Network-based approaches to examining stress in the adolescent brain

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ABSTRACT

Exposure to stress, particularly in periods of rapid brain maturation such as adolescence, can profoundly influence developmental processes that undergird the organization of structural and functional brain networks and that may mediate the association between stressful experiences and maladaptive outcomes. While studies in translational developmental neuroscience often focus on how specific brain regions or targeted connections are altered by stress and psychiatric disease, the emerging field of network science may be especially valuable for elucidating the impact of stress on the intricate connectomics of the adolescent brain. Here we review recent studies that use graph theory and other network science approaches to understand normative adolescent brain development, effects of childhood maltreatment on the brain, and disorders characterized by pathological responses to stress in adolescents. Overall, these studies demonstrate that graph theory can be useful in identifying and quantifying developmental processes related to segregation, integration, and localized hub influence that are affected by stress exposure and that may lead to psychopathology. Finally, we discuss limitations in the current application of graph theory in this area and suggest what we believe are important directions for future work.

1. Introduction

Adolescence is a sensitive period of brain development that coincides with significant changes in psychosocial and physical development (Blakemore and Choudhury, 2006; Ashby and Isaac, 2011). These maturational changes include not only synaptic pruning and dendritic arborization within localized circuits (Ashby and Isaac, 2011; Huttenlocher et al., 1982), but also significant reorganization of network-level connections throughout the cerebrum (Fair et al., 2009; Power et al., 2010). While the effects of stress on the developing brain have been well documented (McEwen, 2012; Lupien et al., 2009; Nelson, 2007; McLaughlin et al., 2017), investigations in this area have focused primarily on functional profiles or morphological characteristics of the three components of the mammalian stress regulatory circuit: the amygdala, the hippocampus, and the prefrontal cortex (PFC). It is becoming increasingly clear, however, that the majority of human cognitive processes—including effective emotion regulation and cognitive control—arise from elaborate coordinated activity across distributed brain regions (Cole et al., 2013; Dwyer et al., 2014; Shine et al., 2016). For example, regions with synchronous tonic activity are posited to constitute intrinsic functional networks (IFNs), which have become a key target of study because of their role in supporting complex cognition (Power et al., 2011; Yeo et al., 2011). Indeed, basic neuroscience research has demonstrated dynamic changes of IFNs in response to

acute stressors and during periods of anxious anticipation (McMenamin et al., 2014; Najafi et al., 2017); large-scale network interactions are now widely considered to be useful for understanding the brain basis of emotional experiences and why systems related to basic cognitive processing, including perception, motivation, and action, are also implicated in affective processing (Pessoa, 2017; Pessoa and McMenamin, 2017). Consequently, clinical neuroscientists have also sought to understand human neuropsychiatric disease from the lens of network connectivity (Menon, 2011; Whitfield-Gabrieli and Ford, 2012).

Developmental neuroscience studies have demonstrated that the adolescent brain undergoes hierarchical maturation in specific circuits that are instantiated within larger IFNs (Casey et al., 2017; Power et al., 2010; Vertes and Bullmore, 2014), the fidelity of which is likely constrained by underlying anatomical connections (Betzel et al., 2015; Vertes and Bullmore, 2014). Thus, understanding the effects of stress on the developing brain requires that researchers use metrics that: 1) capture nuanced facets of the brain connectome in biologically interpretable ways; 2) facilitate comparisons across different imaging modalities (structure and function), as well as across maturational timescales; and 3) are statistically reliable yet sensitive to developmental effects. To this end, graph theory, a mathematical approach from network science, may help translational neuroscientists to characterize neurobiological mechanisms of stress. In this review, we begin with a brief background on graph theory and the most relevant metrics used to

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characterize brain networks. We then discuss current diffusion MRI, anatomical MRI, and resting-state fMRI studies that used graph theory to study normative adolescent development, and effects of stress and stress-related psychopathology (i.e., posttraumatic stress disorder and depression) on brain network topology and organization. Finally, we discuss implications of these findings and highlight caveats and crucial gaps in our knowledge that we hope will guide future research efforts in this area.

2. Background on graph theory

Over the past decade, graph theoretical analyses have increasingly been used to analyze neuroimaging data as part of the nascent field of "brain connectomics"(Bullmore and Bassett, 2010; Fornito and Bullmore, 2014; Rubinov and Sporns, 2010). In the framework of graph theory, a brain network (or *graph*) is composed of regions (or *nodes*) and their structural or functional connections (or *edges*). Connectivity values are estimated between all possible node pairs, resulting in an *adjacency matrix*. In the case of an *unweighted* graph, a threshold is applied such that an edge is present if it exceeds the threshold value (i.e., takes on a value of 1; otherwise is 0), ensuring that the most meaningful and/or reliable connections between nodes are retained. This results in a binary adjacency matrix from which graph metrics are calculated. For weighted graphs, edges are described by weights (e.g., number of streamlines) indicating the strength or some other property of the connection (van Wijk et al., 2010).

In diffusion MRI, the number of streamlines may be considered to be a proxy for the number of white matter fiber tracts and, thus, structural connections; in contrast, in anatomical MRI, structural connectivity matrices can be calculated by computing covariance in measures of cortical thickness, across different regions of the cortex. While the exact mechanism is not well understood, the pattern of structural covariance may depend on pathways detectable with white matter tractography (He et al., 2007; Lerch et al., 2006) and could be interpreted as reflecting the degree of developmental coordination across the brain. In functional MRI, connections are typically represented by statistical dependencies in timeseries data, and can be assessed during resting-state as well as under experimentally manipulated conditions (see Fig. 1). Each neuroimaging modality is designed to optimize specific brain measurements and will inherently reveal not only distinct features of network connectivity but also different networks with distinct nodes and edge strengths. For instance, the structural networks derived from diffusion MRI are those that are directly connected by white matter fibers and, thus, may be more suitable than are functionally derived networks for assessing graph metrics related to neural segregation (Rubinov and Sporns, 2010). Because IFNs typically include regions that are widely distributed throughout the brain and that do not necessarily contain direct anatomical projections, these networks may be more suitable for assessing graph metrics related to neural integration and inter-network communication (Rubinov and Sporns, 2010). Similarly, networks derived from resting-state fMRI are posited to reflect a stable co-history of activation that may predict trait-like cognitive capacities (Congdon et al., 2010; Dosenbach et al., 2007; Rosenberg et al., 2017); in contrast, quantifying dynamic changes in functional networks during an environmental challenge may be informative for probing how specific nodes or regional connections within a given functional network shift adaptively in response to task demands, and for assessing how integrative communication may change across several networks(Cohen and D'Esposito, 2016; Dosenbach et al., 2007). Whether network-based approaches are applied to a single modality or across modalities, summary metrics from a graph analysis can provide insight into *global* brain topology in addition to properties of *local* nodes in a given network.

As we alluded to previously, there are two foundational principles of brain network organization that are captured by graph metrics: *segregation* and *integration* (Rubinov and Sporns, 2010). Segregation allows

specialized processing to occur within densely interconnected groups of brain regions; integration allows the brain to transmit information rapidly across distributed regions. From the perspective of minimizing the cost of information transfer and maximizing efficiency, a network that exhibits organizational properties of both segregation and integration may be capable of efficient processing and communication. As we discuss below, and as others have described in detail (Grayson and Fair, 2017; Di Martino et al., 2014), segregation and integration—and the balance between them—are critical concepts in understanding maturational processes in the brain. Thus, although several global and local metrics may be computed in graph theory, not all metrics necessarily conform to known principles of neurobiology. In the following, we briefly describe the metrics that are most widely derived from neuroimaging data. Please see Table 1 for a summary of these graph metrics and the sections below for more detailed descriptions of each metric.

### 2.1. Network measures of segregation

Graph metrics that reflect segregation are those that quantify the presence of clusters or modules. One such measure is the *clustering coefficient*. When computed on an individual node, this local metric quantifies how connected the node is with its neighbors; when averaged across the entire network, it yields a global measure of segregation. *Modularity* is another measure of segregation that is fundamental to animal neural systems. Modularity quantifies the degree to which there are smaller subgroups (or *communities*) inside larger groups; networks with high modularity have dense connections between brain regions within modules, but sparse connections between regions belonging to other modules (Newman, 2006).

Researchers have used resting-state and task-evoked fMRI data to identify several modules or communities in the human brain; these are commonly interpreted in the framework of canonical IFNs (Cole et al., 2014a; Di Martino et al., 2014; Grayson and Fair, 2017). In addition to hierarchically organized visual, auditory, sensory, and somatomotor modules, the primary networks of interest in the study of the neurobiology of stress have been the salience network (SN), anchored in the dorsal anterior cingulate cortex (ACC) and anterior insula (Seeley et al., 2011; Uddin, 2014); the default mode network (DMN), composed in part of the medial PFC, posterior cingulate cortex/precuneus, angular gyrus, and medial temporal cortex (Buckner et al., 2008; Fox et al., 2005); the central executive network (CEN), centered in frontoparietal cortices (Cole et al., 2014b; Spreng et al., 2012); basal ganglia and limbic networks spanning corticostriatal and corticolimbic connections; and cerebellar networks (Buckner et al., 2011; Power et al., 2011; Yeo et al., 2011). Please see Table 2 for a summary of these IFNs.

2.2. Network measures of integration

Graph metrics that reflect integration are based on the concept of *path length*, formally defined as the number of edges in the shortest path between nodes (Rubinov and Sporns, 2010). The average shortest path length between all pairs of nodes in the network is known as the *characteristic path length* of the network (Watts and Strogatz, 1998) and is the most commonly used measure of integration. A related measure is *global efficiency*, which is the average inverse of the shortest path length between all node pairs. Global efficiency is often considered a measure of the overall capacity of parallel information transfer (Bullmore and Bassett, 2010).

Networks characterized by both high global efficiency and high average clustering coefficients are described as exhibiting *small-world* organization (Watts and Strogatz, 1998), a property that is considered essential to biological systems as means to maximize the tradeoff between the benefits of integration against the costs of long-range wiring (Collin et al., 2013; Vertes and Bullmore, 2014). Recent work has also noted that *hubs*, or highly connected nodes, tend to connect to one
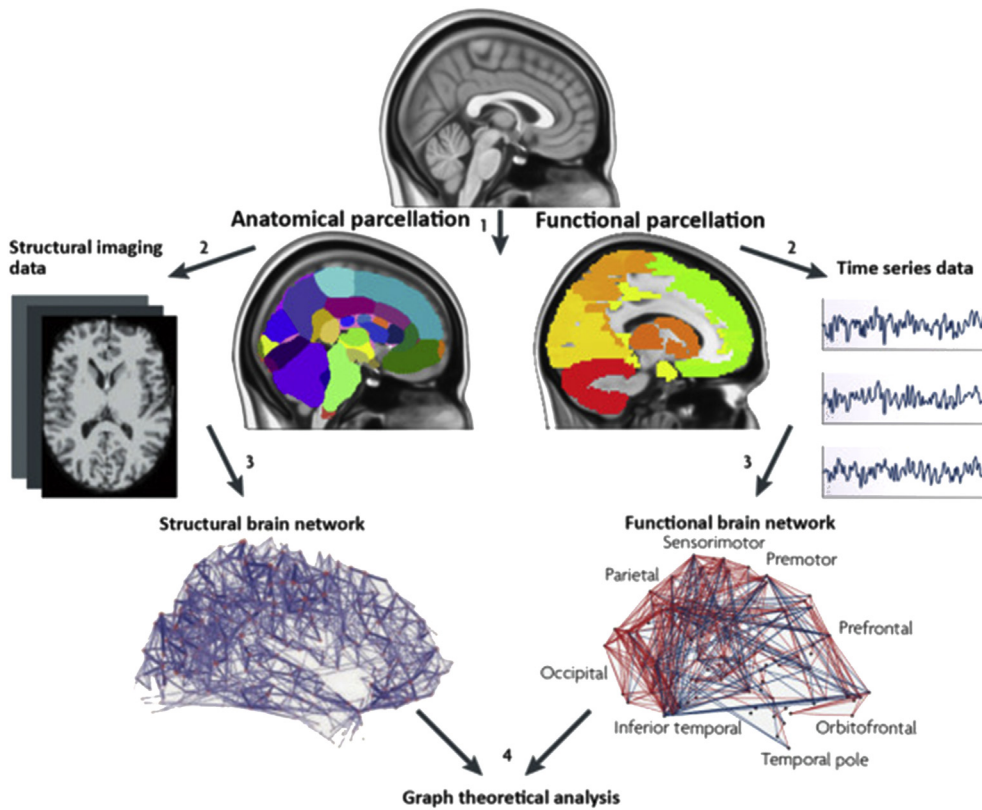
Fig. 1. Graph metrics can be computed from neuroimaging data, whether they be structural or functional, but the selection and implications of node and edge definitions differ. In diffusion MRI, the number of streamlines acts may be considered to be a proxy for the number of white matter fiber tracts and, thus, structural connections; in contrast, in anatomical MRI, structural connectivity matrices can be calculated by computing covariance in measures of cortical thickness, across different regions of the cortex. In functional MRI, connections are typically represented by statistical dependencies in timeseries data. Adopted with permission by Bullmore and Sporns (2009) (Copyright, 2009 *Nature Reviews Neuroscience*).

another to form *rich clubs*, in which highly connected nodes are disproportionately more connected with one another (i.e., more connected than would be expected by chance based on distributions derived from random networks). Thus, the pathways linking rich clubs form high-cost yet high-capacity modes of communication that permit global communication and arguably optimize the integration of information across the connectome (Sporns, 2013; van den Heuvel and Sporns, 2011). Like modularity and the presence of community structures, small-worldness and rich-club topology are organizational properties that are evident even in early developmental stages (Thomason, 2018; Thomason et al., 2014) and remain ubiquitous from childhood through adulthood (Collin and van den Heuvel, 2013; Power et al., 2010).

2.3. Network measures of centrality

In contrast to global graph metrics, local graph metrics of interest typically quantify the amount of influence (or *centrality*) of a single node. Among the most common local graph metrics are *degree,* which reflects a node's total number of connections, and *strength,* a weighted graph metric, defined as the sum of a node's connection weights. *Betweenness centrality* is a metric frequently used in neuroimaging; it reflects the frequency with which a node lies on the shortest paths that connect all other nodes, a property that enables efficient communication (Rubinov and Sporns, 2010). Finally, of particular relevance to the study of IFNs, the *participation coefficient* is also often assessed in order to index the strength of a node's edges among the modules or communities in a graph. A participant coefficient of 0 indicates that a node's edges are entirely restricted to its community; a participant coefficient of 1 indicates that the node's edges are evenly distributed among all communities in the graph. As other investigators have noted (Meunier et al., 2010; Power et al., 2013), centrality measures—such as betweenness centrality—identify key hubs, whereas others—such as participant coefficients—characterize the type or nature of connections a hub with other nodes.

Thus, by using graph theoretical metrics, investigators can now

address questions related to network segregation, integration, and regional influence across adolescence and how stress exposure may affect developmental processes.

3. Graph theoretical studies of normative adolescent development

Before understanding how stress, depression, and other related experiences affect the network architecture of the developing brain, we must understand the typically developing connectome (Di Martino et al., 2014; Grayson and Fair, 2017; Power et al., 2010). Investigations of structural (Dennis et al., 2013a) and functional (Grayson et al., 2014) connectivity have found community organization among anatomically proximal regions in early childhood that then extends to distributed brain regions strengthens as an individual approaches adulthood (Fair et al., 2009). Below we highlight these themes of segregation and integration in the context of structural and functional network development and note important caveats and limitations when interpreting the extant literature.

3.1. Structural network development

Structural networks derived from diffusion MRI are characterized by age-related decreases in path length and clustering (although some investigators have reported increased clustering, see (Wierenga et al., 2016)), in concert with increases in efficiency, node strength, and rich-club connectivity (Dennis et al., 2012b, 2013a, 2013b; Hagmann et al., 2010; Wierenga et al., 2016). Modularity in white matter networks has less consistent age-related effects: one study shows increases in modularity suggesting increased network segregation (Dennis et al., 2012a), one shows decreases in modularity (Chen et al., 2013), and others show no effects of age on modularity (Hagmann et al., 2010; Zhao et al., 2015). These divergent results may be due to differences in computing connectivity matrices (unweighted versus weighted), differences in node definitions, or differences in the specific age range examined (ages in these studies ranged from 12-20 years, 18 months-18 years, and 9–85

Table 1
Common graph metrics in neuroimaging.

Global Metrics

Metric	Equation	Meaning
Characteristic path length	$L = \frac{1}{n}\sum_{i\in n} L_i = \frac{1}{n}\sum_{i\in N}\frac{\sum_{j\in N, j\neq i} d_{ij}}{n-1}$ Where L_i is the average distance between node i and all other nodes	A measure of integration, the average shortest path in the network; normalized path length (λ) is the characteristic path length normalized by a series of random networks of the same size and degree distribution.
Mean clustering coefficient	$C = \frac{1}{n}\sum_{i\in n} C_i = \frac{1}{n}\sum_{i\in N}\frac{2t_i}{k_i(k_i-1)}$ Where C_i is the clustering coefficient of node i	A measure of segregation, the fraction of a node's neighbors that are neighbors of each other, averaged across the network; normalized clustering (γ) is mean clustering coefficient normalized by a series of random networks of the same size and degree distribution.
Global efficiency	$E = \frac{1}{n}\sum_{i\in n} E_i = \frac{1}{n}\sum_{i\in N}\frac{\sum_{j\in N, j\neq i} d_{ij}^{-1}}{n-1}$ Where E_i is the efficiency of node i	The average inverse shortest path length in the network.
Small worldness	$\sigma = \frac{\gamma}{\lambda}$ Where γ is clustering normalized by random networks, and λ is path length normalized by random networks	The balance of integration and segregation in the network, changes indicate a shift in this balance, better understood examining λ and γ to see which are contributing.
Modularity	$Q = \sum_{u\in M}\left[e_{uu} - \left(\sum_{v\in M} e_{uv}\right)^2\right]$ Where the network is fully subdivided into a set of nonoverlapping modules M, and e_{uv} is the proportion of all links that connect nodes in module u with nodes in module v	A measure of segregation, the degree to which a network can be subdivided into communities.

Local Metrics

Metric	Equation	Meaning
Degree	$k_i = \sum_{j\in N} a_{ij}$ Degree of node i	The number of edges connected to a node.
Local efficiency	$E_{loc} = \frac{1}{n}\sum_{i\in n} E_{loc,i} = \frac{1}{n}\sum_{i\in N}\frac{\sum_{j,h\in N, j\neq i} a_{ij}a_{ih}[d_{jh}(N_i)]^{-1}}{k_i(k_i-1)}$ Where $E_{loc,i}$ is the efficiency of node i, and $d_{jh}(N_i)$ is the length of the shortest path between j and h, that contains only neighbors of i	Global efficiency computed only on node neighborhoods; thus, local efficiency of node i characterizes how well information is exchanged by its neighbors when it is removed.
Betweenness centrality	Betweenness centrality of node i, where ρ_{hj} is the number of shortest paths between h and j, and $\rho_{hj}(i)$ is the number of shortest paths between h and j that pass through i	The number of shortest paths in the network that pass through a node.
Clustering coefficient	$C_i = \frac{2\,|\{e_{jk}: v_j, v_k \in N_i, e_{jk} \in E\}|}{k_i(k_i-1)}$ Clustering of node i (undirected graph)	A measure of segregation, the fraction of a node's neighbors that are neighbors of each other.
Participant coefficient	$y_i = 1 - \sum_{m\in M}\left(\frac{k_i(m)}{k_i}\right)^2$ Participation coefficiency of node i, where M is the set of modules, and $k_i(m)$ is the number of links between i and and all nodes in module M	A measure of the diversity of intermodular connections of individual nodes.

years, respectively).

As many studies have documented, developmental changes do not occur uniformly across the cortex (Gogtay et al., 2004; Sowell et al., 2004). White matter connectivity among subcortical regions decreases from adolescence through early adulthood, whereas cortico-subcortical and cortico-cortical connections show a mixture of increases and decreases in connectivity (Baker et al., 2015). Similarly, there is a disproportionate increase in connectivity in hub nodes in the frontal cortex (Baker et al., 2015), whereas nodes in the temporal cortex are among the last to mature (Dennis et al., 2013a), showing a later age-of-peak connectivity than do other areas (Zhao et al., 2015). There is some evidence that longer tracts, including association fibers, mature more slowly than do shorter tracts (Chen et al., 2013; Hagmann et al., 2010; Supekar et al., 2010; Wierenga et al., 2016). Moreover, these changes do not necessarily occur at the same rate across hemispheres; in fact, whereas adolescents exhibit greater efficiency in the right hemisphere,

particularly in the temporal cortex, the networks of young adults do not appear to have this asymmetry (Zhong et al., 2017).

Graph metrics may be calculated on fiber density matrices, or on matrices that are weighted by diffusivity measures such as fractional anisotropy (Chen et al., 2013; Koenis et al., 2015; Wierenga et al., 2016). In contrast to the studies reviewed above, which showed increased efficiency in fiber density-weighted matrices, Koenis and colleagues found that efficiency calculated on FA-weighted matrices increased with age, while efficiency calculated on streamline count showed both increases and decreases with age; in both instances, however, age-related changes corresponded to increases in cognitive functioning (Koenis et al., 2015). Again, the issue of computing metrics based on binarized versus weighted edge matrices may contribute to these conflicting results.

All of the studies reviewed so far constructed connectivity matrices from cortical and subcortical parcellations, combined with tracts

Table 2
Summary of core intrinsic functional networks.

Network	Hub Regions	Functional Roles
Salience network (SN)	Dorsal anterior cingulate cortex, anterior insula	Salience detection, attentional switching
Default mode network (DMN)	Medial prefrontal cortex, posterior cingulate cortex	Internally directed cognition
Central executive network (CEN)	Dorsolateral prefrontal cortex, posterior parietal cortex	Goal-directed cognition, cognitive control
Basal ganglia network	Striatum, cerebellum	Motivation, autonomic function, arousal
Limbic network	Amygdala, hippocampus, thalamus	Motivation, autonomic function, arousal

reconstructed from diffusion MRI. In one study of gray matter networks, consistent with the findings from diffusion MRI graph networks, primary sensorimotor areas matured earlier than higher order regions (Khundrakpam et al., 2012). In the same study, global efficiency increased from early to late childhood, and then decreased into adolescence, whereas both local efficiency and modularity decreased initially and then increased. These age-related changes in graph metrics appear to reflect a temporary shift to a more random configuration before the expected small-world organization emerges. Alternatively, discrepancies among these studies may also be due to differences in the ages of stress exposure, as well as the ages at which event recall and neuroimaging measures were collected (see also Section 7.3 for a more extended discussion on this issue).

3.2. Functional network development

Echoing these structural changes is increased network segregation and integration in functional networks. Structural hubs appear to be highly determined in early development, but functional hubs appear to undergo additional refinement and reorganization throughout development (Grayson and Fair, 2017). Current views on the development of functional brain networks rely strongly on studies with resting-state fMRI data that seek to characterize large-scale IFNs. These studies generally show an increase in both network segregation and network integration. In samples of participants ranging in age from childhood to young adulthood, older individuals generally exhibit decreased short-range connections and increased long-range connections (Fair et al., 2009; Sato et al., 2014). The SN, DMN, and CEN in particular become more cohesive with age, while subcortical and cerebellar networks become less connected (Fair et al., 2007; Gu et al., 2015; Sato et al., 2014). These age-related changes are posited to reflect maturation and an increased reliance on "higher" networks that are distributed more widely across cortex than are more "basic" sensory networks and subcortical circuits, which tend to be more localized. Indeed, the maturation in connectivity between cortical and subcortical regions that occurs during adolescence appears to be further reconfigured through young adulthood with stronger cortico-cortical connections (Fair et al., 2007; Marek et al., 2015; Supekar et al., 2009). Researchers have typically described this transition as maturation from local to distributed; networks come to be defined more by their converging functional specializations and connections and less by solely their proximal connections with anatomical neighbors (Hwang et al., 2013).

In a preliminary investigation, Grayson and colleagues compared structural and functional graph metrics in samples of children (ages 7–11 years) and young adults (ages 24–35 years). By late childhood, rich clubs were already well-formed in white matter networks; in contrast, children showed significantly weaker functional connectivity among rich-club hubs than did young adults (Grayson et al., 2014). These results corroborate prior work showing that resting-state functional connectivity between key nodes of the SN, DMN, and CEN is stronger in adults than in children, and that white matter structural integrity originating from a critical hub of the SN, the frontoinsular cortex, supports several of these functional connections (Uddin, 2014). Together, these results are consistent with the formulation that the topology of structural networks are stable and established by late adolescence, and that they give rise to specific connectivity patterns among the hubs of IFNs, which are still evolving during this developmental period. Thus, it is possible that stressful life experiences may affect maturational processes by initially shaping structural networks, which inform the subsequent development of functional networks and are further remodeled by concurrent environmental influences.

4. Graph theoretical studies on the neurobiological sequelae of childhood adversity

Neuroimaging studies of stress in adults and adolescents have

consistently documented structural deficits in the stress regulatory regions of the amygdala, hippocampus, and PFC, as well as altered striatal and amygdala activation and frontoamygdala connectivity (for reviews, see (Gee and Casey, 2015; Teicher et al., 2016). However, a growing body of research shows that circuit-level connections are embedded in larger networks and that coordinated activity across distributed networks—particularly among canonical IFNs—supports adaptive cognitive control and other higher order cognitive processes (Casey et al., 2017; Cole et al., 2014a; Dwyer et al., 2014; Shine et al., 2016). Thus, graph theory may serve as a useful tool in understanding how stress influences developmental processes that shape network architecture and associated cognition throughout adolescence. No studies to date have examined the effects of life stress on adolescents using such network-based approaches; however, two studies have used graph theoretical analyses on anatomical and diffusion MRI to examine effects of childhood maltreatment on young adults (ages 18–25 years; mean: 22 years).

In a cohort of young adults experiencing varying levels of childhood maltreatment, Teicher and colleagues computed cortical thickness and inter-regional partial correlations to construct gray matter brain networks (Teicher et al., 2013). Compared to young adults with minimal levels of childhood maltreatment, individuals with a history of more severe maltreatment had a lower degree in the left ACC, a region of the SN that was shown to be a member of the rich club in the network derived from the comparison group, concurrent with a greater degree in both the right anterior insula, another region of the SN, and the precuneus, a region of the DMN. As these hub regions of the SN and DMN are likely to participate in adaptive behavioral responses relevant for salience detection, emotion regulation, and self-directed emotional perception, these alterations in hub centrality in individuals who have been exposed to more severe levels of maltreatment may serve as a mechanism for increasing the risk of the development of psychopathology. Even so, it is important to recognize that it is difficult to interpret gray matter covariance results without examining the underlying white matter tracts that connect these regions.

In this context, Ohashi and colleagues used tractography on diffusion MRI in this same cohort of young adults, and found that individuals with a history of moderate to severe levels of maltreatment exhibited alterations in several global graph metrics compared to individuals who had experienced minimal levels of maltreatment (Ohashi et al., 2017). Specifically, individuals with more severe childhood maltreatment had lower degree, strength, and global efficiency coupled with higher path length and a greater degree of small-worldness organization. Surprisingly, the local cluster coefficients did not differ significantly between these two maltreatment-exposure groups. Because Ohashi and colleagues reconstructed tracts, they were also able to estimate the number of fiber streamlines in each groups; those adults with more severe maltreatment exposure had, on average, 7% fewer streamline connections, with significantly fewer fiber streamlines interconnecting the frontal region with the basal ganglia, occipital region, thalamus, and insula, as well as interconnecting limbic regions with basal ganglia and occipital regions. As small-worldness is the ratio of the clustering coefficient to the characteristic path length, the finding that individuals with a history of more severe maltreatment exhibited greater small-worldness could be due to "preserved local modular architecture" (which is consistent with the comparable local cluster coefficients between the two groups) but reduced properties reflecting integration (i.e., reduced connectivity between modules).

The authors suggest that because individuals with minimal maltreatment exposure have a greater number of fiber streams between several interconnecting modular systems, they are able to afford enhanced connectivity between modules, as reflected in higher global measures of degree, strength, and efficiency (Ohashi et al., 2017). From a developmental neuroscience perspective, these findings are also consistent with the formulation that exposure to early adversity alters normative neurodevelopment, which typically shifts from more

localized to distributed connectivity through the formation of cohesive IFNs (Fair et al., 2009; Power et al., 2010). Thus, severe maltreatment during sensitive periods of development may hinder these adaptive shifts toward integration across modules, which would be manifested as disruptions in global graph metrics such as characteristic path length, efficiency, small-worldness, and rich-club topology, particularly in IFNs that span disparate modules and support higher order cognition (e.g., SN, DMN, CEN). However, because the studies conducted in this area thus far have exclusively examined structural networks in young adults after maltreatment exposure, it will be important in future research to also examine IFNs of adolescents and to characterize prospectively the effects of stress on these metrics of segregation and integration.

5. Graph theoretical studies on stress-related psychopathology in adolescents

Increasingly, graph metrics and other network science approaches have been used to better understand the architecture and topology of structural and functional networks in adolescents diagnosed with Posttraumatic Stress Disorder (PTSD) and with Major Depressive Disorder (MDD). We review studies that compare diagnosed adolescents for each respective disorder with healthy controls in the following sections.

5.1. PTSD

In a study of children exposed to a natural disaster who did or did not develop PTSD, Suo and colleagues applied graph theory to both diffusion MRI and resting-state fMRI data (Suo et al., 2015, 2016). These investigators found no group differences in small-worldness in graphs derived from diffusion MRI (Suo et al., 2016); however, children with PTSD showed an increase in characteristic path length accompanied by a decrease in global efficiency, as well as reduced nodal centralities in dorsolateral and ventrolateral PFC, angular gyrus, right insula, left superior parietal gyrus, left lingual gyrus, left middle occipital gyrus, left putamen, and left thalamus. The researchers then sought to characterize a PTSD-related subnetwork composed of nodes that exhibited significant group differences in at least one of the three nodal centralities, along with edges that linked between any two of these altered nodes. To accomplish this, they used network-based statistics (NBS), an approach used to adjust for multiple comparisons when testing for group or experimental condition effects on graph edges (Zalesky et al., 2012). The resulting PTSD subnetwork contained 13 nodes and 21 connections composed primarily of prefrontal-limbic-striatal and ventral and dorsal visual systems.

In this same sample using resting-state fMRI, these researchers also reported no group differences in small-worldness; however, in contrast to their finding of reduced global efficiency in white matter networks in the PTSD group, they found no group differences in this metric in resting-state functional networks (Suo et al., 2015). The PTSD group also exhibited significantly higher global clustering coefficient. With respect to local graph metrics, compared to the non-PTSD controls, the children with PTSD showed higher nodal centralities in the right dorsolateral PFC, left lingual gyrus, left superior frontal gyrus, left gyrus rectus, left superior temporal gyrus, right middle temporal gyrus, bilateral thalamus, bilateral inferior parietal gyrus, and bilateral middle occipital gyrus. Finally, the authors applied NBS to identify a PTSD functional subnetwork. This network yielded 13 nodes and 7 connections composed primarily of hypoconnectivity among dorsolateral PFC, parietal cortex, thalamus, and occipital regions in the PTSD group compared to the non-PTSD group.

Mature structural connections are widely regarded as serving the basis for functional hubs to form an integrative capacity across distinct modules (Bullmore and Sporns, 2009; Power et al., 2013). From this perspective, Suo et al.'s findings may signify important developmental effects of stress exposure that lead to psychopathology. Specifically, Suo

et al. reported that PTSD was characterized by reduced nodal centrality in structural connections, concomitant with greater nodal centrality in functional connections among hubs in the SN, DMN, CEN, and visual networks; further, children with PTSD exhibited pervasively reduced structural and functional connections between these modules (Suo et al., 2016). Certainly, these findings reported by Suo and colleagues will need to be replicated in independent samples but, so far, they are consistent with work by Teicher and colleagues in young adults with history of childhood maltreatment. Considered together, these studies raise the intriguing possibility that stress hampers or prevents adaptive development towards increased integrative organization across modules, leading to suboptimal higher-order behaviors associated with the development of these distributed networks.

5.2. MDD

While a preliminary resting-state fMRI study ($n = 16$ per diagnostic group) found that, compared to healthy controls, adolescents with MDD exhibited higher degree in the ACC, amygdala, insula, temporal cortices, and dorsolateral, medial, and inferior PFC (Jin et al., 2011), a larger resting-state fMRI study by our research team ($n = 55 +$ per diagnostic group) found no global or local graph metrics that distinguished adolescents with MDD from healthy controls (Sacchet et al., 2016). Nevertheless, using NBS, our group found that adolescents with MDD were characterized by large-scale hypoconnectivity. Specifically, adolescents with MDD exhibited hypoconnectivity among the dorsal attention network, SN, DMN, CEN, and somatosensory networks (Sacchet et al., 2016). Importantly, these results were obtained only when using IFNs, and not anatomically defined regions, as nodes in construction of the graphs, which underscores the critical point that investigators must utilize appropriate parcellation schemes in graph theory analyses (Rubinov and Sporns, 2010; Zalesky et al., 2010).

As a related point, we wish to emphasize that Sacchet et al. (2016) based their graph analyses on nodal definitions derived from the 17-network solution of the Yeo atlas (Yeo et al., 2011), which covered large swathes of cortex. In a follow-up study in this same cohort, Ho and colleagues defined 51 smaller, spatially isolated regions spanning the IFNs derived from the Yeo atlas and computed global and local graph metrics during resting-state as well as during task-evoked (i.e., during a cognitive control task) fMRI (Ho et al., 2017). Here, we again did not find group differences in global graph metrics during resting-state fMRI or task-evoked fMRI; however, change in local efficiency of the right dorsal ACC between rest and task states distinguished adolescents with MDD from healthy controls. Specifically, depressed adolescents showed little change (or "flexibility") in local efficiency of the dorsal ACC across brain states, whereas healthy controls showed flexible local efficiency of this node (Ho et al., 2017). Consistent with prior work indicating that large-scale connectivity changes between rest and task-evoked states predict cognitive control performance (Cole et al., 2013; Dwyer et al., 2014; Shine et al., 2016), we also found that individuals exhibiting lower local efficiency of right dorsal ACC during the task relative to rest performed more poorly on the cognitive control task. Finally, we found that lower local efficiency of right dorsal ACC during the task was associated with an earlier age of MDD onset. Because the ACC is an integrative hub that occupies several IFNs (Margulies et al., 2007; Yeo et al., 2011), and because of its role in adolescent development (Lichenstein et al., 2016), we posited that altered development of ACC-based connectivity underlies core symptoms related to, or that may lead to, the development of MDD, including suboptimal self-regulation or cognitive control.

This same cohort of adolescents with and without MDD also underwent diffusion MRI; Tymofiyeva et al. (2017) applied graph theory and NBS to assess group differences in global and local metrics weighted by either tractography streamline count or FA (Tymofiyeva et al., 2017). While we did not find group differences in local or global graph metrics, we did find, using NBS, that depressed adolescents

exhibited lower FA-based connectivity centered in the right caudate, including reduced connectivity with ACC, insula, and frontal gyrus. At the highest statistical thresholds, the most robust finding was reduced connectivity between the right caudate and middle frontal gyrus (MFG) in adolescents with MDD compared to controls. Further, depressed adolescents with lower right caudate-MFG white matter connectivity reported, on average, more stressful life events in the past 6 months; in contrast, the healthy controls exhibited no association between right caudate-MFG connectivity and number of stressful life events. One interpretation of these data is that stress has an adverse effect only on white matter fibers that connect caudate-MFG in individuals with compromised connectivity between these regions (whether it is due to MDD illness or exposure to greater childhood adversity). While speculative, these results underscore the need for longitudinal studies and careful assessments of stressful life events to explore this possibility more explicitly and systematically.

With the exception of the preliminary study by Jin et al., none of the studies reviewed above found differences in global graph metrics between adolescents with and without MDD. One possibility is that metrics such as modularity, small-worldness, and rich-clubness are, as indicated in prior research (Collin and van den Heuvel, 2013; Hagmann et al., 2012; Thomason et al., 2014; Thomason et al., 2017), foundational neurobiological principles of organization that are established far earlier in development than adolescence; in this case, therefore, it would take a psychiatric or neurological insult more extreme than adolescent-onset MDD to detect major disruptions in global topology. Another possibility is that, given evidence that MDD and other psychiatric disorders do not have a significant impact on graph metrics, including small-worldness, above and beyond the effect of maltreatment (Ohashi et al., 2017), it is plausible that adverse effects of early life stress on network development explain psychopathology-related network differences that have been reported in graph theoretical analyses in case-control studies. Unfortunately, however, the majority of such investigations in clinical samples did not take early life stress history into account.

We also wish to note that there are key differences in node and edge calculations from which graph metrics were computed. While both Jin et al. and Tymofiyeva et al. used the Automated Anatomical Labeling (AAL) atlas to define 90 cortical and subcortical nodes (Tzourio-Mazoyer et al., 2002), Sacchet et al. (2016) and Ho et al. (2017) used functionally defined nodes (although the former used large-scale networks as node definitions and the latter used smaller localized nodes) (Yeo et al., 2011). Jin et al. and Tymofiyeva et al. also applied different thresholding and/or weighting when constructing edge matrices, which makes it harder to make interpretable comparisons across these studies. Future work is needed to replicate these findings using similar and distinct parcellation and thresholding methods to determine which results are robust and which findings are sensitive to these factors. Finally, more independent samples are needed to replicate existing findings and to compare graph analyses across stress-related disorders (e.g., PTSD, MDD) to identify convergent and divergent patterns that may inform the transdiagnostic mechanisms by which stress influences brain connectivity and development, and to help identify illness-specific markers.

6. Limitations and caveats

Despite the strengths of graph theory and the results of the reviewed studies in elucidating stress-related effects on the adolescent development of structural and functional connectomes, there are still important points to consider when applying and interpreting graph metrics. As we alluded to throughout our review, the first critical decision point is to select appropriate node and edge definitions.

As Rubinov and Sporns (2010) state, "nodes should ideally represent brain regions with coherent patterns of extrinsic anatomical or functional connections" and "parcellation schemes that lump heterogeneously connected brain regions into single nodes may be less meaningful." While the AAL atlas is the most commonly used parcellation scheme, there is currently no consensus regarding an optimal set of criteria for node parcellations, particularly for IFNs (Gordon et al., 2014; Zalesky et al., 2010). Several of the metrics that reflect fundamental organizational properties (e.g., small-worldness, modularity, clustering, path length, and efficiency) are robust across spatial scales, but the exact parcellation scheme used to define nodes can significantly affect graph theory measures (Zalesky et al., 2010). Thus, researchers aiming to integrate structural and functional networks in a meaningful way should use the same parcellation schemes across both modalities to ensure comparability (Honey et al., 2009; Rubinov and Sporns, 2010). Unfortunately, however, this poses a problem when investigating IFNs that, by their very nature, encompass several regions that do not contain homogenous signals (Gordon et al., 2014), and may contain significant inter-individual variability (Gordon et al., 2017a, 2017b). For instance, in our recent study of adolescents with and without MDD, we documented depression-related effects on connectivity calculated with functionally, but not anatomically, defined nodes (Sacchet et al., 2016). The selection of biologically meaningful units should therefore be informed by the imaging modality as well as the specific networks of interest.

As a related point, the computation of edge definitions and the construction of edge matrices may also significantly affect results. As we noted earlier in this review (see Section 3), metrics such as modularity, which have been shown to be robust against parcellation schemes (Baker et al., 2013; Hagmann et al., 2012; Zhao et al., 2015) appear to have inconsistent age-related effects in white matter networks (Chen et al., 2013; Dennis et al., 2013a). These contrary results may have been driven in part by decisions to threshold and binarize or weight connection strengths in the respective adjacency matrices.

Another major issue that generalizes beyond graph theoretical analyses but is of paramount concern to developmental neuroscientists is the reliability of connectivity measures obtained from MRI scans. In this regard, graph metrics may be a preferred measure of connectivity, as multiple studies have found evidence for limited test-retest reliability when examining resting-state fMRI and IFNs using conventional analytic approaches (Braun et al., 2012; Wang et al., 2011), although for a more extensive discussion see also (Grayson and Fair, 2017). The reliability of graph metrics is generally good, with metrics calculated from structural data providing stronger reliability than those calculated on functional data (Zalesky et al., 2010). In a meta-analysis of 23 studies examining the reliability of graph metrics, Welton and colleagues found an average reliability of 0.79 for structural graph theory measures and 0.67 for functional graph theory measures, although these appeared to further depend on whether the metric in question was global or local (Welton et al., 2015).

Among global structural metrics, the reliability of clustering coefficient and characteristic path length were highest (0.76 and 0.78, respectively), while the reliability of small-worldness was lowest (0.55). Among local structural measures, local efficiency and degree had the highest reliability (0.87 and 0.84, respectively), while betweenness centrality was lowest (0.67) (Welton et al., 2015). Factors that improved reliability in structural studies included using larger regions as nodes (Andreotti et al., 2014; Bassett et al., 2011), using DTI data instead of DSI data (Bassett et al., 2011), using white matter instead of gray matter regions as nodes (Buchanan et al., 2014; Welton et al., 2015), and integrating over a range of thresholds when constructing binarized matrices (Dennis et al., 2013c). For global graph metrics calculated on resting-state fMRI data (as well as other functional data, including MEG and fNIRS), small-worldness and global efficiency had the highest reliability (0.77 and 0.78, respectively), while modularity had the lowest (0.64). For local functional graph measures, reliability was lower, with local efficiency having the highest (0.60) and betweenness centrality lowest (0.43) reliability. Factors which improved reliability among functional studies include low or broad frequency

ranges (Braun et al., 2012; Deuker et al., 2009) and larger nodes (Cao et al., 2014), with mixed results when comparing the reliability of short and long scan intervals (Schwarz and McGonigle, 2011; Wang et al., 2011), and the impact of global signal regression (Braun et al., 2012; Liang et al., 2012; Liao et al., 2013).

To date, no studies have specifically examined the reliability of graph metrics in both structural and functional MRI data in a sample of children and adolescents, which will be important for identifying metrics that are specifically sensitive to the effects of development.

7. Other considerations for future research and recommended directions

7.1. Sex differences

One important issue that has not been formally addressed in any of the papers reviewed here concerns the role of sex differences. For example, there is compelling evidence of sexual dimorphism in network connectivity and development (Lopez-Larson et al., 2011; Satterthwaite et al., 2016; Tyan et al., 2017; van Hemmen et al., 2017), with adolescent and young adult females exhibiting greater small-worldness in white matter tracts that is driven by greater normalized clustering and, thus, potentially reflective of greater network segregation (Dennis et al., 2013a). The reasons for these sex differences are multifaceted; moreover, the factors that drive these effects are likely to interact in complex ways. Nevertheless, we highlight two primary factors that we believe investigators should consider. First, there is a strong possibility that females and males are exposed to different types of stressors (e.g., interpersonal conflict versus physical violence), particularly in this age group (Rudolph and Flynn, 2007); differential exposure to number and/or type of stressors could affect brain development in ways that might explain sex-specific pathways to disorders that are characterized by pathological responses to stress (McLaughlin et al., 2009; Rudolph and Flynn, 2007). Second, pubertal hormones—and the psychosocial consequences of entering puberty and other related factors such as pubertal timing—likely affect the development of these networks in a sex-specific manner (Ahmed et al., 2008; Blakemore et al., 2010; Neufang et al., 2009). Specifically, females undergo puberty earlier than do males (Ellis, 2004; Negriff et al., 2010); therefore, the escalation in gonadal hormones may not only underlie sexual dimorphic development of certain brain networks but they may also render these networks more sensitive to the environment (Blakemore et al., 2010). Taken together, these processes could explain how sex may moderate associations between adversity and outcomes and for the reported sex differences in risk to stress-related disorders, such as PTSD and MDD, during the adolescent period (Ge et al., 2001; Rudolph and Flynn, 2007).

7.2. Type of stress

Another important factor to consider both in terms of interpreting existing data and of moving forward with new studies in this area is the impact of the type of stress or trauma on brain connectivity. Indeed, the theoretical conceptualization of stress as falling along at least two dimensions—deprivation (i.e., absence of cognitive and socioemotional input) and threat (i.e., presence of physically harming input)—is increasingly being highlighted in the field (McLaughlin et al., 2017; Nemeroff, 2016; Sheridan and McLaughlin, 2014). Empirical studies have shown that whereas experiences characterized by deprivation tend to be associated with reductions in cortical thickness in association cortex and in regions of the PFC (Hanson et al., 2011, 2012; McLaughlin et al., 2013, 2017), experiences characterized by threat appear to affect the morphology and connectivity of regions involved in emotional learning, including hippocampus, amygdala, PFC (Lim et al., 2017; Teicher et al., 2016), as well as the functional connectivity of regions in the CEN (Hart et al., 2017). Studies by Teicher and colleagues have suggested further that different types of threatening experiences yield

different neurobiological effects; specifically, whereas individuals exposed to parental verbal abuse exhibit morphological changes in structures responsible for processing auditory and linguistic stimuli, individuals who witnessed domestic violence exhibit morphological changes in structures responsible for processing higher-order visual information (Teicher et al., 2016). Long-term mental health outcomes are also likely dependent on the type of stressors experienced (Kessler et al., 2010; McLaughlin et al., 2012; Rodgers et al., 2004). Therefore, it is critical that future studies use valid and reliable measures to assess the various types of stress individuals could have experienced during childhood and adolescence to elucidate their diverse effects on network development.

7.3. Timing of stress

The discrepant findings in the literature reviewed thus far may be due to differences both in the ages at which stressors were experienced and in the ages at which brain metrics were obtained. Moreover, it is becoming increasingly clear that the adolescent brain is shaped not only by the *types* of stressors encountered during development, but also by *when* in development these stressors were experienced (Andersen and Teicher, 2008; Krugers et al., 2017; Lupien et al., 2009). Given the role of these brain structures in regulating stress responses, investigators have focused in particular on the hippocampus, amygdala, and PFC in examining the impact of the timing of stress. In one study, researchers found that income during childhood (age 9), but not during adulthood (age 24), was associated with impaired emotion regulation, as indexed by reduced PFC activation and heightened amygdala activation to negative stimuli (Kim et al., 2013). In another study, researchers found not only that severity of childhood maltreatment explained amygdala volumes in adulthood, but also that the severity of maltreatment specifically during later childhood (age 10–11) was a significant predictor of amygdala volumes (Pechtel et al., 2014). Finally, in support of our earlier arguments that sex differences and the type of stressful experiences must also be taken into consideration, one recent study found that whereas hippocampal volume of young adult males was predicted by experiences characterized by deprivation and neglect (but not abuse) through 7 years of age, hippocampal volume of young adult females was predicted by experiences of threat (i.e., abuse) but not deprivation at 10, 11, 15, and 16 years of age (Teicher et al., 2017). Interestingly, there is also evidence to suggest that the type and timing of childhood adversity differentially predict symptoms of PTSD and depression; specifically, whereas PTSD may be best predicted by overall severity of childhood adversity, emotional adversity during childhood (ages 8–9) appears to be differentially associated with symptoms of depression in young adults (Schalinski et al., 2016). It is critical, therefore, that future studies investigating the neurodevelopmental processes affected by stress carefully measure and test for the unique and potentially interactive influences of sex and type and timing of stress on brain connectivity metrics.

7.4. Methodological advancements and future directions

There are also clear methodological advancements for future work to apply graph theoretical analyses to understand the neurobiological mechanisms and consequences of stress on the adolescent—and more generally, the developing—brain. These include conducting longitudinal studies that reveal normative trajectories of structural and functional network development across the lifespan, characterizing short-term network-level dynamics (e.g., in response to a stressor or a task probe), and elucidating the correspondence between multimodal data (e.g., structural versus function, resting-state versus task-evoked). Several of these applications will depend on advances in related neuroimaging methods, such as conducting appropriate statistical models on longitudinal brain data (Madhyastha et al., 2017), improved capabilities to resolve trial by trial signals (Zeithamova et al., 2017), and

adequate preprocessing pipelines and mathematical frameworks for integrating multimodal and multi-scale neuroimaging data (Betzel and Bassett, 2016; Bolt et al., 2017; Misic et al., 2016). Other current trends that we anticipate are an increased use of weighted graphs, which arguably contain more biologically relevant information and may deepen our understanding of the relations among various node connections (Grayson and Fair, 2017). Finally, large consortia, such as ENIGMA (Thompson et al., 2014), PING (Jernigan et al., 2015), and more recently, ABCD (Casey et al., 2018), that pool data across multiple sites and apply harmonized preprocessing protocols for large-scale meta- and mega-analyses, will also be critical in identifying the most reproducible and reliable graph metrics associated with normative aging, the effects of stress (including early life adversity and childhood trauma), and psychiatric disease.

As we highlighted throughout this review, we recommend that future work seek to examine, prospectively, the effects of stress on the segregation and integration of IFNs during adolescence. Further, it will be important to determine which aspects of the brain connectome that are perturbed in psychiatric diseases are due to broad and transdiagnostic effects of stress and which are an indicator of a specific illness. Finally, more work is needed to definitively compute the reliability of graph metrics so that researchers use appropriate measures when characterizing normative and disrupted structural and functional development.

8. Conclusions

The developmental processes affected by stress exposure and psychiatric illness have predominantly been examined within specialized circuits; however, these circuits are embedded in larger networks that are spatially distributed throughout the cortex, and that exhibit sophisticated intra and inter-network connectivity. Graph theory provides a framework amenable to developmental neuroscience by quantifying metrics of segregation, integration, and regional influence that summarize biologically complex network-level properties. We propose that these metrics will be useful for understanding the influence of stress on the adolescent brain and represent an approach that is capable of facilitating comparisons across multimodal data in order to yield additional insight into network architecture that may not be adequately measured otherwise. Our review of the state of the science thus far has revealed that there is evidence that stress affects processes related to both segregation and integration. There are also effects of stress on connectivity of regional hubs, but most of these connections are likely to be integrative in nature as they cross distinct modules. Current applications of graph theory to neuroimaging data have yet to reach a consensus about the appropriate parcellation schemes used for defining biologically meaningful nodes, about thresholding or weighting edges for computing graphs, or about the reliability of graph metrics, particularly for functional data. Outstanding gaps in research directions also remain, including prospective studies of the effects of stress on children and adolescents, critical considerations of sex differences, careful examinations of the effects of stressor type and timing on adolescent brain development, and comprehensive investigations on which network-level alterations observed in psychiatric samples can be explained predominantly by experiences of early life adversity. Multisite efforts to standardize behavioral and brain measurements combined with methodological advancements in neuroimaging technology and computational modeling are sure to inspire exciting future work in this area.

Acknowledgments

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ynstr.2018.05.002.

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