CHAPTER

Dysfunctional brain network organization in neurodevelopmental disorders

5

Teague R. Henry, Jessica R. Cohen
Department of Psychology and Neuroscience, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States

CHAPTER OUTLINE

Attention Deficit Hyperactivity Disorder 87
Autism Spectrum Disorder 90
Integration and Segregation as a Framework for Understanding Neurodevelopmental Disorders: Next Steps 94
References 96

The term "neurodevelopmental disorder" covers a wide range of brain disorders that arise from atypical brain development beginning early in life (and in some cases prenatally), and continuing throughout the life span. The etiology of some of these disorders is well known. For example, Fragile X Syndrome is a genetic disorder that arises from a lengthening of the FMR1 gene on the X chromosome, a mutation that leads to disrupted brain development (Hagerman and Hagerman, 2004). For others, such as attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD), the causes are considerably less clear and are likely much more heterogeneous. Recent research investigating the brain basis of many of these neurodevelopmental disorders has led to the hypothesis that the pathophysiology of these disorders involves dysfunctional brain network organization, rather than disrupted functioning of individual brain regions.

Before delving into the research that has led to such a hypothesis, it is critical to understand how brain network organization is measured in humans. Graph theoretical tools from the field of mathematics can be used to describe the brain as a graph, or a network, composed of nodes and edges. The term *node* refers to specific brain regions of interest (ROIs). These ROIs can be anatomically defined, such as the amygdala, or they can be functionally defined, such as a portion of the inferior

Connectomics. https://doi.org/10.1016/B978-0-12-813838-0.00005-4

frontal gyrus that relates to a specific set of cognitive processes. To place the ROIs within the notation of graph theory, we will interchangeably refer to ROIs as nodes. In a brain graph, the term *edge* refers to the connectivity between ROIs (nodes). The operationalization of these connectivity edges will depend on the neuroimaging modality and analysis conducted. A common way of defining a functional connectivity edge is to calculate the correlation between fluctuations in the BOLD signals across time of two ROIs. Alternatively, one can use the spectral coherence between the BOLD signals. A structural connectivity edge typically corresponds to the number of streamlines, or white matter fibers, between a pair of ROIs. In this chapter, we will use the term edge and connection interchangeably, while specifying the modality (functional or structural) of the connection.

Within the whole-brain network, subnetworks are strongly interconnected sets of ROIs. Subnetwork organization can be determined in a data-driven manner using a community detection algorithm (Sporns and Betzel, 2016). Subnetworks can alternately be defined a priori based on existing literature, such as the default mode network (DMN) or the salience network (SN) (Seeley et al., 2007). In human neuroimaging literature, specific subnetworks are often referred to as "networks" due to the history of probing individual subnetworks outside the context of the whole-brain network. Throughout this chapter, we utilize names commonly used in human neuroimaging literature (i.e., DMN), but clarify that they are, in fact, subnetworks within the larger whole-brain network.

One advantage of describing the brain in terms of its network properties is that summary measures of topological organization can be quantified, and therefore single numbers can describe certain network attributes. For example, the average degree of a network is the average, across all nodes, of the number of edges of each node. By utilizing these summary measures, it is possible to describe and analyze large complex networks in simple and easily interpretable ways. For example, the average degree of a network describes how interconnected network nodes are with each other. A framework of network organization emerging as critical for understanding brain function is the balance of integration and segregation across individual subnetworks within the larger whole-brain network (Deco and Kringelbach, 2014; Deco et al., 2015; Shine and Poldrack, 2017; Sporns and Betzel, 2016). Fig. 1 and Table 1 summarize our use of graph theory terminology as well as commonly used metrics describing network attributes.

Dysfunction at the subnetwork level can take multiple forms. Compared to healthy control participants, a clinical population might have reduced or increased connectivity within a subnetwork. As an example, reduced functional connectivity within the DMN during rest has been observed in youth with ADHD (Fair et al., 2010). Alternatively, subnetworks might be aberrantly connected to other subnetworks. For example, increased functional connectivity during rest between a subcortical subnetwork consisting of the basal ganglia and the thalamus, and several cortical subnetworks consisting of primary sensory regions, has been observed in male children with ASD compared with healthy control participants (Cerliani et al., 2015). A growing body of research indicates that there are reliable differences in subnetwork organization between healthy individuals and individuals with

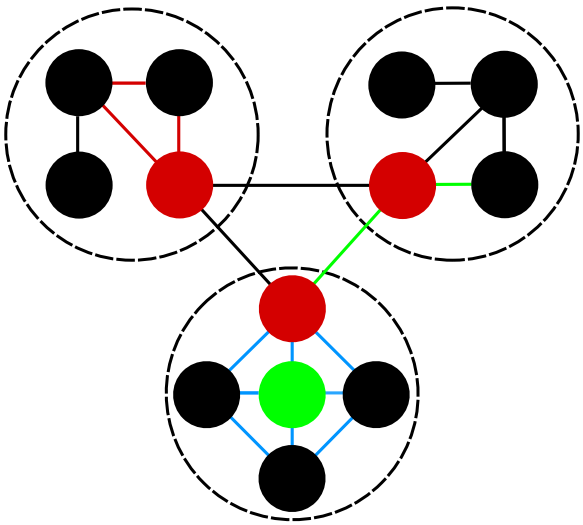

FIG. 1

Network diagram depicting various topological network attributes. *Circles* denote nodes, *lines* denote edges, and the *larger dashed circles* denote individual subnetworks (or communities). See Table 1 for a description of the colored nodes and edges.

Table 1 Topological attributes commonly used to describe brain network organization (see Fig. 1)

Statistic	Description	Figure description/source
Average degree	The average number of edges of a node	The green node has a degree of 4. Freeman (1978)
Clustering coefficient	A proportion describing how interconnected groups of neighboring nodes are to each other	The red edges form a clique of highly interconnected neighboring nodes. Holland and Leinhardt (1971).
Path length	The length of the shortest path between two nodes	The green edges indicate the shortest path between two nodes. Latora and Marchiori (2001).
Nodal efficiency	The average inverse path length from a target node to every other node	NA. Latora and Marchiori (2001).
Global efficiency	The average inverse path length between every pair of nodes	NA. Latora and Marchiori (2001).
Local efficiency	The average nodal efficiency of a node's neighbors	The blue edges represent a highly locally efficient network. Latora and Marchiori (2001).
Modularity	The degree to which a network is segregated into tightly clustered communities	The dashed circles represent individual communities that are highly interconnected. Newman (2006).
Rich club coefficient	The extent to which high degree nodes connect to one another	The red nodes form a rich club. van den Heuvel and Sporns (2011).

psychiatric/neurologic disorders, and a greater understanding of network-based dysfunction may lead to increased knowledge of the mechanisms underlying these disorders (for reviews, see Deco and Kringelbach, 2014; Fornito et al., 2015).

Previous work probing both functional and structural connectivity in neurodevelopmental disorders has primarily examined dysfunction in a hyper/hypoconnectivity framework, where functional and structural connections between regions and between distinct subnetworks are characterized as either stronger or weaker than in healthy individuals. However, the hyper/hypoconnectivity framework does not take into account overall network topology, which has been demonstrated to be an important feature of brain connectivity that differentiates populations (Di Martino et al., 2014; Fornito et al., 2015; Konrad and Eickhoff, 2010). A more recent conceptual framework for understanding functional and structural connectivity patterns emphasizes the importance of balancing the opposing forces of network integration and network segregation (Shine and Poldrack, 2017; Cohen and D'Esposito, 2016; Deco et al., 2015; Sporns, 2013). Network segregation can be conceptualized as strong within-subnetwork connectivity with few interactions across subnetworks, whereas network integration involves greater interactions across distinct subnetworks. This characterization of connectivity patterns focuses less on the strength or weakness of individual functional and structural connections, and instead focuses on how subnetworks of interest are embedded within the overall brain network. This way of thinking opens up avenues of investigation in which the brain dysfunction that underlies neurodevelopmental disorders is not limited to functional or structural *strength* but rather can be described as a disruption of overall *topology*. Notably, previous findings that use the hyper/hypoconnectivity framework can often be recast into a functional or structural integration/segregation approach, making the integration/segregation framework an extension and enrichment of the hyper/hypoconnectivity framework, rather than an opposing approach.

An advantage of the integration/segregation approach is that information about the strength of individual connections is not lost (i.e., whether there is hyper- or hypoconnectivity as related to specific connections or subnetworks), but one is additionally able to calculate summary measures that describe both global (integration) and local (segregation) properties of the whole-brain network (Bullmore and Sporns, 2009; Sporns, 2010). This framework of integration/segregation has been used in recent research to examine properties of cognition in healthy young adults (Cohen and D'Esposito, 2016), preclinical Alzheimer's disease (Brier et al., 2014), and dynamic alternations between integration and segregation of resting state functional connectivity subnetworks (Betzel et al., 2016), among many more topics. In this chapter, we focus on reviewing recent work examining disrupted functional and structural connectivity of brain networks in neurodevelopmental disorders. Given the large emphasis of the literature on ADHD and ASD, we focus on those two disorders. We conclude by discussing extensions of the integration/segregation framework that could help extend our understanding of complex neurodevelopmental disorders. We concentrate on graph theoretic approaches, however, there are two other broad classes of methods for brain connectivity analysis that warrant mentioning. The first

is seed-based connectivity analyses, in which a certain voxel or set of voxels is chosen as a "seed" from which to compute connectivity to the rest of the brain (usually operationalized as correlation strength). The second is independent component analysis (ICA), which uses a data-driven method to segment the brain into subnetworks that are spatially or temporally independent from each other. Please see Chapter 7 for more details on the use of these alternative methods to study brain connectivity in neurodevelopmental disorders.

ATTENTION DEFICIT HYPERACTIVITY DISORDER

ADHD is the most commonly diagnosed neurodevelopmental disorder. It is thought to affect approximately 9% of school-aged children in the United States (Center for Disease Control, 2018). This disorder often appears in childhood around year 8 and is characterized by an inability to sustain attention and/or excessive impulsive behavior and hyperactivity (American Psychiatric Association, 2013). FMRI activation studies of children with ADHD have consistently shown hypoactivation in dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC), supplementary motor area (SMA), temporoparietal cortical regions, and caudate nucleus during the execution of a variety of inhibition and attention tasks, whereas adults with ADHD show hypoactivation in a number of frontal and striatal regions, in addition to regions in the premotor, parietal, and occipital areas during motor and inhibition tasks (for a review see: Cubillo et al., 2012). Research probing altered reward-related functioning in ADHD has additionally shown hypoactivation in adults, children, and adolescents with ADHD in striatal and ventral-striatal regions during reward anticipation tasks (for reviews, see Cubillo et al., 2012; Plichta and Scheres, 2014). These deficits in frontal and striatal regions have been interpreted previously to indicate a disrupted reward circuit composed of the ventral striatum, thalamus, ACC, and orbitofrontal cortex. As part of their dual pathways model, Sonuga-Barke (2005) suggests that disruptions in this reward circuit are one pathway to ADHD symptomatology, with the other pathway involving disruptions in executive control circuitry. For a review of this literature, see Sonuga-Barke (2002, 2005).

In a large metaanalysis, Cortese et al. (2012) examined a body of ADHD activation studies in an effort to uncover *task agnostic* differences in activation. In addition to observing similar hypoactivation in frontal and parietal regions that had been highlighted in previous reviews (e.g., Cubillo et al., 2012; Plichta and Scheres, 2014), they also found hyperactivation in children with ADHD relative to typically developing children in regions of the DMN and the ventral attention network (VAN), as well as the SMA. In adults with ADHD, hyperactivation was similarly observed in DMN regions but additionally observed in the visual cortex and in regions of the dorsal attention network (DAN). Interestingly, the patterns of hyperactivation were found regardless of task, in contrast with previous work that focused on specific tasks. This suggests a general, rather than a task-specific phenomenon. These three lines of activation findings—hypoactivation in frontal, parietal, and striatal regions

during inhibition tasks; hypoactivation in ventral striatal regions during reward anticipation tasks; and hyperactivation in DMN, VAN, and DAN regions regardless of task—suggests that ADHD is characterized by distributed alteration in brain function. However, these activation results are limited to regions studied in isolation, and do not take into account the connections across brain regions.

Functional connectivity measurements can shed light on the nature of the hyper/hypoactivation observed in functional activation studies. As an example, the default mode interference hypothesis (Castellanos and Aoki, 2016; Sonuga-Barke and Castellanos, 2007; Weissman et al., 2006) states that attentional lapses may be due to the DMN "intruding" on regions activated by a task, by either reactivating after temporarily deactivating during the task or failing to deactivate at all (Sonuga-Barke and Castellanos, 2007; Weissman et al., 2006). When applied to individuals with ADHD, the default mode interference hypothesis suggests that the DMN is more likely to "intrude" on task-related regions and subnetworks in individuals with ADHD compared with healthy control participants (Sonuga-Barke and Castellanos, 2007). Reframing this hypothesis in terms of functional connectivity between brain regions suggests that individuals with ADHD should show reduced anticorrelations between the DMN and task-related subnetworks (Sonuga-Barke and Castellanos, 2007). Indeed, research has consistently observed a reduced anticorrelation between the DMN and a variety of task-related subnetworks at rest in children, adolescents, and adults with ADHD (for reviews, see Konrad and Eickhoff, 2010; Posner et al., 2014). Furthermore, studies consistently observe hypoconnectivity *within* the DMN in children and adults with ADHD (for a review, see Posner et al., 2014). This reduced anticorrelation between the DMN and task-related subnetworks can, in part, explain the pattern of hypoactivation of frontal regions and hyperactivation of the DMN that was previously described.

In addition to the default mode interference hypotheses of ADHD, there is a body of literature regarding disruptions in cortico-striatal-thalamic-cortical (CSTC) loops in individuals with ADHD. CSTC loops are neural circuits that project from the cortex to the striatum, to the thalamus, and then back to the cortex. These loops are thought to underlie various cognitive processes (Alexander, 1986; Alexander and Crutcher, 1990). There is a long tradition of functional activation research observing dysfunctional activation in brain regions that are a part of CSTC loops in ADHD (for reviews, see Sonuga-Barke, 2002, 2005; Posner et al., 2014). Recently, a small but growing set of evidence is emerging that functional connectivity of CSTC circuits involved in cognitive and limbic processes are disrupted in individuals with ADHD. Specifically, hypoconnectivity between the putamen and ventral striatum, as well as between the ventral striatum and anterior prefrontal cortex, has been observed in children with ADHD. For a review of this body of literature, refer to Posner et al. (2014).

Within the previously referenced body of literature on the default mode interference and CSTC loop disruption hypotheses, the majority of the studies examined functional connectivity from a strictly hyper/hypoconnectivity framework. Few studies to date examine ADHD from a network integration/segregation framework. In one of these studies, Wang et al. (2009) showed that children with ADHD exhibited decreased global efficiency, a measure of integration, and increased local efficiency

(a measure of segregation) relative to healthy individuals. Further, children with ADHD had significantly decreased nodal efficiency of the orbitofrontal cortex and of regions of temporal and occipital cortex, indicating increased segregation of these regions, as well as increased nodal efficiency in the inferior frontal gyrus, indicating increased global integration of this region. In a study in adults with ADHD, it was found that individuals with ADHD exhibited increased modularity, clustering coefficient, and local efficiency, all measures of network segregation, relative to control participants (Lin et al., 2014). The authors additionally found that network segregation was most increased in the frontal cortex, occipital cortex, and subcortical regions, whereas the SMA was more integrated in individuals with ADHD. A study probing integration within the DMN implemented a measure of network homogeneity and found that the DMN exhibited reduced network homogeneity in adults with ADHD relative to age-matched control participants. Reduced network homogeneity was localized to the precuneus, suggesting that the precuneus was more segregated from other regions of the DMN in adults with ADHD (Uddin et al., 2008). More recently, Fair et al. (2013) demonstrated that a pattern classifier was able to successfully differentiate children with the inattentive subtype of ADHD, the combined (inattentive and hyperactive/impulsive) subtype of ADHD, and typically developing children on the basis of functional connectivity patterns. Critically, the brain subnetworks that most differentiated children with the inattentive subtype of ADHD from typically developing children were different from the brain subnetworks that most differentiated children with the combined subtype of ADHD from typically developing children, implying different etiologies of the two subtypes. Specifically, DMN connectivity was most able to differentiate children with the combined subtype of ADHD from typically developing children, whereas frontoparietal network (FPN) and cerebellar connectivity were most able to differentiate children with the inattentive subtype from typically developing children (Fair et al., 2013).

Synthesizing activation, hyper/hypoconnectivity, and integration/segregation results together, this body of research suggests that dysfunctional subnetwork organization in ADHD is not limited to dysfunction within specific subnetworks, such as VAN, DAN, or DMN, but additionally includes disruptions of functional connections between the DMN and task-related subnetworks, as well as disruption of functional connections between cortical and subcortical structures. The small set of integration/segregation studies further suggest that, on a whole-brain level, disruption of functional network organization is mainly due to decreased integration across distinct subnetworks in individuals with ADHD compared with healthy controls (Lin et al., 2014; Wang et al., 2009). A review of graph theoretic functional and structural imaging results in individuals with ADHD (Cao et al., 2014) reached much the same conclusion, noting that there appears to be both general global disruption of structural and functional connectivity, as well as specific loci of dysfunction, such as the DMN, that correlate with ADHD-related behavior. This combination of results suggests several avenues of research that take advantage of the power of an integration/segregation approach. The first is to examine the integration (or segregation) of the DMN with task-related subnetworks during cognitive task performance. Under the default mode interference hypothesis, individuals with ADHD should exhibit a less segregated DMN during

cognitive task performance relative to healthy individuals. Further, examining DMN connectivity with other subnetworks in addition to task-related subnetworks would clarify whether the DMN displays reduced segregation specifically with task-related subnetworks or globally reduced segregation with all brain subnetworks. With regard to the overall increase in network segregation, future studies could examine the role of CSTC loops in driving whole-brain integration and segregation in individuals with ADHD. Finally, results of studies probing functional brain network organization can be better informed by synthesizing them with structural brain network analyses. Structural connectivity research in individuals with ADHD has been particularly amenable to the integration/segregation approach in the past, and this literature is what we turn to now.

Recent research probing disrupted structural connectivity in ADHD is consistent with the functional integration/segregation findings discussed previously. Beare et al. (2016), in a study in male children and adolescents with ADHD, used high-angular resolution diffusion imaging (HARDI) and probabilistic tractography to examine differences in structural brain network organization between ADHD and typically developing individuals. They found increased modularity and decreased global efficiency in individuals with ADHD. These findings are consistent with functional network research that has observed increased segregation and decreased integration of distinct brain subnetworks in ADHD. Additionally, they found increased structural connectivity within a subnetwork that encompassed bilateral inferior, middle, and orbitofrontal regions, precentral regions, cingulate cortex, and putamen in individuals with ADHD relative to typically developing individuals (Beare et al., 2016). A study in drug-naïve male children with ADHD similarly observed decreased global efficiency in structural brain network organization compared with typically developing children (Cao et al., 2013). The same study also observed within-network connectivity differences in specific subnetworks in children with ADHD. Specifically, they found decreased structural connectivity within a prefrontal-insular subnetwork and increased structural connectivity within an orbitofrontal-striatal subnetwork in children with ADHD. Combined, literature probing structural and functional network organization in ADHD has consistently found decreased integration and increased segregation in individuals with ADHD (Beare et al., 2016; Cao et al., 2013; Lin et al., 2014; Wang et al., 2009). These results indicate that brain dysfunction in ADHD is described well in terms of a disrupted balance between integration and segregation in brain network organization, both globally (i.e., globally reduced integration) and with regard to specific subnetworks (i.e., specific increased integration of DMN with other subnetworks). Further research exploring disrupted integration and segregation of brain networks in ADHD will increase knowledge of the neural basis of the disorder.

AUTISM SPECTRUM DISORDER

ASD is a complex pervasive neurodevelopmental disorder, the severity of which ranges from very high to very low functioning. The classic symptoms of ASD are marked social deficits, difficulty with language comprehension or production,

restricted and repetitive behaviors, and high sensory reactivity (American Psychiatric Association, 2013). ASD is an extremely heterogeneous disorder in terms of presentation. It is also heterogeneous with regard to age of first expression. Typically, the earliest age that a confirmatory diagnosis can be made is 24 months, however in some cases diagnostic symptoms, such as highly repetitive play and lack of social involvement, can present as early as 12 months (Martínez-Pedraza and Carter, 2009).

As with the study of ADHD, neuroimaging studies of ASD began with analyses of fMRI activation in individual brain regions. A recent metaanalysis summarizing a large portion of the brain activation literature suggests two specific patterns of aberrant activation exist in ASD, one related to social processing and the other to nonsocial processing (Di Martino et al., 2009). In the context of social processing, individuals with ASD display decreased activation in the pregenual ACC, anterior rostral medial PFC, amygdala, right anterior insula, and PCC. Each of these regions has been previously implicated in social processing, with the anterior insula and the amygdala of particular interest to ASD research due to the anterior insula's prominent role in the SN (Uddin and Menon, 2009) and the amygdala's connection to facial processing (Baron-Cohen et al., 2000). The metaanalysis also found that, during nonsocial processing, individuals with ASD show decreased activation in dorsal ACC and pre-SMA, regions associated with cognitive control, and increased activation in SMA (Di Martino et al., 2009). Finally, individuals with ASD also demonstrate increased activation in the pregenual ACC during nonsocial processing, similar to what is found during social processing. Based on these results, Di Martino et al. (2009) suggested that disruption of regulatory processes can explain the pattern of hyper- and hypoactivation seen in nonsocial processing. They proposed that the DMN may be the source of this dysfunctional regulation, similar to conclusions from the ADHD connectivity literature.

Functional connectivity research has suggested that there are distributed functional connectivity disruptions throughout the brain in individuals with ASD. Hypoconnectivity has been observed within the DMN, SN (specifically the insular cortex), and the amygdala, while hyperconnectivity has been observed between the striatum and the insular cortex, within the primary motor cortex, and between sensory cortices and the thalamus/basal ganglia (for reviews, see Mueller et al., 2011; Kana et al., 2014; Hull et al., 2016). A recent review summarizing DMN connectivity disruptions in ASD at different ages found that dysfunctional DMN connectivity patterns change across age (Padmanabhan et al., 2017). In children, ASD is associated with hyperconnectivity within the DMN and hypoconnectivity between the DMN and other subnetworks, whereas in adults with ASD, the DMN exhibits hypoconnectivity both within the DMN and between the DMN and other subnetworks. This suggests that, similar to ADHD, the DMN may be a key site of dysfunction in ASD.

In addition to the DMN, another important functional subnetwork with implications for ASD is the SN. This subnetwork, which consists primarily of the insula and the anterior cingulate cortex, is thought to be important for detecting important sources of information across a variety of contexts, as well as switching between

distinct task-relevant subnetworks when task demands change (Menon, 2015; Menon and Uddin, 2010; Seeley et al., 2007). Furthermore, in previous work with healthy individuals, the right anterior insula has been shown to play a vital role in the switching of activation between the central executive network (CEN) and the DMN (Menon and Uddin, 2010). Hypoactivation of the anterior insula is implicated in ASD (Uddin and Menon, 2009). Previous work utilizing a machine learning approach to classify subjects into diagnostic categories using functional connectivity showed that connectivity within the SN was better able to distinguish children with ASD from typically developing children than other brain subnetworks such as the DMN (Uddin et al., 2013). In a recent study in primarily male children with ASD, the anterior insula was shown to be hypoconnected to motor, sensory, and visual processing regions in children with ASD compared with typically developing children (Odriozola et al., 2016). Another recent study in children with ASD showed that subjects with ASD had hyperconnectivity within the DMN and right ECN, and hypoconnectivity within the SN and left ECN. Critically, ASD symptomatology was primarily related to dysfunction within the SN (Abbott et al., 2016). Functional connectivity findings with regard to the insula and SN are not entirely consistent, however. Hyperconnectivity has been observed between the insula and the pons in children with ASD (Di Martino et al., 2011), and hyperconnectivity between the SN and sensory cortex has been related to a behavioral measure of sensory overresponsivity in children with ASD (Green et al., 2016). This mix of findings suggests that the SN, and in particular the anterior insula, plays an important role in ASD, but the precise nature of how the SN is embedded within the functional topology of the brain remains unclear.

It is possible that probing functional connectivity in ASD in terms of network integration and network segregation would better describe the dysfunction observed in ASD network organization. Similarly to ADHD, there has been an emerging set of literature that examines ASD from this perspective rather than from a strict hypo/hyperconnectivity perspective. Rudie et al. (2013) found that children with ASD had reduced modularity and increased global efficiency relative to typically developing children, suggesting a more globally integrated functional brain network in ASD. Consistent with these findings, adults with ASD have been shown to display decreased clustering coefficient and decreased characteristic path length, indicating increased integration in ASD (Itahashi et al., 2014). Keown et al. (2017) similarly observed that adolescents and adults with ASD had decreased cohesion (indicating reduced within-subnetwork connectivity or reduced segregation) and increased dispersion (indicating increased across-network integration) relative to healthy control participants. Henry et al. (2017) showed increased whole-brain integration and decreased whole-brain segregation in adolescents and adults with ASD relative to healthy controls and further showed that the somatomotor cortex is a core region driving decreased whole-brain segregation findings. Finally, children with ASD have been shown to have increased functional connectivity within rich club communities, again indicating increased network integration (Ray et al., 2014).

Similarly to research in individuals with ADHD, research of structural connectivity abnormalities in an integration/segregation framework in ASD has begun to appear more frequently. Lewis et al. (2013) used probabilistic tractography to study global network topology of white matter tracts in a study of adult males with ASD. They found a decrease in both local efficiency and global efficiency in individuals with ASD relative to control participants. The authors interpreted this finding as individuals with ASD having more, but weaker, connections overall, which would result in a globally less segregated but also less integrated structural network. Rudie et al. (2013) reported similar findings. They found that, although global efficiency increased with increasing age in typically developing individuals, it decreased with increasing age in individuals with ASD. Conversely, modularity, a measure of network segregation, decreased with increasing age in typically developing individuals, whereas it decreased at a lower rate in individuals with ASD. Consistent with the previously discussed research, Roine et al. (2015) reported reduced global efficiency, increased normalized path length, and decreased strength (the average degree for a weighted network) of the structural network in adult males with ASD. Taken together, this line of research indicates that individuals with ASD have weaker overall white matter network structure, which impacts both network segregation and network integration.

With regard to network segregation, both functional connectivity and structural connectivity literature points to decreased segregation in individuals with ASD. With regard to network integration, however, functional brain networks tend to be more integrated whereas structural brain networks tend to be less integrated. Importantly, in a study that compared both functional and structural network organization in ASD and in healthy individuals, a negative correlation was observed between structural and functional global efficiency (Rudie et al., 2013), confirming previous literature finding increased functional network integration and decreased structural network integration in ASD. This relationship has been observed in other patient populations as well (i.e., in patients with multiple sclerosis; Hawellek et al., 2011).

Taken together, the hyper/hypoconnectivity and integration/segregation findings suggest important further research needs to be conducted to understand dysfunctional brain network organization in individuals with ASD. As an example, understanding how DMN connectivity contributes to overall patterns of whole-brain integration and segregation would shed light on the role of the DMN in dysfunctional network organization in ASD. Probing DMN connectivity in an integration/segregation framework could clarify the findings of hyperconnectivity within the DMN, but hypoconnectivity between the DMN and other subnetworks in children with ASD (Padmanabhan et al., 2017). A similar approach could be applied to examine the role of the SN in brain network organization in ASD. Evidence suggests that ASD is a complex disorder characterized by differences in overall brain topology, and understanding how individual subnetworks within the brain contribute to overall topology would further our understanding of network organization in ASD.

INTEGRATION AND SEGREGATION AS A FRAMEWORK FOR UNDERSTANDING NEURODEVELOPMENTAL DISORDERS: NEXT STEPS

In this chapter, we summarized an emerging framework for understanding disrupted functional and structural connectivity with a focus on balancing network integration and network segregation. We described the general approach this framework invokes, and demonstrated that it complements and extends the more traditional framework of hyper- versus hypoconnectivity. We summarized extant literature probing functional and structural connectivity in both ADHD and ASD, and suggested that the brain basis of both of these disorders is better described as dysfunctional topology rather than altered connectivity strength. These findings suggest several directions that future research can take.

One straightforward direction is to use the integration/segregation framework to localize differences in whole brain integration and segregation to specific subnetworks or ROIs. As was discussed with regard to both ADHD and ASD, several potential lines of research lie in, for example, examining the role of the DMN in overall network structure. Some extant research has done so by examining nodal efficiency (e.g., Wang et al., 2009), but this general approach can be extended to any feature of network organization. Borrowing from network robustness literature in which lesions are simulated, the change in any metric of interest can be examined as a function of the "removal" of nodes and edges (Albert et al., 2000; Callaway et al., 2000). Network robustness methods can assess effects due to the random removal of nodes and edges, as well as the effect of removing specific nodes and edges from a network. This methodology allows researchers to not only describe differences between clinical and control populations in terms of whole-brain network organization, but also in terms of the contribution of specific nodes and edges, as well as subnetworks, to those whole-brain network characteristics. A prominent example of the use of this methodology is found in a study by Achard et al. (2006), in which they demonstrated that the healthy adult brain is more resilient to targeted removal of hub regions than is a scale-free network. Applying this methodology to the study of neurodevelopmental disorders would allow for a more targeted examination of which regions and edges, and therefore subnetworks, are more or less critical to network functioning in disordered populations versus healthy control populations.

A second extension of the integration/segregation framework has already been applied in several studies: the analysis of both structural and functional brain networks within the same subjects. Rudie et al. (2013) demonstrated in a joint analysis of integration metrics from both structural and functional brain networks that global efficiency has an inverse relationship between the two modalities. Ray et al. (2014) performed rich club analysis on both structural and functional data, though they do not implement a joint analysis of the modalities. These analyses highlight one of the strengths of the integration/segregation approach, as it does not require joint analysis of the imaging data but rather joint analysis of the whole-brain summary metrics of network organization derived from constructed connectivity networks. Applying a

joint analysis of functional and structural integration/segregation in a whole-brain fashion would allow researchers to examine potential differences in the relationship between structure and function in clinical populations in a fairly easy to interpret fashion. For example, the DMN's contribution to whole-brain functional integration can be examined in tandem with its contribution to whole-brain structural integration, as well as probing differences between patient and control groups. This can be used to examine whether structural/functional coupling differs in different populations. Furthermore, this methodology can be combined with the network robustness methodology examining individual subnetworks and nodes to provide a richer understanding of the nature of structural and functional network organization in specific disorders.

A third extension of the integration/segregation framework would be to characterize the dynamics of functional connectivity (Calhoun et al., 2014). By using dynamic functional connectivity methods to estimate how functional connectivity patterns change throughout the course of a functional brain scan, across-group differences in the dynamics of network integration and segregation can be linked to different patient populations. Given the growing body of evidence that dynamic fluctuations in functional connectivity patterns are related to behavior and cognition in healthy subjects (for reviews, see Cohen, 2017; Kucyi et al., 2018), the combined use of the integration/segregation framework and dynamic functional connectivity methods could help shed light on how dysfunctional connectivity dynamics underlie the differences in cognition and behavior found in patients with neurodevelopmental disorders.

Importantly, given both the similarities and differences in network integration and segregation with regard to ADHD and ASD, future research should directly compare the two populations, both in individuals that have *either* ADHD or ASD, and in individuals with *comorbid* ADHD/ASD (Uddin et al., 2017). For example, one study has included both children with ADHD and children with ASD in an analysis of structural and functional rich club organization. When focusing on structural network organization, a pattern of structural hypoconnectivity within rich club regions and hyperconnectivity outside of the rich club in children with ADHD was found, whereas conversely structural hyperconnectivity within rich-club regions (though with the caveat that these connections were weak) and hypoconnectivity outside of the rich club was found in children with ASD (Ray et al., 2014). Further, when characterizing functional connectivity networks, Ray and colleagues demonstrated that children with ADHD showed significantly higher functional connectivity outside of the rich club than both typically developing children and individuals with ASD, although there were no differences in functional connectivity outside of the rich club between typically developing children and children with ASD. This suggests that this hyperconnectivity outside of the rich club can act as a distinctive neural marker for individuals with ADHD. In a single study, these results support the general findings of increased global integration in ASD and increased segregation in ADHD. When comparing differences in network organization across ADHD and ASD populations, these results further highlight the differences in dysfunctional network organization that underlies each disorder.

In closing, neurodevelopmental disorders have complex sets of neural correlates, whose properties appear to go beyond simple hyper/hypoconnectivity, and are perhaps better described by differences in network shape rather than connection strength. The framework of network integration and segregation provides an easily implemented and easily understood set of common tools that researchers can use to better characterize the complex pattern of differences often observed in neuroimaging studies of individuals with these disorders. Adding this framework to the repertoire of neuroimaging research adds a powerful tool for understanding the complex nature of neurodevelopmental and other disorders.

REFERENCES

Abbott, A.E., Nair, A., Keown, C.L., Datko, M., Jahedi, A., Fishman, I., Müller, R.-A., 2016. Patterns of atypical functional connectivity and behavioral links in autism differ between default, salience, and executive networks. Cereb. Cortex 26 (10), 4034–4045.

Achard, S., Salvador, R., Whitcher, B., Suckling, J., Bullmore, E., 2006. A resilient, low-frequency, small-world human brain functional network with highly connected association cortical hubs. J. Neurosci. 26 (1), 63–72.

Albert, R., Jeong, H., Barabási, A.L., 2000. Error and attack tolerance of complex networks. Nature 406 (6794), 378–382.

Alexander, G., 1986. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu. Rev. Neurosci. 9 (1), 357–381.

Alexander, G.E., Crutcher, M.D., 1990. Functional architecture of basal ganglia circuits: neural substrates of parallel processing. Trends Neurosci. 13 (7), 266–271.

American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders, fifth ed. American Psychiatric Publishing, Arlington, VA.

Baron-Cohen, S., Ring, H.A., Bullmore, E.T., Wheelwright, S., Ashwin, C., Williams, S.C.R., 2000. The amygdala theory of autism. Neurosci. Biobehav. Rev. 24 (3), 355–364.

Beare, R., Adamson, C., Bellgrove, M.A., Vilgis, V., Vance, A., Seal, M.L., Silk, T.J., 2016. Altered structural connectivity in ADHD: a network based analysis. Brain Imaging Behav. 11 (3), 846–858.

Betzel, R.F., Fukushima, M., He, Y., Zuo, X.N., Sporns, O., 2016. Dynamic fluctuations coincide with periods of high and low modularity in resting-state functional brain networks. NeuroImage 127, 287–297.

Brier, M.R., Thomas, J.B., Fagan, A.M., Hassenstab, J., David, M., 2014. Functional connectivity and graph theory in preclinical Alzheimer's disease. Neurobiol. Aging 35 (4), 1–25.

Bullmore, E.T., Sporns, O., 2009. Complex brain networks: graph theoretical analysis of structural and functional systems. Nat. Rev. Neurosci. 10 (3), 312.

Calhoun, V.D., Miller, R., Pearlson, G., Adali, T., 2014. The chronnectome: time-varying connectivity networks as the next frontier in fMRI data discovery. Neuron 84 (2), 262–274.

Callaway, D.S., Newman, M.E.J., Strogatz, S.H., Watts, D.J., 2000. Network robustness and fragility: percolation on random graphs. Phys. Rev. Lett. 85 (25), 5468–5471.

Cao, Q., Shu, N., An, L., Wang, P., Sun, L., Xia, M.-R., Wang, J.H., Gong, G.L., Zang, Y.F., Wang, Y.F., He, Y., 2013. Probabilistic diffusion Tractography and graph theory analysis reveal abnormal white matter structural connectivity networks in drug-naive boys with attention deficit/hyperactivity disorder. J. Neurosci. 33 (26), 10676–10687.

Cao, M., Shu, N., Cao, Q., Wang, Y., He, Y., 2014. Imaging functional and structural brain connectomics in attention-deficit/hyperactivity disorder. Mol. Neurobiol. 50 (3), 1111–1123.

Castellanos, F.X., Aoki, Y., 2016. Intrinsic functional connectivity in attention-deficit/hyperactivity disorder: a science in development. Biol. Psych. Cogn. Neurosci. Neuroimag. 1 (3), 253–261.

Center for Disease Control, 2018. Key Findings: National Prevalence of ADHD and Treatment: New statistics for children and adolescents, 2016.

Cerliani, L., Mennes, M., Thomas, R.M., Di Martino, A., Thioux, M., Keysers, C., 2015. Increased functional connectivity between subcortical and cortical resting-state networks in autism spectrum disorder. JAMA Psychiat. 72 (8), 767–777.

Cohen, J.R., 2017. The behavioral and cognitive relevance of time-varying, dynamic changes in functional connectivity. NeuroImage. (In Press, Available Online).

Cohen, J.R., D'Esposito, M., 2016. The segregation and integration of distinct brain networks and their relationship to cognition. J. Neurosci. 36 (48), 12083–12094.

Cortese, S., Kelly, C., Chabernaud, C., Proal, E., Di Martino, A., Milham, M.P., Castellanos, F.X., 2012. Toward systems neuroscience of ADHD: a meta-analysis of 55 fMRI studies. Am. J. Psychiatry 169 (10), 1038–1055.

Cubillo, A., Halari, R., Smith, A., Taylor, E., Rubia, K., 2012. A review of fronto-striatal and fronto-cortical brain abnormalities in children and adults with attention deficit hyperactivity disorder (ADHD) and new evidence for dysfunction in adults with ADHD during motivation and attention. Cortex 48 (2), 194–215.

Deco, G., Kringelbach, M.L., 2014. Great expectations: using whole-brain computational connectomics for understanding neuropsychiatric disorders. Neuron 84 (5), 892–905.

Deco, G., Tononi, G., Boly, M., Kringelbach, M.L., 2015. Rethinking segregation and integration: contributions of whole-brain modelling. Nat. Rev. Neurosci. 16 (7), 430–439.

Di Martino, A., Ross, K., Uddin, L.Q., Castellanos, F.X., Sklar, A.B., Milham, M.P., 2009. Functional brain correlates of social and nonsocial processes in autism spectrum disorders: an activation likelihood estimation meta-analysis. Biol. Psychiatry 65 (1), 63–74.

Di Martino, A., Kelly, C., Grzadzinski, R., Zuo, X.N., Mennes, M., Mairena, M.A., Lord, C., Castellanos, F.X., Milham, M.P., 2011. Aberrant striatal functional connectivity in children with autism. Biol. Psychiatry 69 (9), 847–856.

Di Martino, A., Fair, D.A., Kelly, C., Satterthwaite, T.D., Castellanos, F.X., Thomason, M.E., Craddock, R.C., Luna, B., Leventhal, B.L., Zuo, X., Milham, M.P., 2014. Unraveling the miswired connectome: a developmental perspective. Neuron 83 (6), 1335–1353.

Fair, D.A., Posner, J., Nagel, B.J., Bathula, D., Costa-Dias, T.G., Mills, K.L., Blythe, M.S., Giwa, A., Schmitt, C.F., Joel, T., 2010. Atypical default network connectivity in youth with ADHD. Biol. Psychiatry 68 (12), 1084–1091.

Fair, D.A., Nigg, J.T., Iyer, S., Bathula, D., Mills, K.L., Dosenbach, N.U.F., Schlaggar, B.L., Mennes, M., Gutman, D., Bangaru, S., Buitelaar, J.K., Dickstein, D.P., Di Martino, A., Kennedy, D.N., Kelly, C., Luna, B., Schweitzer, J.B., Velanova, K., Wang, Y.F., Mostofsky, S., Castellanos, F.X., Milham, M.P., 2013. Distinct neural signatures detected for ADHD subtypes after controlling for micro-movements in resting state functional connectivity MRI data. Front. Syst. Neurosci. 6, .

Fornito, A., Zalesky, A., Breakspear, M., 2015. The connectomics of brain disorders. Nat. Rev. Neurosci. 16 (3), 159–172.

Freeman, L.C., 1978. Centrality in social networks conceptual clarification. Soc. Netw. 1 (3), 215–239.

Green, S.A., Hernandez, L., Bookheimer, S.Y., Dapretto, M., 2016. Salience network connectivity in autism is related to brain and behavioral markers of sensory overresponsivity. J. Am. Acad. Child Adolesc. Psychiatry 55 (7), 618–626.e1.

Hagerman, P.J., Hagerman, R.J., 2004. The fragile-X premutation: a maturing perspective. Am. J. Hum. Genet. 74 (5), 805–816.

Hawellek, D.J., Hipp, J.F., Lewis, C.M., Corbetta, M., Engel, A.K., 2011. Increased functional connectivity indicates the severity of cognitive impairment in multiple sclerosis. Proc. Natl. Acad. Sci. 108 (47), 19066–19071.

Henry, T.R., Dichter, G.S., Gates, K., 2017. Age and gender effects on intrinsic connectivity in autism using functional integration and segregation. Biol. Psych. Cogn. Neurosci. Neuroimag. 3 (5), 414–422.

Holland, P.W., Leinhardt, S., 1971. Transitivity in structural models of small groups. Comp. Group Stud. 2, 107–124.

Hull, J.V., Jacokes, Z.J., Torgerson, C.M., Irimia, A., Van Horn, J.D., 2016. Resting-state functional connectivity in autism spectrum disorders: a review. Front. Psych. 7.

Itahashi, T., Yamada, T., Watanabe, H., Nakamura, M., Jimbo, D., Shioda, S., Toriizuka, K., Kato, N., Hashimoto, R., 2014. Altered network topologies and hub organization in adults with autism: a resting-state fMRI study. PLoS One 9 (4), e94115.

Kana, R.K., Uddin, L.Q., Kenet, T., Chugani, D., Mueller, R.-A., 2014. Brain connectivity in autism. Front. Hum. Neurosci. 8.

Keown, C.L., Datko, M.C., Chen, C.P., Maximo, J.O., Jahedi, A., Müller, R.-A., 2017. Network organization is globally atypical in autism: a graph theory study of intrinsic functional connectivity. Biol. Psych. Cogn. Neurosci. Neuroimag. 2 (1), 66–75.

Konrad, K., Eickhoff, S.B., 2010. Is the ADHD brain wired differently? A review on structural and functional connectivity in attention deficit hyperactivity disorder. Hum. Brain Mapp. 31 (6), 904–916.

Kucyi, A., Tambini, A., Sadaghiani, S., Keilholz, S., Cohen, J.R., 2018. Spontaneous cognitive processes and the behavioral validation of time-varying brain connectivity. Netw. Neurosci. (In Press, Available Online).

Latora, V., Marchiori, M., 2001. Efficient behavior of small-world networks. Phys. Rev. Lett. 87 (19), 198701.

Lewis, J.D., Theilmann, R.J., Townsend, J., Evans, A.C., 2013. Network efficiency in autism spectrum disorder and its relation to brain overgrowth. Front. Hum. Neurosci. 7.

Lin, P., Sun, J., Yu, G., Wu, Y., Yang, Y., Liang, M., Liu, X., 2014. Global and local brain network reorganization in attention-deficit/hyperactivity disorder. Brain Imaging Behav. 8 (4), 558–569.

Martínez-Pedraza, F.d.L., Carter, A.S., 2009. Autism spectrum disorders in young children. Child Adolesc. Psychiatr. Clin. N. Am. 18 (3), 645–663.

Menon, V., 2015. Salience network. In: Toga, A.W. (Ed.), Brain Mapping: An Encyclopedic Reference, vol. 2. Academic Press, pp. 597–611.

Menon, V., Uddin, L.Q., 2010. Saliency, switching, attention and control: a network model of insula function. Brain Struct. Funct. 1–13.

Mueller, R.A., Shih, P., Keehn, B., Deyoe, J.R., Leyden, K.M., Shukla, D.K., 2011. Underconnected, but how? A survey of functional connectivity MRI studies in autism spectrum disorders. Cereb. Cortex 21 (10), 2233–2243.

Newman, M.E.J., 2006. Modularity and community structure in networks. Proc. Natl. Acad. Sci. 103 (23), 8577–8582.

Odriozola, P., Uddin, L.Q., Lynch, C.J., Kochalka, J., Chen, T., Menon, V., 2016. Insula response and connectivity during social and non-social attention in children with autism. Soc. Cogn. Affect. Neurosci. 11 (3), 433–444.
Padmanabhan, A., Lynch, C.J., Schaer, M., Menon, V., 2017. The default mode network in autism. Biol. Psych. Cogn. Neurosci. Neuroimag. 2 (6), 476–486.
Plichta, M.M., Scheres, A., 2014. Ventral-striatal responsiveness during reward anticipation in ADHD and its relation to trait impulsivity in the healthy population: a meta-analytic review of the fMRI literature. Neurosci. Biobehav. Rev. 38, 125–134.
Posner, J., Park, C., Wang, Z., 2014. Connecting the dots: a review of resting connectivity MRI studies in attention-deficit/hyperactivity disorder. Neuropsychol. Rev. 24 (1), 3–15.
Ray, S., Miller, M., Karalunas, S., Robertson, C., Grayson, D.S., Cary, R.P., Hawkey, E., Painter, J.G., Kriz, D., Fombonne, E., Nigg, J.T., Fair, D.A., 2014. Structural and functional connectivity of the human brain in autism spectrum disorders and attention-deficit/hyperactivity disorder: a rich club-organization study. Hum. Brain Mapp. 35 (12), 6032–6048.
Roine, U., Roine, T., Salmi, J., Nieminen-von Wendt, T., Tani, P., Leppämäki, S., Rintahaka, P., Caeyenberghs, K., Leemans, A., Sams, M., 2015. Abnormal wiring of the connectome in adults with high-functioning autism spectrum disorder. Mol. Autism 6 (1), 65.
Rudie, J.D., Brown, J.a., Beck-Pancer, D., Hernandez, L.M., Dennis, E.L., Thompson, P.M., Bookheimer, S.Y., Dapretto, M., 2013. Altered functional and structural brain network organization in autism. NeuroImage Clin. 2, 79–94.
Seeley, W.W., Menon, V., Schatzberg, A.F., Keller, J., Glover, G.H., Kenna, H., Reiss, A.L., Greicius, M.D., 2007. Dissociable intrinsic connectivity networks for salience processing and executive control. J. Neurosci. 27 (9), 2349–2356.
Shine, J.M., Poldrack, R.A., 2017. Principles of dynamic network reconfiguration across diverse brain states. NeuroImage . (In Press, Available Online).
Sonuga-Barke, E.J.S., 2002. Psychological heterogeneity in AD/HD—a dual pathway model of behaviour and cognition. Behav. Brain Res. 130 (1), 29–36.
Sonuga-Barke, E.J.S., 2005. Causal models of attention-deficit/hyperactivity disorder: From common simple deficits to multiple developmental pathways. Biol. Psychiatry 57 (11), 1231–1238.
Sonuga-Barke, E.J.S., Castellanos, F.X., 2007. Spontaneous attentional fluctuations in impaired states and pathological conditions: a neurobiological hypothesis. Neurosci. Biobehav. Rev. 31 (7), 977–986.
Sporns, O., 2010. Networks of the Brain. MIT Press, Cambridge, MA.
Sporns, O., 2013. Network attributes for segregation and integration in the human brain. Curr. Opin. Neurobiol. 23 (2), 162–171.
Sporns, O., Betzel, R.F., 2016. Modular brain networks. Annu. Rev. Psychol. 67 (1), 613–640.
Uddin, L.Q., Menon, V., 2009. The anterior insula in autism: under-connected and under-examined. Neurosci. Biobehav. Rev. 33 (8), 1198–1203.
Uddin, L.Q., Kelly, A.M.C., Biswal, B.B., Margulies, D.S., Shehzad, Z., Shaw, D., Ghaffari, M., Rotrosen, J., Adler, L.A., Castellanos, F.X., Milham, M.P., 2008. Network homogeneity reveals decreased integrity of default-mode network in ADHD. J. Neurosci. Methods 169 (1), 249–254.
Uddin, L.Q., Supekar, K., Lynch, C.J., Khouzam, A., Phillips, J., Feinstein, C., Riyali, S., Menon, V., 2013. Salience network-based classification and prediction of symptom severity in children with autism. JAMA Psychiat. 70 (8), 869–879.

Uddin, L.Q., Dajani, D.R., Voorhies, W., Bednarz, H., Kana, R.K., 2017. Progress and roadblocks in the search for brain-based biomarkers of autism and attention-deficit/hyperactivity disorder. Transl. Psychiatry 7 (8), e1218.

van den Heuvel, M.P., Sporns, O., 2011. Rich-club organization of the human connectome. J. Neurosci. 31 (44), 15775–15786.

Wang, L., Zhu, C., He, Y., Zang, Y., Cao, Q., Zhang, H., Zhong, Q., Wang, Y., 2009. Altered small-world brain functional networks in children with attention-deficit/hyperactivity disorder. Hum. Brain Mapp. 30 (2), 638–649.

Weissman, D.H., Roberts, K.C., Visscher, K.M., Woldorff, M.G., 2006. The neural bases of momentary lapses in attention. Nat. Neurosci. 9 (7).