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Brain connectivity in normally developing children and adolescents

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ABSTRACT

The developing human brain undergoes an astonishing sequence of events that continuously shape the structural and functional brain connectivity. Distinct regional variations in the timelines of maturational events (synaptogenesis and synaptic pruning) occurring at the synaptic level are reflected in brain measures at macroscopic resolution (cortical thickness and gray matter density). Interestingly, the observed brain changes coincide with cognitive milestones suggesting that the changing scaffold of brain circuits may subserve cognitive development. Recent advances in connectivity analysis propelled by graph theory have allowed, on one hand, the investigation of maturational changes in global organization of structural and functional brain networks; and on the other hand, the exploration of specific networks within the context of global brain networks. An emerging picture from several connectivity studies is a system-level rewiring that constantly refines the connectivity of the developing brain.

Introduction

The structure and function of neural connections are continuously shaped by several events that constitute brain maturation. Our understanding about these major events has largely been derived from animal models and postmortem studies (Huttenlocher, 1979, 1984, 1990; Huttenlocher et al., 1982a, 1982b; Becker et al., 1984; Bourgeois, 1997; Bourgeois et al., 1994; Huttenlocher and Dabholkar, 1997). Neuroimaging studies provided a paradigm shift by allowing comprehensive *non-invasive* investigation of brain structure and function in humans (Giedd et al., 1999; Gogtay et al., 2004; Raznahan et al., 2011; Shaw et al., 2006a, 2006b; Thompson et al., 2000; Dosenbach et al., 2010; Ameis et al., 2014; Khundrakpam et al., 2015). However, much of the studies to date have focused on focal developmental changes in brain structure and function. As such, detailed description of the developing neural circuitry, especially the changing relationships among disparate brain components, has not been adequately addressed till recently. Recent developments in characterizing brain networks, referred to as the field of 'connectomics' (Bassett and Bullmore, 2009; Bullmore and Sporns, 2009; Bullmore and Bassett, 2011; Evans, 2013; He and Evans, 2010; Khundrakpam et al., 2013; Hagmann et al., 2010a; Sporns, 2011, 2013), have helped untangle maturational changes in brain connectivity and provide evidence for 'connectomic' biomarkers for the detection of neurodevelopmental disorders (Fair et al., 2012; Worbe et al., 2012; Lewis et al., 2013, 2014; Kaiser, 2013).

In this review, we outline a perspective on connectivity in the developing human brain (with focus on childhood and adolescence) and deliberate on how recent advances in the field of 'connectomics' using graph-theoretic approaches have increased our understanding of the maturing brain architecture. We first provide an overview of the major events that occur during normal brain development. Next, we discuss the anatomical and functional MRI studies that have shown focal changes in brain structure and function with development. We then elaborate on traditional approaches (read as, seed-based and region-of-interest (ROI)-based studies) toward understanding brain connectivity in the developing brain. We deliberate on the need for whole-brain connectivity approach and how graph theory provides a valid framework for addressing the same. We then discuss graph-theoretic studies that have been done with several imaging modalities including diffusion tensor imaging (DTI), MRI, and functional MRI (fMRI) in terms of two perspectives: i) whole-brain organizational changes with development as inferred with global topological parameters and ii) system-level changes with development. Lastly, we discuss the mediation of genes and environment in the developing brain.

Brain maturation

Major events during normal brain development

The structural architecture and functional organization of the human brain are continuously shaped by an amazing sequence of events. Fig. 1 depicts the timelines of the important events. Formation of the neural tube, which is completed by gestational age (GA) 4 weeks, is the first major event and is the foundation of all further development. Differentiation of the neural tube occurs from GA 4 to 12 weeks with new neurons formed in proliferative zones (Huttenlocher, 1990; Huttenlocher et al., 1982a; Rakic, 1990). Between

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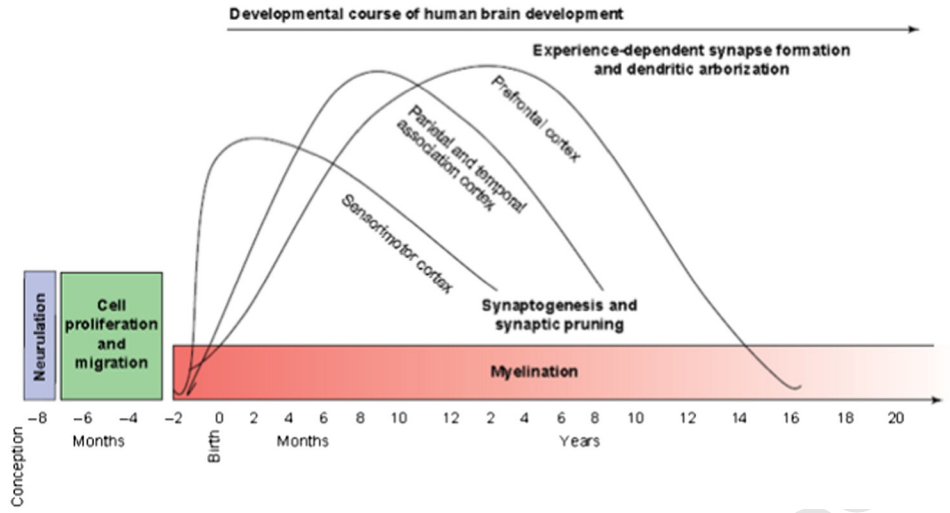

Fig. 1. Important events during normal brain development. Neurulation, cell proliferation, and migration start around gestational age (GA) 4 and 12 weeks. Synaptogenesis and synaptic pruning start around GA 20 weeks and continue till adolescence, whereas myelination starts around GA 30–32 weeks and displays a well protracted maturation till adulthood (Taken with permission from Casey et al., 2005).

GA 12 and 20 weeks, the neurons multiply followed by migration to cortical destinations (Rakic, 1978, 1995, 2003; Hatten, 1993). The migration of neurons is followed by a period of apoptosis (programmed cell death), which results in a massive reduction in the number of neurons (Levitt, 2003; Cowan et al., 1984). It must be noted that synaptic elimination is different from apoptosis, and both processes are vital in early brain development (Levitt, 2003). Between 2 and 7 postnatal years, it is unclear whether synaptogenesis is balanced by elimination of cells and synapses (Becker et al., 1984; Bourgeois, 1997; Bourgeois et al., 1994; Johnson, 2003; Chan et al., 2002; Lossi and Merighi, 2003); however, reduction in the number of synapses is prominent by early childhood (Levitt, 2003; Petanjek et al., 2011). Around GA 29 weeks, the process of myelination starts at the brain stem and continues generally in an inferior-to-superior and posterior-to-anterior path (Levitt, 2003; Paus et al., 2001). Myelination of proximal pathways tends to occur first, followed by myelination of distal pathways (Volpe, 2000). Additionally, cortical myelination seems to mirror functional maturational trajectories, with sensory tracts myelinating before motor tracts accompanied by protracted myelination of association tracts (Huttenlocher, 2002). Use of diffusion tensor imaging, DTI-derived metrics (such as fractional anisotropy, FA) has provided quantitative ways to delineate the heterogeneous cortical microstructural changes that occur during human fetal development (Huang, 2010a, 2010b). Additionally, DTI tractography of well-fixed fetal brains has allowed 3D reconstruction of individual white matter tracts and their developmental patterns (Huang and Vasung, 2014). Findings from such studies have demonstrated the emergence of major white matter tracts such as the corpus callosum, uncinate, and inferior longitudinal fasciculi during GA 13–22 weeks (Huang et al., 2009). Overall, differential development of the white matter tracts has been observed: the limbic tracts being the earliest and association tracts the latest. The commissural and projection fibers seem to develop in an anterior to posterior direction (Huang et al., 2006). Further evidence has also come from a whole brain diffusion tractography study that has shown regional emergence of fetal brain connectivity proceeding from a posterodorsal to anteroventral direction (Takahashi et al., 2012).

Thus, a picture that emerges from these major developmental events is that progressive and regressive forces shape the architecture and development of neural connections. Additionally, these progressive and regressive events (e.g. synaptogenesis and synaptic elimination) have been observed to have distinct regional variations: beginning earlier in primary sensorimotor regions and later in association regions such as the prefrontal cortex (Huttenlocher, 1990; Huttenlocher and Dabholkar, 1997; Petanjek et al., 2011). Interestingly, distinct regional variations in the timelines of the progressive and regressive events (e.g. synaptogenesis and synaptic pruning) are reflected in brain measures at macroscopic resolution e.g. GM density or cortical thickness, as discussed in detail below (Gogtay et al., 2004).

Anatomical MRI studies of brain development

The advent of non-invasive neuroimaging techniques along with advanced image processing tools led to the rapid advancement in our understanding of maturational changes in brain structure. As shown in Fig. 2A, total WM volumes have been shown to increase with age during childhood and adolescence, a trend that continues well into adulthood (Giedd et al., 1999; Shaw et al., 2006b; Lebel and Beaulieu, 2011). The increases in WM volumes with development possibly reflect increasing myelination thereby leading to better connectivity as well as enhanced integration of distributed brain areas. On the other hand, total GM volumes and mean cortical thickness have been shown to follow an inverted U-shaped developmental trajectory (Giedd et al., 1999) (Fig. 2A), possibly indicating synaptic overproduction and pruning (Petanjek et al., 2011).

At the regional level, cross-sectional as well as longitudinal studies have revealed differential patterns of cortical GM maturation, with different areas developing at different rates and different times (Fig. 2B) (Gogtay et al., 2004; Sowell et al., 2003; Shaw et al., 2008). For instance, the age of peak GM density has been observed earliest in primary sensorimotor areas and latest in higher-order association areas such as the dorsolateral prefrontal cortex and the inferior parietal and superior temporal gyri (Gogtay et al., 2004; Sowell et al., 2003). In terms of regional WM maturation, variability in age-related increases has also been observed, with greatest increase in occipital (~2.14% per year) and smaller increase in frontal cortex (~1.37% per year) (Fig. 2C) (Brain Development Cooperative, G., 2012). A picture that emerges from these differential developmental trajectories of regional GM and WM is that the late maturation of frontal white matter in conjunction with late GM maturation of frontal cortex (Gogtay et al., 2004; Sowell et al., 2004) may serve as a scaffold for higher cognitive functions (Shaw et al., 2006a; Casey et al., 2005; Moll et al., 2005; Blakemore and Choudhury, 2006; Jung and Haier, 2007). Indeed, increased white matter maturation with age has been shown to be associated with specific cognitive development: prefrontal–parietal white matter maturation with working memory capacity (Olesen et al., 2003), and fronto-striatal with inhibitory control (Liston et al., 2006). It may be