Hubs of Human Brain Networks and their Development (a Review)

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The anatomical arrangement of the human brain can be considered as a network, where distinct regions on the surface of the cortex (grey matter) are considered as nodes, and the set of white matter bundles in between them are taken as edges. A feature common to all structural brain networks is that of hubs: a small set of highly connected or highly important nodes. The present paper reviews how these structures are defined in neuroscientific studies, as well as the nature of their topological importance. It further examines the notion that hubs do not change through the course of development by contrasting the findings and methodologies of the existing literature.

The human brain is known to undergo important developmental changes within the first two decades of life: from birth until age two, drastic pruning of synaptic connections and refinement of the connectivity profile between brain regions takes place (Collin & van den Heuvel, 2013). Within this same early period, myelination of axons is thought to begin (Haynes et al., 2005), a protracted process shown to continue into early adulthood by MRI measures of white matter volume, which also takes place in parallel to reductions in cortical thickness (Giedd & Rapoport, 2010). Research has shown that these refinements to brain structure play an important role in the normative emergence of healthy cognition, affection and behavior; therefore making the brain particularly vulnerable to disease and neurological disorders in the early-life time window (Giedd & Rapoport, 2010). In particular, adolescence represents the period within the human lifespan with the highest risk and incidence of a variety of psychiatric disorders (Paus, Keshavan, & Giedd, 2008). Therefore, understanding how normative development from childhood and until the end of adolescence takes place can provide insight into the ways in which brain maturation trajectories diverge in mental illness.

A convenient approach for the characterization of brain morphology is through a complex networks perspective. Within this context, distinct regions of grey matter of the cortex are considered as nodes, whilst the macroscopic axon fiber bundles connecting them are taken as edges (Bullmore & Sporns, 2009). The resulting representation of the brain as a network is often referred to as a *connectome* (Hagmann, 2005; Sporns, Tononi, & Kötter, 2005). This conceptualization has enabled the identification of the rules that dictate the organization of macro-connections between different brain regions, as well as their common topological properties as measured by graph theoretical metrics (Bullmore & Sporns, 2012), allowing the comparison between healthy and clinical populations (Braun, Muldoon, & Bassett, 2015) and the description of patterns of brain development (Collin & van den Heuvel, 2013; Vértes & Bullmore, 2015).

Understanding the evolution of the connectome from childhood to adolescence is of particular interest, as this has the potential to elucidate the developmental steps leading towards normative brain organization. Therefore, the present review aims at outlining the current state of knowledge concerning one of the main attributes of human brain networks, the presence of hubs (Bullmore & Sporns, 2012). Hubs refer to a few nodes whose importance, as determined by either their number of connections or other metrics, is rather high in comparison to the rest of the nodes in the network (van den Heuvel & Sporns, 2013). To achieve this the topological and biological importance of these special nodes is first highlighted. Following, an in-depth examination on the existing literature concerning their nature within the first two decades of life is provided (see table 1). Finally, the notion that hubs do not change during this period is examined.

Hubs and Their Definition

One of the relevant aspects in the organization of structural brain networks is that connections are not evenly distributed across nodes. Specifically, the probability that a given node has number of connections equal to k, where the number of connections is known as the node's *degree*, is given by a truncated fat-tailed distribution (Iturria-Medina, Sotero, Canales-Rodríguez, Alemán-Gómez, & Melie-García, 2008). This phenomenon signals the existence of a few highly-connected nodes, where the rest are sparsely connected. These outlier nodes are known as *hubs*, and are one of the topological trademarks of brain and other physical networks (Bullmore & Sporns, 2012). However, it can be argued that degree alone is not a sufficient measure for the identification of hubs within a network. More generally, these nodes are taken to be "*positioned to make a strong contribution to global network function*" (van den Heuvel & Sporns, 2013, p. 684). Therefore, this conceptualization ought to consider other measures capable of summarizing the different aspects of a given node's contribution. Consequently, the detection of hubs can be approached through many distinct, but highly correlated, graph theory measures rather than degree alone (van den Heuvel & Sporns, 2013). Some examples of these include betweenness centrality – the number of communication paths that a node participates in-, closeness centrality – the average distance between a given node and the rest of the network-, or eigenvector centrality – a quantity expressing the importance of a node based on whether it is connected to other nodes deemed to be highly important, such as one with high degree (Rubinov & Sporns, 2010; van den Heuvel & Sporns, 2013).

In an ideal situation, important nodes are identified by aggregating their ranking across different measures of *hubness* (Bassett et al., 2008; van den Heuvel, Mandl, Stam, Kahn, & Pol, 2010). However, there is no common protocol for selection of graph metrics in the process of hub isolation, and most studies tend to choose a single measure as their guideline (Baker et al., 2015; Hagmann et al., 2008; Huang et al., 2015). This later approach implies that there will be an ambiguous ranking for nodes who happen to score highly in some measures but moderately in others - i.e. the top three hubs will not be the same in betweenness centrality vs. eigenvector centrality (Sporns, Honey, & Kötter, 2007). However, this issue is mitigated by the fact that nodes -or brain areas- whose importance is most prominent, will still be robustly identified as hubs regardless of the chosen metrics (van den Heuvel & Sporns, 2013). In line with the former, these important regions are commonly found to lie within superior-frontal and parietal areas (Hagmann et al., 2008; van den Heuvel & Sporns, 2013).

Hubs' Contribution to Topology

A crucial remaining question, however, is how the importance of hubs can be understood in terms of a network's spatial arrangement. To answer this, it is relevant to first note that the global

organization of brain networks is characterized according to the principles of a *small-world* topology (Bassett & Bullmore, 2006). Spatially adjacent brain regions tend to have a lattice-like arrangement of highly clustered connections, forming modules which are oftentimes functionally specialized and segregated. However, biologically costly long-distance fiber bundles are found in between these modules, facilitating integration of information exchange and increasing the randomness of the network (Bullmore & Sporns, 2012). The right balance between segregation and integration is what brings about the small-world properties (Watts & Strogatz, 1998); highly clustered modules become easily accessible by virtue of a diminished characteristic path length as facilitated by these long-range connections. What is notable about said connections is that these favor linking to hubs when it comes to the brain (Bullmore & Bassett, 2011; Markov et al., 2011). Thus, hubs reduce the overall steps necessary to reach some node i from any node j (i.e. decrease the characteristic path length), by virtue of both their high degree as well as their propensity to interconnect different modules. However, hubs' contribution to integration is not of a uniform fashion. These structures are embedded within the network's topology in two forms: either as provincial hubs, which preferentially link to nodes within the module they belong to, or as connector hubs, which preferentially connect to nodes in modules other than their own (Guimerà, Sales-Pardo, & Amaral, 2007; Hagmann et al., 2008). Additionally, integration is further enhanced by the propensity of hubs to interconnect with each other at a rate higher than would otherwise be predicted by their degree. The resulting structure is known as the so-called "Rich-Club" (van den Heuvel & Sporns, 2011).

Notably, it appears that the topological properties of brain networks also reflect the functional properties of the connections they represent. For instance, the way in which the brain's anatomical configuration favors functional segregation is echoed in the modular organization of its respective structural networks (Meunier, Lambiotte, Fornito, Ersche, & Bullmore, 2009; Tononi, Sporns, & Edelman, 1994). It can be argued that another example may be found in the rise of higher cognitive processes, such as working memory, problem solving, and planning. These forms of cognition are not distinctly localized within the cortex and are thought to arise through global communication between different regions (Dehaene, Kerszberg, & Changeux, 1998; Singer, 1993). There is evidence that such communication necessitates a structural backbone of axonal interregional projections (Fuster, 1997; Goldman-Rakic, 1988). Interestingly, one of the properties of hub regions is their preferential attachment to long distance intra-modular fibers, an already highly important anatomical role (Hagmann et al., 2008). From a purely graph theoretical perspective, these fibers make hubs an element of network integration. Assuming a close link between mathematical topology and function, it is possible that by virtue of their connections hubs facilitate the emergence of the type of communication necessary in the aforementioned cognitive processes. Potential evidence for this line of reasoning is further emphasized by the fact that brain regions commonly classified as hubs are oftentimes association cortical areas, known to play a role in the unification of multimodal stimuli (Meunier et al., 2009; Sporns et al., 2007).

From the evidence highlighted above, it is reasonable to conclude that hubs play a central role in brain function and behavior. It is therefore unsurprising that these network structures are often compromised in disease, such as in the case of schizophrenia, temporal lobe epilepsy, as well as others (Crossley et al., 2014; Rubinov & Bullmore, 2013). To understand the role of hubs in pathology, it is of importance to first elucidate the mechanisms behind their normative development in roughly the first two decades of life. Specially, since the processes taking place in this time window make the brain particularly vulnerable to adolescent-onset psychiatric disorders (Paus, Keshavan, & Giedd, 2008). Therefore, the following section further explores current

research findings concerning structural changes, or lack thereof, of hubs from childhood to adolescence.

Brain Network Hubs in Development

In the final weeks of gestation, and right after birth, the brain undergoes dramatic changes at the microscopic level (Lagercrantz, Hanson, Ment, & Peebles, 2010). However, even though cortico-cortical connections are also undergoing physiological maturation, these already display features characteristic to the adult connectome. For instance, an MRI study of 27 neonates born preterm -scanned at a gestational age (GA) of approximately 30 weeks- revealed that a modular, as well as a small world organization, are already present in the human brain at this point. Follow up at GA= 40 weeks showed an increase in the small-world index of the neonate's networks, signaling that global configuration is still maturing in the weeks preceding full term birth. Most importantly, the adult-like arrangement was further evidenced by the existence of hubs organized in a Rich-Club configuration upon preterm birth. Among the detected hub regions were the cingulate cortex, as well as subsections of the superior frontal and superior parietal cortices (van den Heuvel et al., 2015), showing some commonalities with adult networks (van den Heuvel & Sporns, 2013). These findings concerning global organization are consistent with connectome studies in full term neonates (Ratnarajah et al., 2013).

Approximately 85% of all cortico-cortical connections found on average in the adult brain are already present at birth (van den Heuvel et al., 2015). By age two, there are almost no discrepancies in the existing macroscopic pathways between children and adult brains. From there, until the end of adolescence, very few white matter axonal connections are being created or pruned (Hagmann et al., 2010). However, these fiber bundles are still undergoing important maturational processes: their white matter volume increases due to escalation of myelination and axonal diameter, and the axons are becoming more aligned and densely packed together; changes which are considered to favor improvement of neural communication (Paus, 2010). These facts imply that, from a strictly topological and unweighted perspective, brain regions regarded as network hubs should not fundamentally change through the course of child-adolescent development. Instead, the significant changes associated with hubs ought to be found in the connections that reach them (Baker et al., 2015).

Variability in Hub-Linked Connections Through Development

Graph theory metrics used to identify structural network hubs rarely consider the brain as a binary system. Rather, weights describing some property of the connections are commonly assigned to the edges, and consequently incorporated in the calculation of the desired metrics (Rubinov & Sporns, 2010). Some of the most commonly weight-described-properties are fractional anisotropy (FA) which is a proxy measure for the integrity of the fiber bundles, number of streamlines (NOS) which represents the amount of connections detected between two ROIs, and probabilistic tractography (PT) which gives the likelihood that two regions are connected given the water diffusion profile of the tracts between them (Beaulieu, 2002; Behrens, Berg, Jbabdi, Rushworth, & Woolrich, 2007; Hagmann et al., 2007). Such measures provide insight into the state of the aforementioned cellular refinement processes taking place along the axon bundles during development (Assaf & Pasternak, 2008). Additionally, they enable us to create a more realistic picture of the network's features, as the fact that not all edges contribute equally is properly acknowledged.

The incorporation of weights into graph metrics potentially explains why some studies report the emergence and fading of certain brain regions as hubs, in the course from childhood to

adolescence. For instance Huang and colleagues (2015) examined differences and commonalities in brain hubs amongst neonates, toddlers (mean age 2.3 years) and preadolescents (mean age 11.8 years). The weight of the connections was given by probabilistic tractography, and a node was classified as a hub when its efficiency was one standard deviation higher than the average efficiency of the network. The study found sets of hubs that were either distinct for the neonate-toddler age groups, or the groups of toddlers and preadolescents. Since the number of connections between any two regions can be considered as stable from childhood to adolescence (Luo & O'Leary, 2005), these findings highlight how changes in the physiology of the macroscopic connections can alter the importance a given node has in the network. Nonetheless, supporting the idea that the most relevant nodes will be robustly identified regardless of the implemented methodology, Huang and colleagues (2015) also found a set common to all age groups: the precuneus, precentral gyrus, and the right cuneus.

However, it is still possible for white matter microstructure to drive longitudinal changes in hub selection when the brain is considered as a binary network (Dennis et al., 2013). The reason behind this is that network construction necessitates algorithmic fiber tract reconstruction, based on the acquired diffusion weighted images of the brain (Hagmann et al., 2010; Wen et al., 2011). Even though sometimes connections between any two regions may exist, if their integrity is not consistent enough or if the measurement is noisy (e.g. motion), it is possible they are missed by the algorithm (Behrens et al., 2007). Thus, as the fiber bundles mature through development, the generated networks of older individuals seem to possess "newly formed" connections or edges. This is illustrated by a study from Dennis and colleagues (2013) comparing both adolescents (ages 12 to 16) and adults (ages 20 to 30). Here, a connection was deemed to exist if at least one streamline connected two given ROIs, yielding an unweighted network. Analyses recognized 14 common high degree nodes (hubs) in both age groups from a total of 18. The discrepancy in the remaining four nodes is attributed by the authors to significant maturational processes capable of influencing the connectome. We speculate that these processes are of such nature that they affect the ability of the MRI and DTI technologies to detect already existing fiber tracts, and thus differences in hubs could be attributable to newly *detected* connections instead of newly *formed* ones. Additionally, it is not possible to rule out other sources capable of introducing variability in edge detection, such as head motion artifact differences between children and adults (Yendiki, Koldewyn, Kakunoori, Kanwisher, & Fischl, 2014).

Nonetheless, most studies work under the reasonable assumption that no new macroscopic connections are created in the brain from age two onwards (Hagmann et al., 2010; van den Heuvel & Sporns, 2013). Therefore, variability in hub structures across studies and developmental trajectories could be attributed to differences in methodology or changes in connection weights, respectively. Consequently, the development of structural brain hubs is better understood by profiling the changes taking place across the connections attached to them. In line with the former, Baker and colleagues (2015) investigated the characteristics of two specific sets of edges suffering significant microstructural changes over the course of late adolescence: a first one containing edges which sustained increases in FA and NOS values between ages 16 to 18, and a second one with edges sustaining a reduction in NOS in the same time period. These sets comprised a relative small proportion of the existing links within the network, however, they tended to connect regions located throughout the entire brain rather than being spatially confined. Most importantly, Rich-Club connections (those bridging hubs with hubs) were proportionally overrepresented in both sets.

Table 1: Methodological variations and results of studies assessing early developmental changes in hubs of the human structural connectome from 2010 to 2015.

Study (Year)	Longitudinal/ Cross-sectional	N	Age range	Connection Weights	Hub identification	Main findings
Hagmann et al., 2010)	Cross-sectional	30 (16 female)	0.8 months – 18 years	SVD	Highest betweenness centrality	Adult-like hubs and modular structure are placed by age two.
Dennis et al. (2013)	Cross-sectional	102 (56 female)	12-16 years	Unweighted*	Not specified	14 adult hubs (from a set of 18) are present in the adolescent connectome.
Ratnarajah et al.(2013)	Cross-sectional	124 (58 female)	Neonates	Streamline Volume Density	Betweenness centrality	Hubs structures are present at birth and are asymmetrically distributed across hemispheres.
Huang et al. (2015)	Cross-sectional	50 (19 female)	0 months – 13 years	Probabilistic Tractography	Highest efficiency	Most hubs change between the neonate, toddler (mean age 2) and preadolescent (mean age 11) age groups; Excepting: bilateral precentral gyrus, bilateral precuneus and right cuneus.
van den Heuvel et al. (2015)	Longitudinal	27 (13 female)	30 weeks GA – 40 weeks GA	NOS	Highest degree	Hubs are a feature of the preterm brain.
Baker et al. (2015)	Longitudinal	31 (13 female)	15-19 years	SVD	Highest degree	Hubs do not change between ages 15 and 19.

SVD = Streamline volume density, which describes the number of streamlines between two ROIs normalized by the sum of their volumes; NOS = number of streamlines; *= the connection was deemed to exist if at least one streamline was present between two ROI's.

The findings by Baker and colleagues (2015) signal that adolescence is associated with changes in the microstructure of a selected group of cortico-cortical connections, and more specifically, that hub-associated network architecture undergoes the bulk of these refinements. Given the relevance of the aforementioned connections for network wide communication (van den Heuvel, Kahn, Goñi, & Sporns, 2012), it is possible that these neurodevelopmental processes have "potentially important implications for… mental health" (Baker et al., 2015, p. 9084). This is further contextualized by evidence that purposeful model attacks on Rich-Club connections have a clear impact on communication capacities within the network, of which behavior is the ultimate outcome (de Reus & van den Heuvel, 2014). Even though model-studies lack a direct neuropsychological link, compromised integrity of the links lying between hub regions has been shown to be a feature of certain psychiatric diseases such as schizophrenia (van den Heuvel et al.,

2013). These findings further support the line of reasoning stating that deviations from the normal course of microstructural refinement within hub-hub fiber tracts can have detrimental outcomes. Therefore, the conclusions from Baker and colleagues (2015) ought to motivate further research on the integrity of connections within hub's network embedding across earlier stages of the lifespan, such as childhood.

Conclusion

It can be stated that hubs are highly important structures within brain network architecture. They have an integrative role which is both reflected in their topological embedding as well as in the functional characteristics of the neuronal populations within them (Bullmore & Sporns, 2012; Sporns et al., 2007). Despite the fact that their identification is prone to variability facilitated by methodological discrepancies across studies, a certain set of hub areas is often robustly identified (van den Heuvel & Sporns, 2013). Moreover, throughout the course of development, the number of connections attached to hubs experience little to no change, and their degree remains constant. Therefore, observed variability on the nodes that are classified as hubs over the first decades of life is partly attributable to maturational changes in the weights of their associated connections. Finally, there is direct evidence that, at least during adolescence, links between hub regions are withstanding a proportionally greater amount of refinements relative to the rest of the connections within the brain (Baker et al., 2015). This signals that the maturation of the set of fiber tracts involved in the characteristic patterns of hub connectivity (i.e. Rich-Club edges) is a complex process of potential importance for behavior and mental health, further highlighting the relevance of hub structures in brain networks.

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