together with increased effects in children compared to adults (Valk et al. 2015).

In addition to methodological factors, diverse findings in human studies may be driven by intrinsic variability across the autism spectrum, which should be more directly addressed for a better understanding of the disorder. At the level of histopathology, several studies have pointed toward a rather complex substrate with multiple etiologies. A *postmortem* study by Bailey and colleagues, for instance, reported increased cortical thickness and/or increased neuronal numbers in the

frontal cortex in 3/6 of cases (Bailey et al. 1998). Another study observed laminar rearrangement together with a poorly defined gray and white matter interface in some specimens (Avino and Hutsler 2010). Such cortical interface *blurring* is generally considered a common sign of atypical migration and aberrant organization, emerging in prenatal developmental stages. These findings may suggest an increased frequency of processes resembling known malformations of cortical development (MCD, generally considered to be a common cause of epilepsy) in ASD. Notably, several MCDs have indeed been shown to frequently co-occur with ASD, ranging from disruptions of cell proliferation, such as tuberous sclerosis complex, to those occurring during migration and cortical organization, such as polymicrogyria and schizencephaly. Their co-occurrence with ASD underlines that specific, possibly genetically mediated, developmental disruptions may result in variable neuropsychiatric and neurological phenotypes, emphasizing etiological commonalities across different clinicopathological entities.

Variable histopathological findings motivate the use of novel imaging biomarkers in ASD. Surface-based approaches most frequently applied to measure cortical thickness also provide a range of meaningful indices relating to cortical surface geometry (Hong et al. 2015), such as the folding complexity, sulcal depth, surface area, and geodesic distance mapping. Several recent studies have reported alterations in these features (Nordahl et al. 2007) in ASD, enriching the possibilities to perform an integrative neuroimaging phenotyping of the disorder. In a series of studies, Ecker and colleagues compared the spatial distribution of alterations in cortical thickness, volume, and surface area when comparing ASD to controls and reported relatively non-overlapping morphological anomalies across these feature dimensions (Ecker et al. 2013). Moreover, they have shown that patients can be accurately discriminated from controls based on supervised pattern learners that took advantage of these surface-based markers (Ecker et al. 2010). However, replicating these findings and demonstrating their discriminability from a plethora of other neurodevelopmental disorders (akin to differential diagnoses made in the clinic setting) is required before their potential clinical utility can be truly evaluated. It is conceivable that different morphological indices probe complementary facets of cortical architecture, myelination, connectivity, and development. Cortical thickness, for example, is assumed to reflect combinations of neuronal density, dendritic arborization, and myelin (Huttenlocher et al. 1982). Conversely, folding anomalies may indicate disrupted mechanical properties of the cortex, possibly secondary to disruptions in underlying white matter connectivity (Nordahl et al. 2007). Lastly, surface area changes may be driven specifically by radial unit progenitor cells that divide at the ventricular surface, thereby generating more proliferation units that ultimately lead to increased numbers of cortical columns (Ecker et al. 2015). Notably, a previous postmortem study of Casanova and colleagues suggested a smaller width but increased number of so-called *mini-columns*, neuronal assemblies centered on radially oriented pyramidal neurons, in ASD (Casanova et al. 2002).

3 Disturbances in Inter-regional Networks

Complex patterns of structural alterations in ASD may be reflective of reconfigurations of large-scale brain networks, a key determinant of functional, behavioral, and clinical outcomes. Recent advances in imaging acquisition and analysis techniques offer several opportunities to assess inter-regional structural and functional brain networks.

To study brain structural networks in the living human brain, the most well-established approaches are diffusion MRI tractography and structural MRI covariance analysis. Diffusion MRI data allows for the estimation of directionality and magnitude of water diffusion at each imaging voxel. As diffusivity is influenced by membrane permeability, myelination, and fiber packing (Concha et al. 2010), diffusion markers can serve as proxies of fiber microstructure and architecture. The most widely used parameters are fractional anisotropy (FA), estimating the deviation of water diffusion from random displacement, and mean diffusion (MD), a marker of bulk diffusion. Via tractographic techniques (Mori et al. 1999), it is possible to reconstruct plausible fiber tracts running through the white matter. While challenged close to gray mater regions, such as the neocortex and subcortical nuclei, where multiple fiber populations may intersect or merge (Jones et al. 2012), tractography within deep white matter achieves good correspondence with anatomically plausible tracts. Tractography of several deep bundles has furthermore been directly cross-validated using several different paradigms, for example, with functional connectivity analysis in humans (Johansen-Berg et al. 2005) and using manganese tracing in pigs (Knosche et al. 2015).

Structural networks can also be derived from covariance of MRI-derived morphology across subjects, such as cortical thickness or gray matter density (Lerch et al. 2006). In contrast to diffusion tractography, this framework is not tailored to an approximation of the course of anatomical connections between regions and only shows partial correspondence to diffusion-derived structural connectivity. On the other hand, high correlations in structural markers have been shown to relate to manifestations of persistent functional-trophic cross-talk, maturational interchange, together with common developmental and pathological influences (Alexander-Bloch et al. 2013). Compared to the diffusion anomalies, covariance analysis offers a direct seeding from cortical gray matter in a high-resolution space that only suffers from limited geometric distortions. It, thus, represents a meaningful complementary statistical approach to network mapping. Moreover, given the ubiquity of T1-weighted images in almost every clinical and research protocol, covariance analysis represents a pragmatic and cost-effective approach for network mapping in large populations.

In ASD, both approaches have generally suggested large-scale structural network breakdowns, contributing to the *underconnectivity theory* of autism. Several diffusion MRI studies, for example, have reported alterations in multiple fiber bundles in ASC (Fletcher et al. 2010; Barnea-Goraly et al. 2004; Sundaram et al. 2008). A recent analysis observed convergent decreases in FA, gray matter volume,

and functional integration of the TPJ area in adults with ASD, and suggested an association between diffusion alterations and decreased emotionality (Mueller et al. 2013). Diffusion alterations have recently been confirmed by a systematic meta-analysis of 14 studies; in that report, consistent abnormalities were highlighted especially in pathways mediating frontal connectivity, such as in superior longitudinal and uncinate fasciculi as well as the corpus callosum (Aoki et al. 2013). Interestingly, a recent study showed a similar structural compromise in children with ASD and their unaffected siblings, suggesting a possible genetic basis for white matter anomalies in these conditions (Barnea-Goraly et al. 2010). Complementing diffusion MRI work, covariance analyses in ASD were also suggestive of compromised inter-regional structural integration (Bernhardt et al. 2014). A majority of covariance studies reported reduced network-level embedding of regions primarily involved in social cognition and affective processes, including the TPJ area (Bernhardt et al. 2014) and medial and lateral prefrontal cortices (Valk et al. 2015). In the latter study, the authors observed consistently decreased covariance between medial prefrontal and midline parietal regions across three independent imaging sites, indicating that structural segregation of these networks may be a reproducible finding in ASD (Fig. 2b) (Valk et al. 2015).

   In the functional domain, several groups have studied inter-regional functional MRI time series, particularly during task-free conditions. Advantages of such *resting-state* over task-related paradigms include the possibility to examine multiple cortical areas in one relatively short session and relatively little demands on individuals with a reduced ability to perform tasks. Resting-state networks have been shown to be highly reproducible across subjects and are thought to correspond closely to systems engaging in specific tasks (Smith et al. 2009). Comparative (Mantini et al. 2011) and modeling (Honey et al. 2007) studies have furthermore suggested that anatomical pathways, in part, determine functional connections. In ASD, atypicalities in functional coupling of several large-scale networks have been reported, with the majority of findings supporting underconnectivity (Geschwind and Levitt 2007; Gotts et al. 2012), particularly of long-range inter-regional functional associations. Yet, several studies have emphasized that differential head motion may contribute to observing connectivity differences (Power et al. 2012), a finding important to consider given that many studies include children and the elevated comorbidity of ADHD with ASD. Moreover, systematic analyses and multi-method simulations have suggested a sizable impact of analytical choices on group differences reported in functional imaging studies, supporting efforts to establish consistent analytical routines, transparent reporting practices, work on openly accessible data, and more rigorous attempts to cross-validate functional connectivity measures (Muller et al. 2011). Based on ABIDE data, for example, the multi-site analysis by Di Martino and colleagues reconciled seemingly inconsistent findings of under- and overconnectivity in ASD. Evidence of both mechanisms were present but varies as a function of the circuits involved. Underconnectivity encompassed cortico-cortical connections and was predominant; yet, overconnectivity was also present and largely characteristic of subcortico-cortical circuits (Fig. 2c) (Di Martino et al. 2014).

Task-free functional studies suggesting connectivity differences have also been complemented by results based on alternative analytical paradigms and neuroimaging modalities. Task-based studies, for example, have suggested underconnectivity during social cognition tasks in ASD (Kana et al. 2009). On the other hand, a recent magnetoencephalography study suggested that connectivity alterations in ASD relative to controls may vary as a function of the frequency band. Moreover, findings may be different depending on the inclusion of frontal nodes in the analysis (Kitzbichler et al. 2015).

Methodological options for evaluating large-scale networks in ASD have recently been extended by the introduction of graph theory to neuroimaging (Bullmore and Sporns 2009). Systematic connectivity mapping among all pairs of regions (usually derived from parcellations) can be used to build a connectivity matrix, the substrate for graph-theoretical analyses. Brain graphs representing these matrices can be visualized, which facilitate an intuitive understanding of topological properties. Fundamental topological parameters include *clustering coefficient*, a measure of local network integration that also relates to network stability, and *characteristic path length,* a proxy for global network efficiency. Graph theory can also be used to calculate the *centrality* metrics that quantify the embedding of regions within the network; high centrality scores are a feature of hub regions relevant for the overall network architecture and communication.

Graph-theoretical analyses of healthy human brain networks have consistently demonstrated a *small-world* topology that is characterized by separate groups of densely clustered regions (modules) interconnected by short paths passing through core hub regions (such as the midline parietal cortex). Several neurological and neuropsychiatric conditions, including schizophrenia (Bassett et al. 2008), ADHD (Cao et al. 2013), and epilepsy (Bernhardt et al. 2011, 2015a), have recently been associated with topological disruptions based on this framework. While only relatively few graph-theoretical assessments have been published in the ASD literature to date, initial findings have shown decreased clustering, suggesting that overall connectomic alterations may be indicative of network reorganization toward a more random arrangement (Rudie et al. 2012). These findings have recently been confirmed (Itahashi et al. 2014); moreover, they have been complemented by data indicating shifts in the overall hub organization in ASD (Di Martino et al. 2013).

4   Summary and Outlook

Neuroimaging has greatly advanced our understanding of brain anomalies associated with ASD. As detailed above, the previous literature has revealed a rather complex pattern of structural and functional alterations in cohorts of individuals with ASD. Among structural MRI studies, a frequently reported finding has been gray matter increases in frontal and temporal regions that might be developmentally constrained and related to aberrant growth patterns in early age and possibly to malformation processes. Investigations of functional and structural network

alterations have primarily suggested global underconnectivity, together with islands of focal connectivity increases. Initial graph-theoretical reports have suggested an association between ASD and topological randomization, together with shifts in the spatial distribution of network hubs. Nevertheless, findings at all levels have not been free from controversy, and ongoing as well as future efforts to increase homogeneity and transparency of subject inclusion criteria as well as analysis routines are highly recommended.

ASD is likely best understood as a developmentally dynamic disorder, motivating longitudinal studies that carefully assess brain development and aging-related change in large cohorts across the life span. The increasing use of high and ultra-high field MRI has the potential to achieve an adequate resolution to address layer-specific structural as well functional alterations and connectivity arrangements in vivo. This scale of analysis is likely needed to detect possibly an elusive pathological substate in specific ASD subgroups (e.g., those with subtle cortical malformations). Based on increasingly complex and high-dimensional neuroimaging datasets, machine-learning techniques offer an appropriate analytic framework to integrate data and to discover and evaluate imaging biomarkers of ASD. In other brain disorders, these techniques are able to discover latent subtypes within seemingly homogeneous cohorts (Bernhardt et al. 2015b). The high variability documented across prior studies of ASD is indicative of claims that this population is very likely composed of different biological subtypes. Variability across the spectrum, thus, needs to be explicitly addressed in research rather than ignored. In this light, cross-site collaborative efforts to aggregate and share large datasets, such as the ABIDE initiative, represent useful and urgent avenues to pursue in our efforts to better understand the neural underpinnings of the complex autism spectrum.

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