

The development of brain network hubs

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ABSTRACT

Some brain regions have a central role in supporting integrated brain function, marking them as network hubs. Given the functional importance of hubs, it is natural to ask how they emerge during development and to consider how they shape the function of the maturing brain. Here, we review evidence examining how brain network hubs, both in structural and functional connectivity networks, develop over the prenatal, neonate, childhood, and adolescent periods. The available evidence suggests that structural hubs of the brain arise in the prenatal period and show a consistent spatial topography through development, but undergo a protracted period of consolidation that extends into late adolescence. In contrast, the hubs of brain functional networks show a more variable topography, being predominantly located in primary cortical areas in early development, before moving to association areas by late childhood. These findings suggest that while the basic anatomical infrastructure of hubs may be established early, the functional viability and integrative capacity of these areas undergoes extensive postnatal maturation. Not all findings are consistent with this view however. We consider methodological factors that might drive these inconsistencies, and which should be addressed to promote a more rigorous investigation of brain network development.

1. Introduction

The human brain undergoes profound changes during the first two decades of life. Key developmental events, such as the initial growth of axons during the second trimester, or the pruning of excess synapses during childhood and adolescence, are critical in sculpting the anatomical wiring that links spatially distributed neural elements (de Graaf-Peters and Hadders-Algra, 2006; Stiles and Jernigan, 2010). These developmental changes in neuronal connectivity parallel the maturation of social, cognitive, and motor skills from birth to young adulthood (Lamblin et al., 2017; Marek et al., 2015; Marrus et al., 2018), and alterations of normal development can augment risk for neurodevelopmental disorders such as autism spectrum disorder, attention-deficit hyperactivity disorder, and schizophrenia (Dennis and Thompson, 2013; Fornito et al., 2015; Paus et al., 2008).

The complete network of neuronal connections comprising the human brain is called the connectome (Sporns et al., 2005). Connections within this intricate network are distributed unevenly, such that certain network elements possess a relatively large number of connections, marking them as putative network hubs (van den Heuvel and Sporns, 2013a). Brain hubs facilitate the integration of functionally specialized and anatomically disparate neural systems (van den Heuvel

and Sporns, 2011), a role supported by their tendency to form long-range connections (Arnatkevičiūtė et al., 2018; Fulcher and Fornito, 2016; Harriger et al., 2012; van den Heuvel et al., 2012), and their topological position within the brain, which suggests that they mediate a large fraction of signal traffic (Mišić et al., 2014, 2015; van den Heuvel et al., 2012). Hubs are also implicated in many phenotypically diverse psychiatric and neurological disorders (Crossley et al., 2014; Fornito et al., 2015). In the mature adult human brain, hubs typically localize to areas of association cortex, basal ganglia and thalamus – regions that play a central role in higher-order cognition (Buckner and Krienen, 2013; van den Heuvel and Sporns, 2013a).

Given the apparent importance of network hubs for integrated brain function, and their involvement in diverse diseases, it is natural to ask how hubs arise throughout brain development. Are they present from the earliest stages of brain development, or do they emerge later in life? What are the mechanisms that lead to the emergence and functional prominence of hubs? Advances in developmental neuroimaging have begun to shed light on these and related questions (Bassett et al., 2018; Cao et al., 2017, 2016; Morgan et al., 2018; Richmond et al., 2016; Vértes and Bullmore, 2015; Zhao et al., 2018). In this article, we review developmental studies that have examined how hubs of the human brain arise and mature. We first examine how hubs are identified, and

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then review empirical studies of hub connectivity during the perinatal, child, and adolescent periods of development. We consider some of the major challenges facing studies of brain network development and describe new research frontiers which we expect will shed further light on brain network maturation.

1.1. How are hubs identified?

Analyses of brain hubs typically begin by representing the brain as a network, or graph, of nodes connected by edges (Bullmore and Sporns, 2009; Fornito et al., 2016; Rubinov and Sporns, 2010). Nodes represent distinct neural elements, such as specialized neuronal populations or brain regions, and the edges represent connections between nodes. In human neuroimaging studies, nodes are typically macroscopic brain regions, defined using some parcellation scheme (Arslan et al., 2018; Fornito et al., 2013; Wig et al., 2011). Edges represent some measure of structural or functional connectivity. The former is estimated using either diffusion MRI tractography, which identifies putative white matter pathways based on the diffusion of water molecules in the brain, or (less directly) as inter-regional correlations in cortical morphometric parameters, such as cortical thickness or grey matter volume; functional connectivity is often estimated as a correlation between regional functional MRI signal fluctuations. Further details on different approaches to brain network construction have been provided elsewhere (Alexander-Bloch et al., 2013; Bullmore and Bassett, 2011; Fornito et al., 2016, 2013).

Network representations of the brain can be either directed or undirected, and unweighted or weighted. The brain is intrinsically a directed and weighted network (Fornito et al., 2016, 2013) – that is, each connection has a source and a target, and these connections vary in their strength – but directionality is difficult to resolve with non-invasive imaging and many studies to date have used unweighted and undirected graphs to represent brain networks.

Once a network has been constructed, the mathematics of graph theory (Barabási, 2016; Newman, 2010, 2003) can be used to quantify different properties of the network. One such property is centrality, which can be defined as the capacity of a node to influence, or be influenced by, other system elements by virtue of its connection topology (Borgatti, 2005; Borgatti and Everett, 2006; Fornito et al., 2016; Freeman, 1978). A node scoring highly on a given centrality measure

can be considered a hub, depending on the specific aspect of centrality that one wishes to emphasize (e.g., Fig. 1A). The simplest and most commonly used measure of centrality for defining hubs is node degree, which is the number of connections attached to a node (by extension, in weighted network analyses, the weighted degree, or node strength, is the sum of the edge weights attached to a node).

Node degree is a simple and intuitive measure, but it can give a limited impression of a node's role in the network. For example, the red node in the network in Fig. 1A has relatively low degree but acts as a bottleneck for all information passing through the blue and green clusters of the network. One could easily make a case that this red node should also be considered a hub, despite its low degree. Similarly, two different nodes i and j , may have equivalent degree, but i may connect to other high-degree nodes whereas j connects only to low-degree nodes. Intuitively, node i should be more influential, but this distinction will not be quantified using node degree alone. Various metrics have been proposed to capture these and other more nuanced aspects of centrality; in fact, some 200 different centrality measures have been proposed to date (Jalili et al., 2015). Prototypical measures of centrality (see Fig. 1A) include degree, shortest-path closeness (the average shortest path between an index node and all others), and shortest-path betweenness (the extent to which an index node lies on shortest paths between other node pairs) (Freeman, 1978; Sabidussi, 1966), but other metrics have been developed that assume more complex communication dynamics (Avena-Koenigsberger et al., 2017; Borgatti, 2005). In practice, many centrality measures are often correlated with each other (Li et al., 2015; Oldham et al., 2018; Ronqui and Travieso, 2015; Valente et al., 2008), and these correlations can be exploited to define hubs using consensus scores that aggregate values across several centrality metrics (Sporns et al., 2007; van den Heuvel et al., 2010).

Despite the wide array of centrality measures, and methods for defining hubs, most studies in neuroscience have relied on node degree or related variants. It is common to designate the nodes with the highest scores on a particular centrality measure as hubs, but whether such nodes represent influential hubs will depend on the distribution of the metric used to define hubness. If the distribution is right-tailed, the network contains a subset of nodes (those in the tail of the distribution) that are disproportionately more central than others; it is this disproportionate centrality that is the defining feature of an influential hub (Fig. 1B). If the distribution is approximately Gaussian (or more

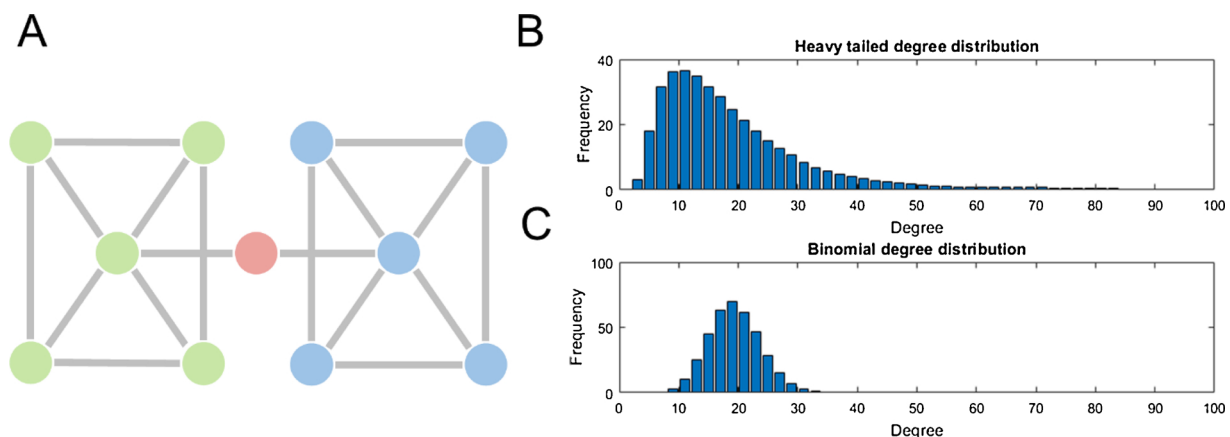


Fig. 1. Issues in hub detection. A) Example of different aspects of centrality. The nodes located in the center of the blue and green clusters have the highest degree (number of connections), but all their connections are to other nodes in the same cluster and they have no direct connectivity with the other cluster. These nodes therefore act as local hubs, but play a minor role in network-wide integration. Conversely, the red node has the lowest degree in the network but is positioned as a bottleneck for any communication between the two clusters. More formally, the red node has higher betweenness (it is located on many of the shortest-paths between nodes) and closeness (its average topological distance to other nodes is small) than any of the other nodes. B) Example of a heavy-tailed degree distribution. The extended tail contains putative hub nodes that have a very high degree relative to most of the other nodes. C) Example of a binomial degree distribution, which lacks heavy tails. In this network, most nodes have an average, modal level of degree and the probability of finding nodes with very high degree is low. Note that while degree is used here as an example, the same reasoning is applicable to other centrality measures (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

precisely for degree, binomial), then the network contains no “outlying” nodes that exert undue influence on network function (Fig. 1C). Moreover, even in the presence of a skewed centrality distribution, there is no clear cut-off for distinguishing hubs from non-hubs. As such, the distinction between hubs and non-hubs is, to some extent, arbitrary.

Another consideration in defining hubs is that different centrality measures may be appropriate for different kinds of networks. For instance, node degree in correlation-based (e.g., functional connectivity) networks is biased to identify ‘local’ hubs that are highly connected within a specific sub-network of the brain, rather than hubs that integrate information across diverse subnetworks, suggesting that other measures of centrality may be more appropriate in correlation networks (Power et al., 2013). Finally, the designation of a node as a hub very much depends on the scale at which nodes are defined. Most MRI studies map connectivity at the macroscale, between coarsely defined brain regions. Many of these regions are themselves functionally heterogeneous, and a finer-grained parcellation may affect the region’s status as a hub. For example, the thalamus, despite comprising 50–60 specialized sub-nuclei (Herrero et al., 2002), is often treated as a single node in human connectomics.

1.2. Properties of brain network hubs in the adult brain

Despite the various methods available for quantifying centrality, these measures often identify the same regions of brain networks as being the most influential (see Fig. 2). In structural connectivity networks, these putative hub regions typically reside in medial parietal, frontal and subcortical (basal ganglia and thalamus) regions, with some evidence for occipital, insula and cingulate regions (Bell and Shine, 2016; Gong et al., 2009; Hagmann et al., 2008; van den Heuvel et al., 2010; van den Heuvel and Sporns, 2011, 2013a). Hubs in functional networks are reported in similar areas, including precuneus, cingulate, frontal and inferior parietal areas, and notably overlap with regions comprising the default-mode network and executive control networks (van den Heuvel and Sporns, 2013a; Zuo et al., 2012), which are and are involved in numerous complex cognitive domains (Dosenbach et al., 2008, 2006). In general, hubs of the adult brain localize predominantly to association and subcortical regions.

Structural hubs of the brain are more densely interconnected amongst themselves than expected by chance, forming a so-called rich-club (Colizza et al., 2006; Zhou and Mondragón, 2004). Rich-club organization has been observed in humans (van den Heuvel et al., 2012; van den Heuvel and Sporns, 2011), macaques (Harriger et al., 2012), rats (van den Heuvel et al., 2016), mice (Fulcher and Fornito, 2016), *Drosophila* (Shih et al., 2015), and in the nematode worm *Caenorhabditis elegans* (Arnatkevičiūtė et al., 2018; Towlson et al., 2013). Computational modelling indicates that hubs and rich-club connections are topologically positioned to mediate a large fraction of signal traffic in the brain (Mišić et al., 2015, 2014), synchronize peripheral brain regions, promote complex brain dynamics (Gollob et al., 2015; Senden et al., 2014, 2017; Zamora-López et al., 2010), and imaging evidence shows that they link distinct functional networks (van den Heuvel and Sporns, 2013b). This integrative role is thought to underlie complex cognitive processes, such as language and abstract thought (van den Heuvel and Sporns, 2013a). Rich-club connections extend over longer distances, on average, than other connections, marking them as highly costly aspects of connectome organization (Arnatkevičiūtė et al., 2018; Fulcher and Fornito, 2016; Harriger et al., 2012; Towlson et al., 2013; van den Heuvel et al., 2012). This high wiring cost parallels a high metabolic cost of hub activity (Liang et al., 2013; Tomasi et al., 2013; Vaishnavi et al., 2010), which may underlie the involvement of hubs in diverse brain disorders (Crossley et al., 2014; Fornito et al., 2015). Modelling studies indicate that disruption of hubs is likely to have a particularly deleterious impact on brain network function (Achard et al., 2006; van den Heuvel and Sporns, 2011), a prediction supported by evidence from lesion studies (Achard et al., 2012; Warren et al.,

2014). Together, these findings indicate that hubs in the adult brain are functionally valuable, costly elements of the connectome that play a central role in integrated brain function and adaptive behavior.

2. The development of hub connectivity

Human brain development unfolds over a protracted period, extending across 2–3 decades and following a series of sequential yet overlapping stages, including neuronal migration, axonal growth, synaptogenesis, synaptic pruning and myelination (de Graaf-Peters and Hadders-Algra, 2006). The precise point at which hubs emerge is difficult to determine, because we lack the tools for precise mapping of whole-brain connectivity at very early stages of development. In the following sections, we review studies examining hub connectivity during prenatal and infant development, childhood, and adolescence, focusing on where hubs are located, how hub connectivity changes through development, and how hubs may be related to cognitive abilities. We draw a distinction between structural connectivity networks, which reflect the physical infrastructure of the brain and constrain the potential communication capacity between brain regions, and functional connectivity networks, which more directly index the actual dynamics taking place in the network.

2.1. Prenatal and infant development

Perhaps the clearest evidence for the early emergence of hubs comes from studies of *C. elegans*, the only organism to have had its connectome mapped nearly completely at the level of every neuron and synapse (Varshney et al., 2011; White et al., 1986). The birth time of each neuron is known, allowing precise delineation of when the hubs of this network emerge (Varier and Kaiser, 2011). Analysis of these data has shown that hub neurons are amongst the earliest-emerging neurons, all being born prior to any signs of movement in the animal (Towlson et al., 2013). Whether this result holds for mammals is unclear. Indeed, the construction of temporally-resolved atlases of connectome development in mouse and primate models will be highly valuable for revealing the timing and mechanisms underpinning hub formation. However, indirect evidence for the early formation of does come from non-human primate studies. A general trend has been observed in the primate cortex, such that areas with high degree have lower neuronal density (Beul et al., 2017; Scholtens et al., 2014). Low neuronal density is considered to be a proxy of early completion of neurogenesis, because a shorter developmental period results in less cell migration and consequently reduced neuronal density (Barbas and García-Cabezas, 2016; Dombrowski et al., 2001; Hilgetag et al., 2016).

Comparable measures of regional neuron density and neuron birth times in the human are lacking, and studying fetal and neonate brains with MRI is methodologically challenging, due to poor signal-to-noise ratio, poor anatomical contrast between grey and white matter, high motion, and difficulties in mapping parcellations between brains (Ouyang et al., 2017; van den Heuvel and Thomason, 2016). Nonetheless, the available evidence from this developmental period confirms an early emergence of structural hubs. Indeed, the structural connectome of neonates shows a right-tailed degree distribution, with high-degree nodes located primarily along the midline and in lateral frontal and temporal areas (Fig. 3A) (Ball et al., 2014; van den Heuvel et al., 2015). A number of these neonate hubs overlap with those in adult networks, such as those in association (e.g., superior frontal, parietal), subcortical, and visual regions, indicating that several hub regions in adults are also hubs in neonates. However some of these hubs may be infant specific, such as those in sensorimotor and temporal areas (Ball et al., 2014; Huang et al., 2015; Tymofiyeva et al., 2013; van den Heuvel et al., 2015; Yap et al., 2011).

Studies of preterm infants suggest that hubs can also be identified prior to term birth. One study examining diffusion MRI scans of infants born at approximately 30 weeks gestational age (GA) found hubs in

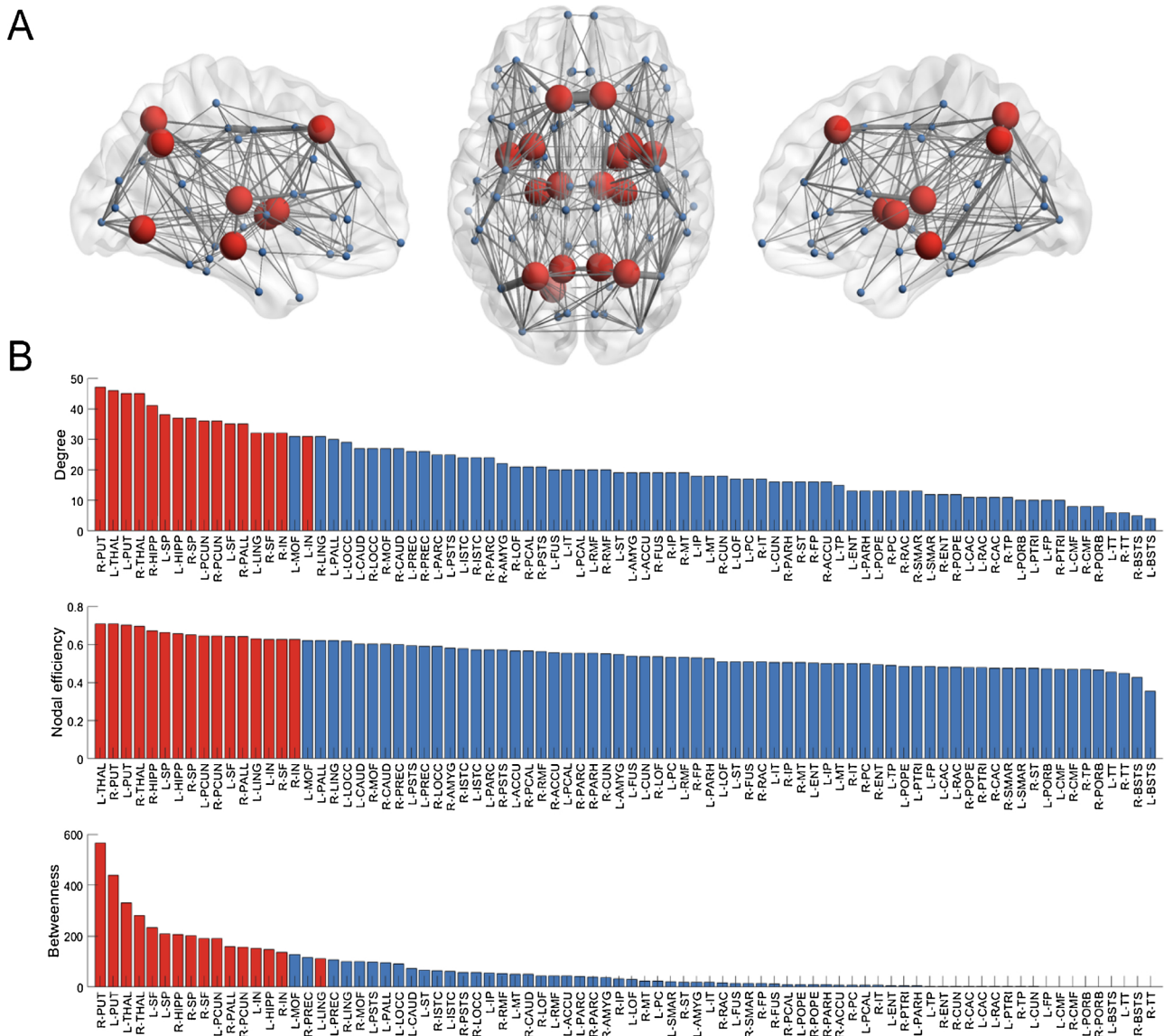


Fig. 2. Structural hubs of the adult human brain. A) Spatial distribution of brain network hubs. Here, hubs (red) have been defined as nodes scoring ≥ 1 standard deviation above the mean on at least one centrality measure (degree, nodal efficiency, or betweenness). Hubs are in the bilateral putamen, thalamus, superior parietal, superior frontal, precuneus, hippocampus, insula, right pallidum, and left lingual gyrus. B) Node centrality scores for degree, nodal efficiency, and betweenness. Each bar chart shows each node's score on each of the three prototypical centrality measures, ordered from highest to lowest. Degree is defined as the number of connections attached to each node. Nodal efficiency (also known as closeness) is the average of the inverse shortest path between a node and all others. Betweenness is the number of shortest-communication paths between other nodes that pass-through a given index node. Red bars mark hub nodes across all measures. As can be seen, hubs are consistently ranked highly across all three different centrality measures. See supplementary information for the definition of each abbreviation. Data is from a group averaged connectome, generated from 973 participants of the Human Connectome Project (for further details, see Oldham et al., 2018) (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

superior frontal, superior parietal, and occipital regions (Fig. 3B) (Ball et al., 2014). Like in adult and term neonate structural networks, hubs at 30 weeks GA were highly interconnected, forming a rich-club, and hub-to-hub connections were significantly longer than other types of connections (Ball et al., 2014). Moreover, most of the longitudinal changes occurring in the network between 30 and 40 weeks GA affected connections between hubs and non-hub areas rather than the rich-club connections between hubs (Ball et al., 2014). Consistent with this finding, other work has shown that the strength of connections in a putative network core of the brain, which typically involves connections between hub nodes, undergoes minor changes during the third trimester of development (Batalle et al., 2017). The early formation of hubs and a rich-club suggests that these nodes and connections form a stable scaffold to which other elements are added in subsequent

development (Csermely et al., 2013). The rich club thus forms an early anatomical infrastructure for interregional communication. However, the strength of these connections is still relatively weak, indicating that the full integrative capacity of the rich club may only be realized as hub connectivity matures. Indeed, functional connectivity is constrained, but not completely determined, by structural connectivity (Goñi et al., 2014; Honey et al., 2010; Skudlarski et al., 2008), and if structural hubs are immature early in development, one might expect a functional network topography that deviates from the underlying structural network. Consistent with this view, early studies of functional connectivity hubs in prenatal and neonate networks are consistently found in primary sensorimotor, auditory, motor, and visual areas (De Asis-Cruz et al., 2015; Fransson et al., 2011; Gao et al., 2011; van den Heuvel et al., 2018).

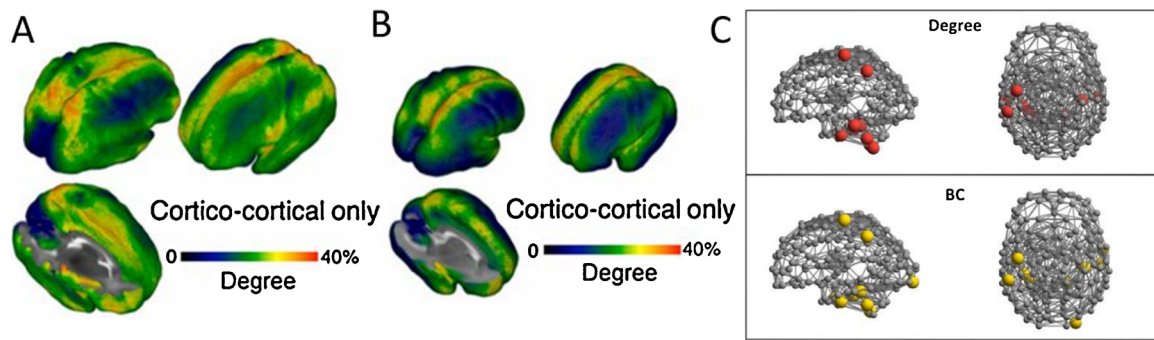


Fig. 3. Hubs in prenatal and neonate connectomes. A) Degree of cortical regions in the structural connectivity network of neonates at 40 weeks GA. B) Degree of cortical regions in the structural connectivity network of neonates at 30 weeks GA. These figures show that hubs (red/yellow areas) are present by 30 weeks GA. Several of these hub areas, including superior frontal, superior parietal and occipital regions, are also hubs in adults (see Figure X). C) Degree and betweenness centrality (BC) hubs in a foetal functional connectivity network (degree hubs are in red and betweenness hubs are in yellow). Functional hubs are primarily localised to primary regions in the prenatal/infant period. In contrast, functional connectivity hubs in adults are located in association areas (see Fig. 4). Both measures show a high level of consistency in the regions identified as hubs. Panels A and B adapted from Ball et al., 2014, and panel C from van den Heuvel et al., 2018. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

Some more recent studies of neonates have detected hubs in association (De Asis-Cruz et al., 2015; van den Heuvel et al., 2018) and frontal areas (Gao et al., 2011; Scheinost et al., 2016), suggesting the functional networks of neonates may be in a more mature, adult-like form than previously thought. However, some of these studies used suboptimal motion correction techniques (Gao et al., 2011; Scheinost et al., 2016) or had to remove large amounts of data due to motion artefacts (van den Heuvel et al., 2018). Given the major challenge that motion confounds pose for imaging studies of early development (Satterthwaite et al., 2012), these findings require further validation. Functional connectivity hubs have also been identified in the cerebellum of fetuses (van den Heuvel et al., 2018), a region that is often overlooked in adult studies of the connectome, but which plays a critical role in cognitive development (Volpe, 2009).

The localization of functional hubs to primary sensory and motor areas of the prenatal/neonate brain is thought to be linked to the initial development of cognitive, motor and visual processes (van den Heuvel et al., 2018). It may also reflect the relative structural immaturity of long-range fibers that link spatially disparate association areas, given that these long-range fibers undergo myelination well into the third and fourth decades of life, and that primary systems are relatively localized, and dominated by short-range connectivity. Thus, an adult-like binary topology of hub connectivity may be established early, but its relative immaturity may limit its role in promoting integrative dynamics, which are only fully realized when long-range projections have completely myelinated. This early immaturity would be expected to produce dynamics that are predominantly segregated, resulting in a preponderance of functional connectivity hubs in early-developing primary areas. Functional hubs may then shift to association areas as long-range projection fibers myelinate and enable more integrated processing.

2.2. Childhood development

Nearly all long-range axonal connections are established by birth (Cabungcal et al., 2006; Larsen et al., 2006), and human imaging studies have confirmed that the topography of structural hubs in children resembles the adult brain, with hubs being predominantly localized to association cortex and subcortical regions (Fig. 4A) (Chen et al., 2013b; Grayson et al., 2014; Hagmann et al., 2010). Structural rich-club connectivity is also largely like that of adults (Grayson et al., 2014).

While the binary topology of the structural connectome is highly stable by childhood, the strength of hub connectivity undergoes further changes (Cao et al., 2016). During childhood, the fractional anisotropy (FA) of hub connections increases, and these increases are greater than those observed for other types of connections (Wierenga et al., 2018). In

parallel, the mean diffusivity (MD) in frontal and parietal association fibers also showed the largest changes during childhood and adolescence (Wierenga et al., 2016). FA and MD measure the extent to which axonal bundles constrain the direction and magnitude of water diffusion and are often taken as markers of white matter integrity. Thus, changes in these measures are thought to reflect the maturation of hub connections, possibly due to factors such as myelination and denser packing of axons (Lebel and Beaulieu, 2011). However, FA and MD can be affected by numerous microstructural changes and other factors related to data acquisition, meaning that their physiological significance can be hard to interpret (Beaulieu, 2002; Jones, 2010; Jones et al., 2013).

As the strength of hub connectivity increases in childhood, it is expected that hub areas should occupy a more topologically central role in the network when connection weights are considered in the analysis. Several studies of weighted networks have found that the centrality of hubs in medial frontal and parietal regions does indeed increase from early to late childhood, but that the centrality of lateral cortical hubs decreases during this time (Chen et al., 2013b; Huang et al., 2015). Others have reported that the centrality of hubs remains relatively stable across childhood and adolescence (Hagmann et al., 2010). These differences could be due to the choice of centrality measure. Studies that found developmental changes used nodal efficiency (a measure of the average topological distance of a node to others; Achard and Bullmore, 2007). Studies that did not find changes used betweenness centrality (a measure of the number of shortest communication paths in the network that pass through a node). Differences across studies in the way edge weights are measured across studies (for example, whether weights are measured using FA, MD or some other metric) make it difficult to compare results across studies (Cao et al., 2016; Koenig et al., 2015).

As with networks derived from diffusion MRI, those based on patterns of structural covariance (typically covariance in cortical thickness) in childhood have also found that hubs are located in parietal, frontal, and temporal regions (Fan et al., 2011; Khundrakpam et al., 2013; Nie et al., 2013). Within these regions, hubs were found in language-related areas (e.g., superior/middle temporal gyrus, angular gyrus), a result that is thought to parallel the significant development of language during this period (Khundrakpam et al., 2013). By adolescence, hubs are more prominently found in frontal cortex (Khundrakpam et al., 2013), consistent with frontal areas exercising an increasingly dominant role in cognition (Lewis and Todd, 2007). Changes in structural covariance may be driven by increasing myelination of connected areas, although other microstructural features, such as changes in glial cell density and neuronal size may also

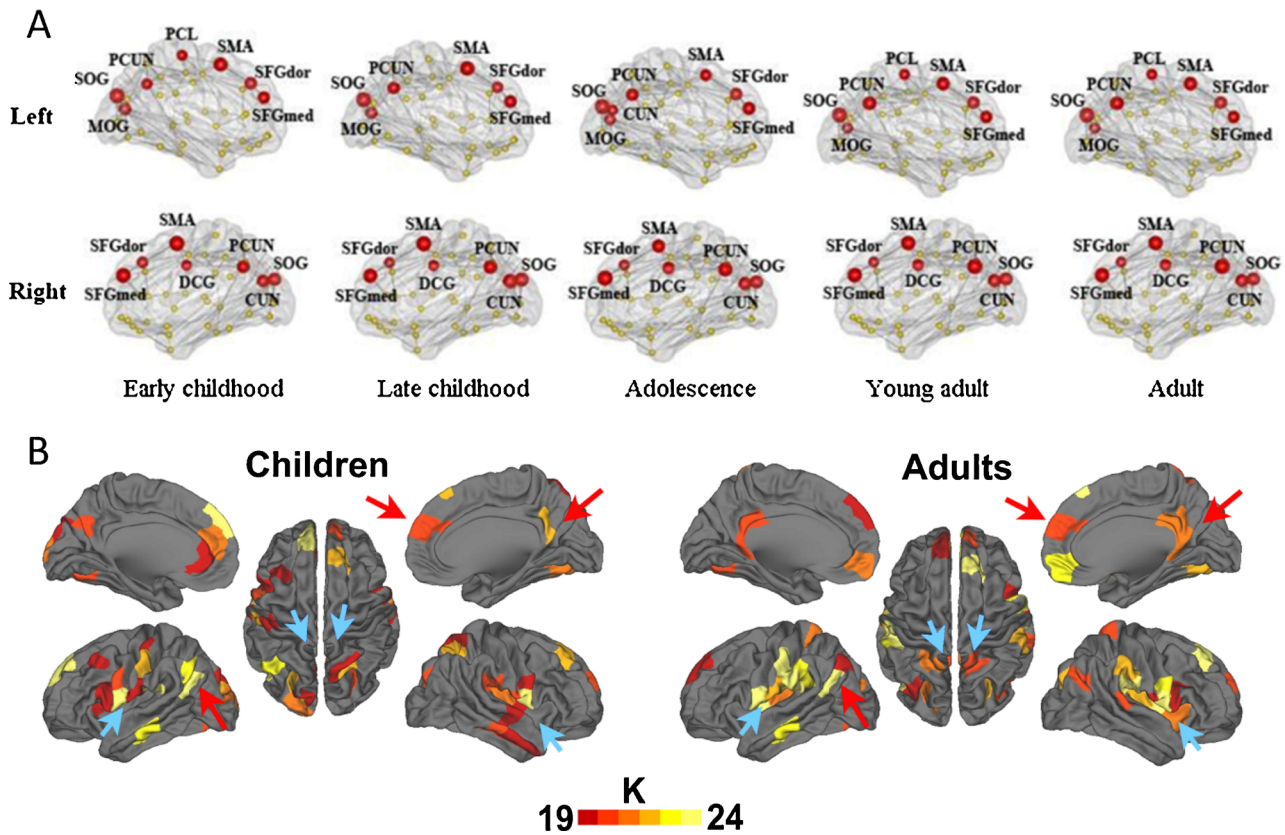


Fig. 4. The spatial topography of structural and functional hubs is consistent from childhood to adulthood. A) Spatial distribution of structural connectivity hubs, as determined by nodal efficiency, from early childhood to adolescence. Structural hubs are found in frontal, parietal and visual areas and remain stable across development. CUN = cuneus, DCG = median cingulate and paracingulate gyrus, MOG = middle occipital gyrus, PCL = paracentral lobule, PCUN = precuneus, SFGdor = superior frontal gyrus, SFGmed = superior frontal gyrus, medial, dorsolateral, SMA = supplementary motor area, SOG = superior occipital gyrus. Adapted from [Chen et al., 2013b](#) with permission. B) Spatial distribution of rich-club nodes (nodes with a degree > 19) in child and adult functional networks. Red arrows highlight areas of overlap (including medial prefrontal, posterior cingulate cortex/precuneus, inferior parietal, ventral visual, ventral somato-motor, and some insula areas) while blue arrows show bilateral regions only present in adults (including superior parietal cortex, the supramarginal cortex, and other parts of the insula). Adapted from [Grayson et al., 2014](#) with permission (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

contribute ([Paus et al., 2008](#); [Tamnes et al., 2010](#); [Zatorre et al., 2012](#)).

Where the topography of structural hubs is considered stable by childhood, functional networks transition to a more adult-like pattern during this time. Hubs shift from being localized in primary sensory and motor areas perinatally to a more distributed pattern extending across frontal, visual, temporal and subcortical areas between age 5–10 ([Fig. 4B](#)) ([Betzel et al., 2014](#); [Cao et al., 2014](#); [Grayson et al., 2014](#); [Hwang et al., 2013](#); [Wu et al., 2013](#)). The shift of hubs from primary to association areas mirrors the development of higher-order cognition during this period ([Casey et al., 2005](#)). This shift in the location of functional hubs may be driven by the gradual maturation of long-range axonal projections.

Despite the consistent localization of functional hubs, the precise nature of the developmental changes taking place during childhood remains unclear. Relatively few studies have examined the period from infancy to early childhood, but there is some evidence for an increase in frontal and parietal hub centrality ([Gao et al., 2011](#)). The picture is more complicated in late childhood, and appears to depend on whether weighted or unweighted networks were analyzed – weighted degree has been found to decrease in lateral frontal, parietal and temporal regions ([Cao et al., 2014](#)), whereas unweighted measures of hub centrality show no change ([Wu et al., 2013](#)). A third study used the first principal component of different weighted and unweighted centrality measures to capture common variance in centrality ([Hwang et al., 2013](#)). Using this measure, no changes in hub connectivity were identified throughout late childhood and adolescence, although functional

connectivity between frontoparietal hubs and non-hub areas did increase over this time.

There is some evidence that functional connectivity between network hubs strengthens during childhood. For example, adults show evidence of stronger rich-club organization, implying stronger functional connectivity between hubs, than children ([Cao et al., 2014](#); [Grayson et al., 2014](#); [Uddin et al., 2011](#)). Functional connectivity within the default mode network—which contains several cortical hubs—is also increased in adults compared to children ([Fair et al., 2008](#); [Sato et al., 2014](#); [Supekar et al., 2010](#)). Increased connectivity between hubs is expected to enhance functional integration ([van den Heuvel and Sporns, 2013a](#)), and may thus facilitate the transition from neural dynamics dominated by local, short-range, and segregated interactions to globally coordinated activity. This view is supported by evidence that long-range connectivity (such as connections that link hubs) increases while short-range connectivity decreases during this developmental period ([Dosenbach et al., 2010](#); [Fair et al., 2009, 2007](#); [Supekar et al., 2009](#)). However, it is well-documented that head motion artifacts can also reduce short-range and inflate long-range connectivity ([Power et al., 2012](#)). This effect presents a major confound to developmental studies, since younger people tend to move more in the scanner. Some evidence indicates that this distance-dependent developmental trend is still apparent when using stringent controls for motion, but the effects are weaker than those initially reported ([Fair et al., 2013](#); [Power et al., 2012](#); [Satterthwaite et al., 2013, 2012](#)).

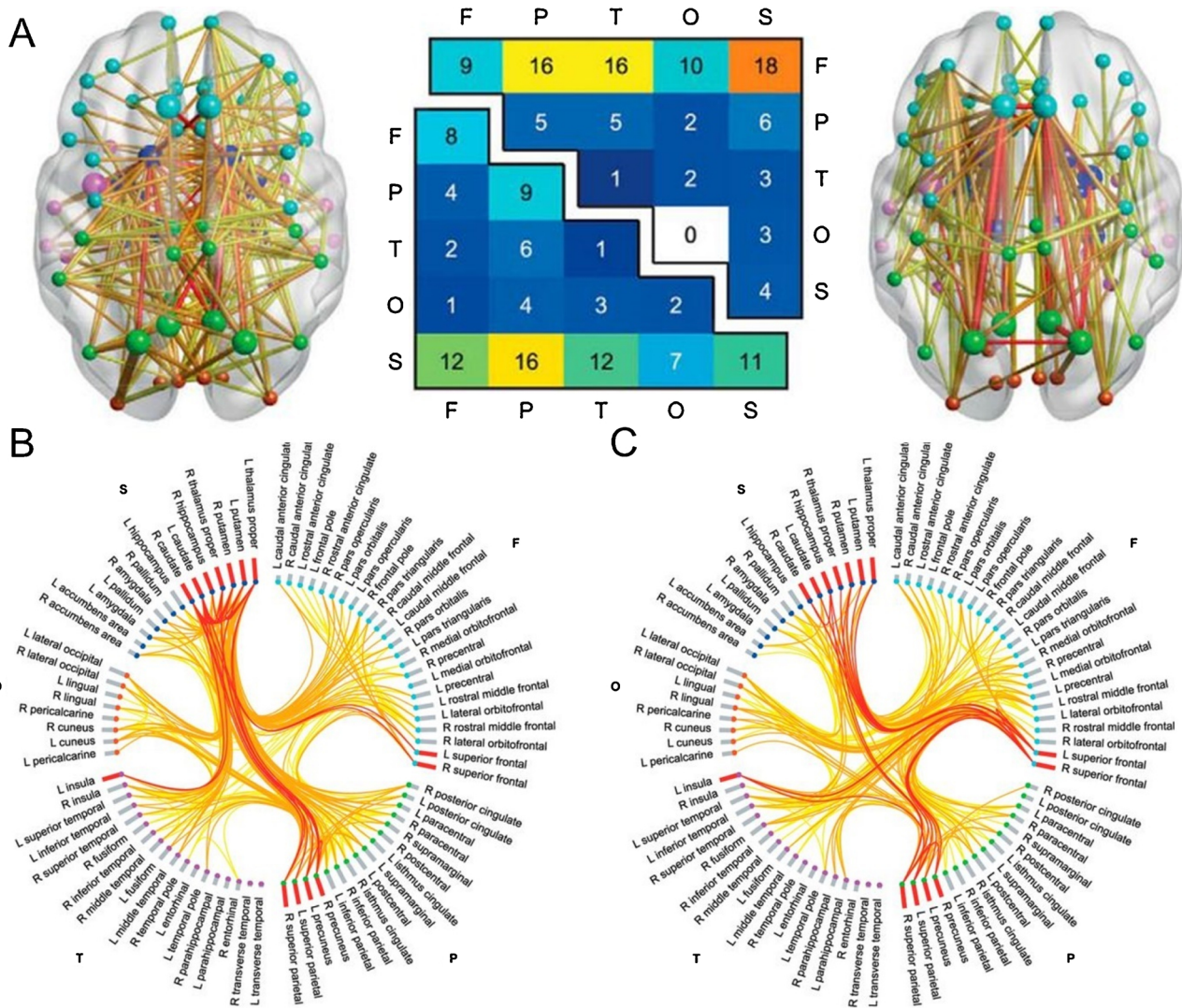


Fig. 5. Changes in hub structural connectivity during adolescence. A) Connections showing significant decreases (left) and increased (right) in the number of streamlines between the ages of 15 and 19. The color of each edge indicates the connection type: non-hub to non-hub (yellow), non-hub to hub (orange), and hub to hub (red) and the thickness of each edge is weighted by its associated one-tailed *t*-test statistic (FWE corrected, $p < 0.05$). The color of each node indicates its assignment to one of five broad anatomical divisions: frontal (cyan), parietal (lime), temporal (magenta), occipital (orange-red), or subcortical (blue). Large nodes are hubs while smaller nodes are non-hubs. The matrix indicates the distribution of developmental increases (upper matrix) and decreases (lower matrix) across the anatomical divisions. The value of each matrix element represents the ratio between the frequency of edges linking each pair of divisions and the total number of edges belonging to the two divisions. B) Connectograms of decreases (left) and increases (right) in streamline density. Nodes are grouped according to anatomical division and are further ordered by degree (the height of the bar chart is proportional to degree). Red bars indicate hubs. Edges and nodes are colored according to the scheme described for panel A. F = Frontal; L = left; O = occipital; P = parietal; R = right; S = subcortical; T = temporal. These figures illustrate that developmental increases are concentrated in frontal, parietal, and subcortical regions, with many of these changes occurring in hub connections. Adapted from Baker et al., 2015, with permission. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

2.3. Adolescent development

Continuing the trend observed in childhood, structural connectivity hubs in adolescence have a similar spatial configuration as adults (Fig. 4A), but their connectivity continues to strengthen. One longitudinal study of structural network development between the ages of 15 and 19 mapped changes in edge strength, as measured by both streamline density (number of streamlines connecting two regions weighted by the summed volume of those two regions) and FA, across the entire connectome. These changes were both specific – only 8% of edges showed increased connectivity and 6% showed decreased connectivity – and spatially widespread – 90–93% of brain regions were attached to edges showing developmental changes. Proportionally, connections between hub areas were the most frequently implicated in these changes, with decreased connectivity being observed for links

between subcortical and parietal hubs, and increased connectivity being observed for links between frontal and subcortical, and frontal and parietal hubs (Fig. 5) (Baker et al., 2015). These findings are consistent with studies showing that long-range association fibers show the greatest rates of maturation during adolescence and young adulthood (Lebel and Beaulieu, 2011; Wierenga et al., 2016), and with the well-known extended period of association, in particular frontal, cortex development (Casey et al., 2008, 2005; Gogtay et al., 2004; Hill et al., 2010).

Several studies suggest that the centrality of hub areas, as indexed by measures such as betweenness and nodal efficiency, is largely stable throughout adolescence (Z. Chen et al., 2013b; Hagmann et al., 2010), although some studies have found that frontal and parietal regions increase in degree/strength and nodal efficiency (Dennis et al., 2013; Huang et al., 2015). As mentioned previously, these differences could

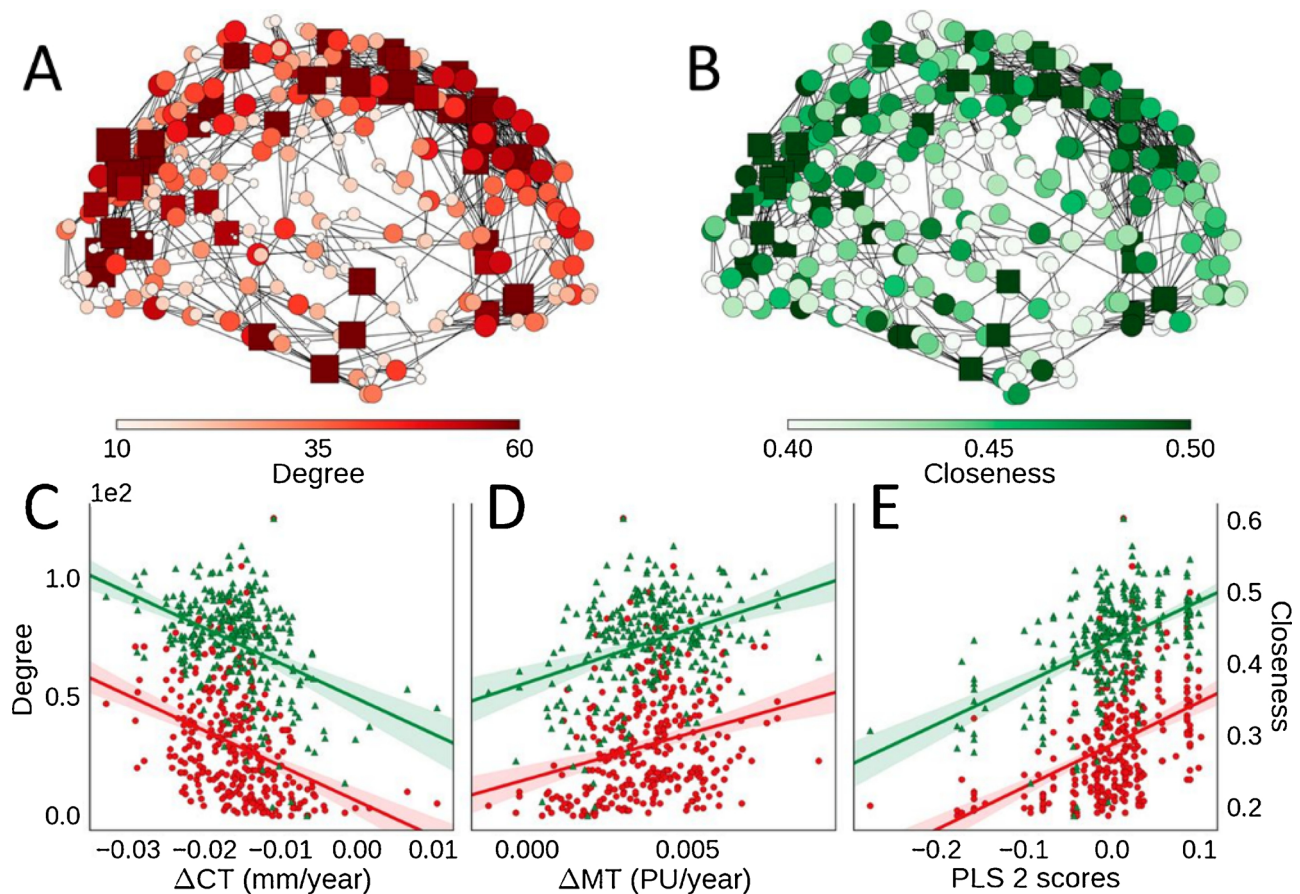


Fig. 6. Consolidation of hubs during adolescence. A) The degree of each node in an adolescent/young adult (14–24) structural covariance network. Square nodes are part of the rich-club. B) The closeness of each node in an adolescent/young adult structural covariance network. Square nodes are part of the rich-club. C) Scatter plot of node degree (red) and closeness (green) with rate of cortical thinning (CT). D) Scatter plot of node degree (red) and closeness (green) with rate of myelination. Nodes with high centrality show higher rates of cortical thinning and myelination in adolescence. E) Scatter plot of node degree (red) and closeness (green) with node loadings on a component, identified through partial least squares, of transcriptional variance across 20,737 genes. Genes associated with this component include those related to synaptic transmission, glutamatergic signalling, potassium iron channels, and oligodendrocyte function. Adapted from Whitaker et al., 2016, with permission (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

be due to different definitions of edge weights and other differences in network construction, such as the tractography algorithm used and the quality of the data.

Structural covariance studies of adolescence find that hubs are in parietal, frontal and temporal association areas (Fig. 6A,B), and that hubs undergo significant microstructural and morphological changes during this period of development (Váša et al., 2018; Whitaker et al., 2016). At the outset of adolescence, hubs are among the least myelinated regions in the brain, but the rate at which hub areas myelinate intracortically during adolescence is higher than for other areas (Fig. 6D) (Whitaker et al., 2016). Thus, enhanced myelination of these areas is thought to be a key driver of decreasing cortical thickness in hubs (Fig. 6C) (Paus et al., 2008), and cortical areas with higher degree and closeness centrality show stronger loadings on a component of variance in the expression of genes regulating oligodendrocyte and synaptic function (Fig. 6E) (Whitaker et al., 2016). However, myelination could not completely explain the observed changes in cortical thickness, suggesting a potential role for synaptic pruning (Váša et al., 2018; Whitaker et al., 2016). Development of cortical association regions, especially frontal areas, parallels the development of executive cognition and other higher-order cognitive abilities (Casey et al., 2008; Spear, 2013), however it is important for future work to understand precisely how these changes in connectivity are related to cognitive development.

In functional connectivity networks, the spatial topography of hubs

largely matches the adult pattern at the outset of adolescence, but the specific way in which functional connectivity networks mature through adolescence remains a topic of contention. Some studies have found that the centrality of functional hub regions decreases (Cao et al., 2014; Zuo et al., 2012), while others have reported evidence of stability (Hwang et al., 2013; Wu et al., 2013). Several studies have indicated that the strength of functional connectivity between hub areas increases, as measured in different ways (Cao et al., 2014; Grayson et al., 2014; Uddin et al., 2011); others have found that changes in adolescence only affect hub to non-hub connections (Hwang et al., 2013). The age range being examined could also influence these results. Studies that have reported consistent levels of hub centrality only examined late childhood, adolescence, and early adulthood (Hwang et al., 2013; Wu et al., 2013) whereas those that found changes in hub centrality looked for trends across the entire lifespan (Cao et al., 2014; Zuo et al., 2012). Thus, developmental changes in hub centrality may only be apparent when looking over a sufficiently long timeframe. In some of these studies, individuals under 20 years of age were either over or under represented relative to the rest of the sample, which may have biased the estimation of developmental trends (Cao et al., 2014; Zuo et al., 2012).

3. Challenges and frontiers

Developmental studies are often fraught with methodological

challenges. For example, many analysis tools in neuroimaging have been designed for application to adult brains, and are not always directly portable to younger cohorts (Howell et al., 2018; Li et al., 2018; Makropoulos et al., 2018). The interpretation of developmental effects in measures of brain structure and function can also be ambiguous (Poldrack, 2010). Network-based analyses introduce an additional set of free parameters which, despite offering greater flexibility in studying developmental processes, often rely on choices and assumptions that can further complicate interpretation. As the field develops, it will be necessary to develop best-practice standards to facilitate comparisons across different investigations.

One of the key challenges of constructing brain networks, both structural and functional, from neuroimaging data is their susceptibility to motion artefacts (Power et al., 2012; Yendiki et al., 2014). These artefacts can lead to both false-positive and false-negative connections, and spurious changes in connectivity strength (Baum et al., 2018; Fair et al., 2013; Satterthwaite et al., 2013, 2012). Different strategies are available for addressing these artefacts. These methods vary in their efficacy and can have a major impact on the findings (Baum et al., 2018; Ciric et al., 2017; Parkes et al., 2018). Head motion is more prevalent in younger cohorts, representing a serious obstacle in assessing the validity and reliability of brain networks during development (Grayson and Fair, 2017; Satterthwaite et al., 2012; Tamnes et al., 2017). Many developmental studies of functional connectivity thus far have used only simple strategies for motion correction, such as linear regression of translation and rotation parameters, that have been shown to be inadequate (Ciric et al., 2017; Parkes et al., 2018). The effects of motion on structural connectivity networks are only beginning to be understood, but it seems that similar contamination is apparent (Baum et al., 2018). As such, head motion artefacts may explain at least some of the inconsistencies found across different studies (Grayson and Fair, 2017).

Careful consideration also needs to be given to how a network is constructed and analyzed. For instance, the choice of whether unweighted or weighted networks are examined should be made judiciously, based on the most appropriate method for evaluating the study hypotheses. The available evidence indicates that the binary topology of the connectome is established very early, prior to birth (Hagmann et al., 2012). It will therefore be important to understand how post-natal development affects variations in structural connection weights, and how these, in turn, shape brain dynamics. The method used for defining connection weights is also a critical consideration, and may influence whether developmental decreases, increases, or even no changes are observed (Cao et al., 2016; Koenis et al., 2015).

The appropriateness of a given centrality method for a specific network should also be taken into consideration. For example, some topological measures may be disproportionately susceptible to slight changes in network structure (Newman, 2010), and in correlational networks, measures such as degree, nodal efficiency, and betweenness can be difficult to interpret (Power et al., 2013; Rubinov and Sporns, 2011). Moreover, most centrality measures examined to date assume a shortest-path form of communication, where information is transferred by a single, direct route. This is not a realistic model for neuronal communication (Goñi et al., 2013), and the contribution of other paths should also be considered (Avena-Koenigsberger et al., 2017; Mišić et al., 2015).

Many developmental studies published to date have relied on small sample sizes, and few have used longitudinal data (Morgan et al., 2018). The field will benefit from the release of large, longitudinal, high-quality developmental datasets such as the ABCD study (Casey et al., 2018; Volkow et al., 2017), Baby Connectome Project (Howell et al., 2018), Developing Human Connectome Project (Makropoulos et al., 2018), IMAGEN (Schumann et al., 2010), and the Lifespan Human Connectome Project Development (HCP-D, 2017). Additionally, the further development of enhanced processing techniques to deal with the specific challenges posed by imaging data acquired in early

development (Howell et al., 2018; Li et al., 2018; Makropoulos et al., 2018) will be important for the field to progress.

One approach that we expect will shed new light on the how hubs emerge in brain networks involves moving from a description of the changes that occur through development to the specification and evaluation of predictive models of developmental processes, based on hypothesized mechanisms. In this work, networks are grown *in silico*, according to specific rules for connecting nodes, as specified by a generative model of network development (see Betzel and Bassett, 2017 for a detailed review of generative models). The networks that emerge under different types of rules can be compared to see which best replicates the properties of actual brains. Several wiring rules thought to mimic plausible mechanisms of hub development have been proposed. One, termed the “old-get-richer” effect (Kaiser, 2017), proposes that regions that begin forming and accepting connections early in development have the longest time to develop connections and therefore become hubs. The evidence we have reviewed here is indeed consistent with an early establishment of hub areas. Another possible mechanism is non-linear growth, in which nodes are added to a network at an exponential rate. Under this model, neural structures divide into finer, more specialized regions, leading to the formation of new areas (Ebbesson, 1980; Kaiser, 2017). This process increases the variance of degree across nodes and results in a right-tailed degree distribution (Bauer and Kaiser, 2017).

Other models have emphasized the role of wiring costs in network formation (Bullmore and Sporns, 2012). In these models, the probability of a connection forming between two regions is inversely related to the distance between them, as has been shown in empirical data (Arnatkevičiūtė et al., 2018; Ercsey-Ravasz et al., 2013; Fulcher and Fornito, 2016). Sometimes, this distance-dependent rule is balanced against another parameter that favors forming connections that are topologically advantageous. For example, one model that has proven successful in capturing several features of adult human brain networks, including modularity, clustering and efficiency, involves a trade-off between penalizing long-range connections and favoring connections between nodes with similar inputs (Betzel et al., 2016; Vértes et al., 2012). However, a limitation of these models is they do not completely reproduce the spatial topography of hubs. A different trade-off model that balanced wiring cost minimization with favoring connections that enhance global network efficiency was able to approximate the location of hubs in *C. Elegans* and the macaque monkey, but it could not replicate the degree distribution (Chen et al., 2013a).

To our knowledge, the only generative model for a connectome that has shown success in predicting the topography of hubs has been posited for *C. Elegans*. This model, which incorporated information on neuronal birth times, the physical growth of the organism, and a trade-off between spatial constraints and nodes preferentially connecting to highly connected nodes, was able to reasonably approximate the presence and location of hubs in the organism (Nicosia et al., 2013). These findings suggest that an interaction between wiring costs, topological value, and developmental staging may lead to the emergence and specific location of brain network hubs. A hitherto unexplored phenomenon is how the geometry of the developing brain interacts with connectome development. When axonal connections are forming near the end of the first trimester (Müller and O’Rahilly, 2006; Vasung et al., 2011, 2010), the brain is over 200 times smaller than an adult (Huang et al., 2009; Tallinen et al., 2016). As the size of the brain increases, this may dynamically change wiring costs throughout development, which may affect which connections are more likely to form at different developmental periods.

The further development of accurate models of hub development may also help understand the mechanisms of developmental disorders. Abnormal hub connectivity is found in numerous neurodevelopmental disorders, including Attention Deficit Hyperactivity Disorder (ADHD), Autism Spectrum Disorder (ASD), and schizophrenia (Crossley et al., 2014). These changes may emerge early on, given evidence that

children and neonates at risk or diagnosed with one of these disorders have dysfunctional hub connectivity (Collin et al., 2017; Lynch et al., 2017; Ray et al., 2014; Shi et al., 2012; Xia et al., 2014). One study using generative network modelling found that differences in functional network topology between patients with childhood onset schizophrenia and healthy controls could be reproduced by tuning the parameters of a generative network model such that the penalty on forming long-range connections was reduced (Vértes et al., 2012). In this way, a series of disparate findings were explained by variations in a single model parameter. Thus, combining both generative models and studies of abnormal connectivity may offer a way to unravel how both normal and abnormal hub connectivity develops.

An additional critical area for further exploration is to understand how hub maturation relates to cognitive development. Relatively few studies have explicitly related hub development to measurable changes in cognition. One might expect that even small changes in hub connectivity could have large effects on cognition, given that complex cognitive processes have been shown emerge following small neuroanatomical changes (Vendetti and Bunge, 2014).

Another avenue that can be used to examine how hub development impacts brain function is using biophysical models of large-scale brain dynamics. These models simulate brain dynamics using systems of differential equations that describe the temporal evolution of population-level (regional) neuronal activity, coupled according to an empirically derived structural connectivity matrix (Breakspear, 2017; Murray et al., 2018). The models have been used to show that rich-club hubs promote functional complexity and synchronization (Deco et al., 2017; Gollo et al., 2015; Senden et al., 2017, 2014; Zamora-López et al., 2010). In principle, one could artificially tune the weights of the structural connectome to simulate different developmental processes, and then examine the impact that this re-weighting has on the resulting dynamics.

4. Conclusions

To summarize, developmental studies of hub connectivity indicate that structural hubs are present from a very early stage, with the binary topology of hub connectivity being established prior to birth and the location of hubs being consistent throughout development. These structural links appear to be immature however, as functional connectivity networks appear to transition through childhood from a topography in which hubs are localized to primary cortical areas to one that mirrors the adult configuration, in which hubs localize mainly to association cortex. This transition appears to be supported by a consolidation of structural connectivity between hubs, which continues into the second and third decades of life, and which appears to be closely linked to ongoing myelination. Despite this broad trend, considerable inconsistencies are found throughout the literature, and there are several methodological limitations affecting current research. The increasing availability of large, well-characterized samples, the refinement of data processing, denoising and network construction algorithms, the development of biologically-grounded models of network growth, and a more concerted effort to understand how network maturation parallels cognitive development will lead to a more detailed picture of the impact that hubs have on the developing brain.

Declarations of interest

None.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.dcn.2018.12.005>.

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