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Short-range connections in the developmental connectome during typical and atypical brain maturation

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Abstract

The human brain is remarkably complex with connectivity constituting its basic organizing principle. Although long-range connectivity has been focused on in most research, *short-range* connectivity is characterized by unique and spatiotemporally heterogeneous dynamics from infancy to adulthood. Alterations in the maturational dynamics of short-range connectivity has been associated with neuropsychiatric disorders, such as autism and schizophrenia. Recent advances in neuroimaging techniques, especially diffusion magnetic resonance imaging (dMRI), resting-state functional MRI (rs-fMRI), electroencephalography (EEG) and magnetoencephalography (MEG), have made quantification of short-range connectivity possible in pediatric populations. This review summarizes findings on the development of short-range functional and structural connections at the macroscale. These findings suggest an inverted U-shaped pattern of maturation from primary to higher-order brain regions, and possible "hyper-" and "hypo-" short-range connections in autism and schizophrenia, respectively. The precisely balanced short- and long-range connections contribute to the integration and segregation of the connectome during development. The mechanistic relationship among short-range connectivity maturation, the developmental connectome and emerging brain functions needs further investigation, including the refinement of methodological approaches.

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Keywords

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1. Introduction

Information transfer in the human brain at a macroscopic level arises from both interactions between adjacent areas, referred to as “short-range” or local connections, and projections from distant areas, referred to as “long-range” or distant connections, together forming a complex distributed network (Bullmore and Sporns, 2009; Sepulcre et al., 2010). Short-distance connections are thought to predominate both structural (e.g. Hagmann et al., 2008; Ouyang et al., 2016a) and functional networks (e.g. Alexander-Bloch et al., 2013; Honey et al., 2009; Salvador et al., 2005).

During brain development, the interconnections of billions of neurons follow a precisely regulated spatiotemporal sequence that includes neurogenesis and neuronal migration (Rakic 1972, 1995; Sidman and Rakic, 1973), synaptic formation (Huttenlocher, 1979; Huttenlocher and Dabholkar, 1997), dendritic arborization (Sidman and Rakic, 1973; Bystron et al., 2008), axonal growth (Kostović and Jovanov-Milosević, 2006; Innocenti and Price, 2005) and myelination (Miller et al., 2012; Yakovlev and Lecours, 1967). Human brain network topology has been conceptualized as an economic trade-off between minimizing wiring costs through reducing connection distance and allowing the emergence of ‘expensive’ but adaptively valuable topological patterns through increasing connection distance (e.g. Bassett et al., 2010; Bullmore and Sporns, 2012) important for efficient cortical processing (Kaas, 2006; Bullmore and Sporns, 2012). Disturbance of the balance of long-range and short-range connections is thought to be associated with mental disorders such as autism spectrum disorder (ASD) and schizophrenia (SZ) (e.g. Courchesne and Pierce, 2005; Innocenti and Price, 2005; Paus et al., 2008).

Neuroimaging techniques, including functional magnetic resonance imaging (fMRI), diffusion MRI (dMRI), magnetoencephalography (MEG) and electroencephalography (EEG), offered unprecedented insight into brain functional and structural connectivity (Bullmore and Sporns, 2009; Rubinov and Sporns, 2010). Diffusion tensor imaging (DTI) (Basser et al., 1994) is used to quantify the microstructure of white matter (WM) tracts constituting structural connectivity (SC). DMRI-based tractography (e.g. Behrens et al., 2007; Mori et al., 1999) has been widely used to trace fiber pathways. The functional connectivity (FC) can be quantified typically as the Pearson’s correlation coefficient between the blood-oxygen-level-dependent (BOLD) time series from different brain regions with resting-state fMR (rs-fMRI) (Biswal et al., 1995), or the coherence measuring the degree of correlation between spatially discrete electrode groupings in different frequency bands with EEG or MEG (e.g. Engel and Singer, 2001; Lachaux et al., 1999). With the progression of these neuroimaging techniques, brain can be mapped as a complex network at the macroscale. This comprehensive map of brain connectivity consists of a set of nodes (e.g. voxels, regions, sensor and magnetometers) and set of connections between the nodes

also called as edges (e.g. WM pathways from dMRI, functional correlations from fMRI, EEG or MEG) (Sporns et al., 2005). Graph theoretic approaches can be applied to these structural and functional connectivity data, and provides an uncomplicated but powerful mathematical framework for characterizing the topological properties of nodes, edges and the entire network such as modularity, efficiency and hubs (see e.g. Bullmore and Sporns, 2009 for review).

Since the human brain "connectome", a complete set of neural elements (e.g. neurons, brain regions) and their interconnections (e.g. synapses, fiber pathways, temporal signal correlations), became a major NIH neuroscience initiative in 2009 (NIH RFA-MH-10-020), the emergence and maturation of the brain connectivity from around birth to young adults (The Developing Human Connectome Project (dHCP) in Europe and The Lifespan Human Connectome Project of NIH) have been of particular interests. With recent technical advances in neuroimaging techniques towards higher resolution and with specific focus on pediatric populations, short-range structural and functional connections can be delineated to understand typical and atypical brain maturation. For example, currently advanced MRI parameters enhance dMRI spatial resolution to around 1.5mm isotropic (e.g. Yu et al., 2016) in neonatal brain compared to conventional resolution of 2–3mm isotropic. Specific MEG systems tailored for infant brain has also been recently established (e.g. Roberts et al., 2014; Edgar et al., 2015; Okada et al., 2016).

With no comprehensive review on the topic of short-range connections found in the literature, the purpose of this review is to consolidate recent studies relating to short-range structural and functional connectivity in both typical and atypical human brain maturation. We argue that the short-range connections are as neuroscientifically and clinically important as the rather well-studied long-range connections in the developmental connectome during brain maturation. Most of this literature is derived from studies using MRI technique (dMRI and fMRI), with some MEG and EEG studies also included. First, we present a short-range connectivity definition, providing illustrations of short- vs. long-range connections. Second, we describe the major findings in the area of short-range connections during typical brain development. Third, we review findings of short-range connections in neurodevelopmental disorders, focusing primarily on ASD and SZ. Fourth, we identify remaining challenges for short-range connectivity research, including lack of an analytic computational platform tailored for quantification of short-range structural and functional connectivity, and suggest avenues that could be explored for future research.

2. What is short-range structural and functional connectivity?

2.1 Short-range structural connectivity (SC)

SC is usually described as the physical axonal pathways linking sets of neurons at the microscale or fiber tracts linking different brain regions at the macroscale, and their associated biophysical attributes (Sporns, 2007; Johansen-Berg and Rushworth, 2009). SC properties such as length and strength can be characterized using dMRI and dMRI-based tractography. The connectivity strength is usually related to axonal microstructure that can be quantified by dMRI-derived metric measurements. There have been different definitions of short-range SC in the literature (shown in Table 1). One definition of short-range SC is

the connectivity constituted by the fiber tracts connecting adjacent gyri (e.g. Ouyang et al., 2016a, 2017a, 2017b; Im et al., 2014, 2015). Most of these axonal fibers are located in superficial WM (SWM) regions (Dejerine, 1895; Meynert, 1872), in contrast to well-defined long axonal fiber bundles located in deep WM (DWM). This definition of short-range SC, shown in Fig 1A, is consistent with anatomically well-defined U-fibers or short-range association fibers (SAFs) (Meynert, 1872). Short-range SC under this definition, therefore, is proposed in this review. As a (partial) alternative, other definitions of short-range SC include the connectivity constituted by fibers less than a certain physical distance regardless of their location (e.g. Shukla et al., 2011; Guevara et al., 2017).

2.2 Short-range functional connectivity (FC)

FC is usually referred to as the degree to which neural activity in one brain region correlates with neural activity in another brain region (David, et al., 2004; Friston, 1994). FC can be quantitatively characterized by fMRI, EEG and MEG. There have been different definitions of short-range FC, also described as local FC, in the literature (shown in Table 2). One definition of short-range FC is the FC between the regions close in space measured by Euclidean distance (e.g. Sepulcre et al., 2010), ranging from 12mm (Mueller et al., 2013) to 75mm (e.g. Guo et al. 2014, Liang et al 2013, Guo et al 2015), to be differentiated from long-range FC. Short-range FC, quantified as regional homogeneity (ReHo) (Zang et al., 2004), has also been defined as the connectivity of a given voxel to those of its nearest neighboring voxels, ranging from 6 voxels (Shukla et al., 2010) to 26 voxels (e.g. Anderson et al., 2014; Dajani and Uddin, 2016; Lopez-Larson et al., 2011). In addition, short-range FC has been defined as the connectivity within the same lobe (e.g. Ghanbari et al., 2015; Repovs et al., 2011; Sala-Llonch et al., 2014). Short-range FC defined by FC with less than a certain Euclidean distance and within neighboring voxels are essentially the same. Short-range FC under this definition, as illustrated in Fig 1B, is proposed in this review.

3. Typical development of short-range connectivity and its role in developmental connectome

Short-range connections, serving as part of the cortico-cortical networks, have been investigated with neural histology (e.g. Meynert, 1972) and radiographic tracing (Schmahmann and Pandya, 2006) previously. The connections are characterized by the overproduction of axons, axon branches and synapses followed by selective pruning (Innocenti and Price, 2005; Huttenlocher and Dabholkar, 1997). It has been suggested that the development of exuberant connections followed by pruning represents a fundamental mechanism in the development and tuning of neural circuits and brain networks (Innocenti and Price, 2005). More recently, the development of noninvasive neuroimaging modalities capable of studying this process *in vivo* has provided new insights into the development of short-range SC and FC in both normal development and developmental disorders.

3.1 Typical maturation of short-range structural connectivity and its role in developmental structural connectome

Short-range SC, reflected by SAFs located in SWM regions, is characterized by unique and spatiotemporally heterogeneous dynamics throughout infancy to adulthood. The

maturational process of short-range SC, along with other significant maturational processes, is illustrated in Figure 2. SAFs are among the slowest to myelinate, and may remain incompletely myelinated until the third decade of life (Barkovich, 2000; Parazzini et al., 2002; Wu et al., 2016). Major SAF tracts located in SWM have been identified reproducibly among the adult human brains (Oishi et al., 2008; Zhang et al., 2010a; Catani et al., 2012; Guevara et al., 2012; Guevara et al., 2017) and macaque brain (Zhang et al, 2010b; Oishi et al., 2011) using dMRI-based tractography. It is likely that these reproducibly traced SAFs are those below the dense WM zones beneath the infragranular layers of the cortex (Reveley et al., 2015). Unlike long association fibers (LAFs) that usually project along the direction perpendicular to the cortical surface to another cortical regions distal from the projection region, the SAFs run mostly parallel to the cortical surface and connect two adjacent gyri.

DTI-derived metrics (i.e. fractional anisotropy (FA), mean, axial and radial diffusivity (MD, AD and RD)) and measures (i.e. fiber number and fiber length) from dMRI-based tractography are often used to quantify the microstructure of SWM and SAF pathways, respectively. In infants with postmenstrual age from 26 to 40 weeks, it was observed that FA increased and MD decreased in SWM of primary motor, primary visual, visual association and prefrontal brain regions with age (Smyser et al., 2016). During late childhood and adolescence (10–18 years), it was found that FA increased with age in most of SWM at a depth from 1 mm to 5 mm at the GM/WM boundaries, including but not limited to bilateral precentral, orbitofrontal cortex (OFC), insula, bilateral posterior cingulate, bilateral superior temporal and left lingual, while MD, and RD decreased in SWM underneath bilateral motor sensory cortices and superior temporal auditory cortex (Wu et al., 2014). Within a similar age range of 9 to 19 years, increased FA were reported in SAFs with a fiber length from 4 mm to 35mm in frontal, parietal and temporal lobes of typical developmental brains (Shukla et al., 2011). Based on measures of SAF pathways, it has been found the ratio of the fiber number of whole brain SAFs in the entire brain cortico-cortical connectivity fibers decreased with age from 2 to 16 years then followed by an increased from 16 to 25 years (Ouyang et al., 2016a). The developmental pattern of SAFs quantified as fiber volume traced from postcentral gyrus (PoCG, the primary somatosensory cortex) is illustrated in Figure 3 as an example.

Short-range SC plays a pivotal role in the brain structural network development. The monotonic increase of brain structural network strength and efficiency, and the decrease of clustering coefficients and small-worldness through infancy and childhood, suggest that the integration increase and segregation decrease of the human brain structural network start as early as birth and continue until the onset of adolescence (Huang et al., 2015). The network density and network mean strength contributed by SAFs (connecting the first neighboring gyri) are relatively lower compared to long-range connections, with lower FA, MD and AD but higher RD values of the SAFs (Im et al., 2014; Im et al., 2015). Nevertheless, SAFs play significant role in reshaping the developmental connectome. A few recent studies on structural network of developing brains (e.g. Dennis et al., 2013; Hagmann et al., 2010; Huang et al., 2015; Yap et al., 2011) suggested that emergence of the maturing brain networks are associated with both enhancement of some WM fibers and elimination of other fibers. Network-based measurements of local connectivity efficiencies were found to decrease significantly, possibly due to synaptic pruning (Huang et al., 2015). In addition, the

normalized whole brain SAFs fiber number decrease was associated with an increase in brain network efficiency in typical brain development from 2 to 7 years (Ouyang et al., 2017a). From the aspect of wiring "cost", a decrease in the fraction of 'low wiring-cost' short-range connection and the emergence of 'expensive' long-range connections could result in higher efficiency of information transfer between distant brain regions.

Based on the summarized studies of short-range SC listed in Table 1, an inverted U-shaped developmental course of short-range SC changes from birth to adulthood was suggested, as illustrated in Figure 5A. In addition, the developmental trajectories of regional SAFs also vary across cortical regions reflecting the earlier maturation of primary sensorimotor cortex and later maturation in higher-order association cortices like prefrontal cortex (Ouyang et al., 2016a; Phillips et al., 2013), as illustrated in Figure 5B. This pattern is similar to DTI studies of deep white matter (DWM) maturation (e.g. Lebel et al., 2008; Delpolyi et al., 2005; McKinstry et al., 2002), and structural MRI study of GM volume (e.g. Gogtay et al., 2004) that show prefrontal cortex mature after lower-order somatosensory and visual cortices.

3.2 Typical maturation of short-range functional connectivity and its role in developmental functional connectome

Knowledge of short-range FC is derived primarily from investigations using the rs-fMRI technique, which measures connectivity by examining the task-independent levels of co-activation (baseline BOLD signal) between brain regions to investigate the spatially distributed connectivity networks (Biswal et al., 1995). The connectivity patterns obtained from rs-fMRI are thought to reflect the stable and intrinsic functional architecture of the brain (Buckner et al., 2009).

A few studies have reported on short-range FC changes in the early development period. With *in utero* fMRI, short-range FC has been found to increase with the gestational age in fetuses during the second trimester (Jakab et al., 2014). For the early developmental newborn brains from 31–42 postmenstrual weeks (PMW), age-related FC strength increases were found primarily in the connections of short to middle distance, as shown in Figure 4 (Cao et al. 2016). A longitudinal study focused on preterm infants aged from 26 PMW through term equivalent age showed a prevalence of short-range FC, with long-range FC identifiable only in older infants and between more midline locations (Smyser et al. 2010). In contrast, from late childhood to adulthood, the short-range FC of the whole brain was found to decrease. Age-dependent changes of short-range FC have also been shown to be heterogeneous across functional networks. For example, intrinsic connectivity networks (ICNs) related to complex social and emotional processing exhibit the largest increase in long-range FC and decrease in diffuse short-range FC (Kelly et al. 2009). While a general reduction of short-range FC throughout the whole brain was demonstrated as subjects aged, the cingulate and right temporal lobe (Lopez-Larson et al. 2011), and the subcortical grey nuclei (Anderson et al. 2014) exhibited a stark decrease. The weakened short-range FCs may serve as a good predictor of brain maturity as indexed by chronological age (Dosenbach et al. 2010). These results support the idea that during development systematic pruning

improves brain efficiency and eliminates redundancy in brain networks (Supekar et al., 2009).

The developmental functional connectome is reconfigured through the integration and segregation processes, contributed by increasing long-range FC and decreasing short-range FC, respectively (Cohen et al., 2008; Fair et al., 2007; Fair et al., 2009). The integration and segregation are spatiotemporally varying in typical brain maturation. For example, a gradually enhanced functional network segregation was reported in the third trimester, which is primarily driven by the rapid increase of short-range FC of the primary functional regions (Cao et al., 2016). Although as early as second and third trimesters of pregnancy inter-hemisphere long-range FC between primary functional regions has been demonstrated to exist and increase with age in healthy fetuses (Thomason et al., 2013, 2015; Jakab et al., 2014), the development of long-range FC mainly involved in global information integration occurs mostly after birth (e.g. Gao et al., 2009; Dosenbach et al., 2010; Fair et al., 2009; Supekar et al., 2009). A study for developmental brains aged from preterm to 4-year reported networks changes from strong local connectivity into an interhemispheric network (Lee, et al. 2013). These findings suggest a transition from a more local to a more distributed organization during development, likely the result of age-dependent systematic pruning of short-range FC (Supekar et al. 2009).

Taken together, the typical maturational process of short-range FC is characterized by spatiotemporally heterogeneous dynamics, with overall strengthening of short-range FC in early development followed by weakening of short-range FC in later stage. Based on the summarized studies of short-range FC listed in Table 2, an inverted U-shaped developmental course of short-range FC changes from birth to adulthood was also suggested, similar to that of short-range SC with a possible delay, as illustrated in Figure 5A.

4. Atypical development of short-range connectivity in human brain

ASD and SZ are two common developmental brain disorders that are associated with alterations in short-range connectivity. ASD is possibly associated with “hyperconnectivity” and SZ associated with “hypoconnectivity” in short-range connections, but such association between ASD or SZ and hyper- or hypo-connectivity is not conclusive. Aberrant short-range connections have also been observed in other brain disorders such as Alzheimer’s disease (e.g. Carmeli *et al.*, 2014; Fornari *et al.*, 2012; Phillips *et al.*, 2016a), tuberous sclerosis complex (e.g. Im et al., 2015), Huntington’s disease (e.g. Philips et al., 2016b) and Tourette’s syndrome (e.g. Wen et al., 2016). It is beyond the scope of this review to discuss all brain disconnectivity in greater depth (for review on disconnection syndromes, see e.g. Catani and ffytche 2005; Geschwind. 1965a, 1965b). In this review we focus exclusively on short-range connections changes in ASD and SZ, as they are two common and complex spectrum disorders with possible early clinical onset (toddler age for ASD and childhood-onset for SZ), highly related to developmental connectome, and manifesting no readily observed alterations in structural brain appearance or morphometry.

4.1 Atypical maturation of short-range connectivity in autism spectrum disorder

ASD is a complex neurodevelopmental disorder with multiple causes (Peñagarikano *et al.*, 2011; Zhao *et al.*, 2007) and can be behaviorally defined based on impairments in communication and social interactions, repetitive and ritualized behaviors, and restricted interests (American Psychiatry Association (APA), 2013). It affects 1 in every 68 children as reported a Center for Disease Control and Prevention survey done in 2012. ASD has been extensively studied during brain development using neuroimaging methods such as fMRI, EEG/MEG and dMRI. One of the most striking findings in ASD is that the pattern of local or short-range "hyperconnectivity" has been frequently suggested in the brain of individuals with ASD (Belmonte *et al.*, 2004; Courchesne and Pierce, 2005) especially in young age groups (Rudie and Dapretto, 2013). Short-range hyperconnectivity in ASD contrasts with typically observed long-range "hypoconnectivity" (e.g. Monk et al., 2009; Ouyang et al., 2016b; Travers et al., 2012).

With fMRI, short-range FC was found to increase bilaterally in temporo-occipital regions of adolescents with ASD (Keown *et al.* 2013). In slightly younger individuals with ASD (7–13 years), hyperconnectivity was observed in the whole brain and also at the subsystems levels in both long- and short-range connections and the strength of hyperconnectivity correlated with the symptom severity in ASD (Supekar *et al.* 2013). In another study with a large age range (6–40 years) (Long *et al.*, 2016), both short-range (<30mm) and long-range (>90mm) FC were found to decrease, but no change was observed in medium-range FC (>30mm and <90mm) in posterior cingulate cortex and medial prefrontal cortex regions in individuals with ASD. In studies that incorporated ReHo analyses of fMRI data, there was an increase in short-range connectivity in default-mode network (DMN), visual, motor resting-state networks in individuals with ASD (6–17 years) (Washington et al., 2014) while other studies found more mixed results such as both hypo- and hyperconnectivity of short-range connections (e.g. Dajani and Uddin, 2016; Maximo et al. 2013; Shukla et al., 2010). Specifically, individuals with ASD showed decreased short-range FC in superior parietal and prefrontal regions (Shukla et al., 2010), middle/posterior cingulate and medial frontal regions (Maximo et al., 2013), sensory processing brain regions (Dajani and Uddin, 2016) and increased short-range FC in lateral and medial temporal regions (Shukla et al., 2010), occipital and posterior temporal regions (Maximo et al., 2013) and complex information processing regions (Dajani and Uddin, 2016). In general, short-range "hyperconnectivity" was suggested for children with ASD. Some mixed findings in these studies might be related to varying age ranges, data acquisition, processing method, the different definition of short-range (or local) connectivity, as well as intrinsic heterogeneity of the ASD population, which challenges the generalizability of studies with small sample size.

Short-range FC in ASD has also been studied using EEG and MEG. Alterations in short-range connectivity in ASD was reported in a region-specific and frequency-dependent manner in these studies (e.g. Barttfeld et al., 2011; Ghanbari et al., 2015; Khan et al., 2013; Khan et al., 2015; Ye et al., 2014). Using EEG data acquired during resting state in participants with ASD, there was an increase of short-range connectivity in lateral-frontal regions of delta band, low frequencies ranging from 1–4 Hz, and this short-range coherence was more pronounced as ASD severity increased (Barttfeld et al., 2011). Similarly, studies

examining the resting state brain activity in ASD with MEG reported increased short-range connectivity in ASD in the frontal lobe in the delta band (Ghanbari et al. 2015), as well as temporal and subcortical regions in beta (15–30Hz) and gamma (above 30 Hz) bands (Ye et al., 2014). Decreased short-range connectivity ASD was also observed in the fusiform face area (Khan et al., 2013) and somatosensory cortex (Khan et al., 2015) in task-based MEG studies.

Prior studies have shown abnormalities in WM microstructure and alterations in long-range connectivity in individuals with ASD (e.g. Alexander et al., 2007; Barnea-Goraly et al., 2004; Monk et al., 2009; Ouyang et al., 2016b). The studies on SAFs in ASD revealed atypical WM microstructure indicated by decreased FA and increased MD and RD (Shukla et al., 2011; Sundaram et al., 2008). Schukla et al found reduced FA, increased MD and RD in SAFs (fibers with 4–35mm length) in frontal lobe, and increased MD and RD in SAFs in temporal and parietal lobes SAFs in children with ASD in the age range of 9 to18 years. Sundaram et al (Sundaram et al., 2008) reported reduced FA of SAFs (defined as intra-lobe fibers) in frontal lobe in children with ASD with age of 4.8±2.4 years, but no difference in averaged SAFs fiber length or total number between ASD group and typical developing group. Focusing on the normalized SAF fiber number, Ouyang et al (Ouyang et al., 2017b) revealed that the normal decrease of short-range SC in prefrontal and posterior-cingulate cortex did not occur for children aged 2–7 years with ASD, suggesting “structural” hyperconnectivity. Future research is needed to test the reproducibility of global and regional short-range structural hyperconnectivity in children with ASD using dMRI-derived metric measurement and dMRI-based tractography.

With graph theory analysis, alterations in both functional and structural brain network organization in ASD have been shown (e.g. Rudie et al., 2013; Keown et al., 2017; Fishman et al., 2015; Itahashi et al., 2014). Reduced functional integration with weaker short and long-range connectivity within functional systems, and reduced functional segregation with stronger connectivity between functional systems were found in individuals with ASD (Keown et al., 2017; Fishman et al., 2015; Rudie et al., 2013). The topological properties of functional networks exhibited a randomized tendency of segregation with reduced local efficiency (Rudie et al., 2013), and reduced clustering coefficient (Itahashi et al., 2014) in ASD. In structural network, contrary to increased global efficiency with age in healthy individuals (Hagmann et al., 2010), global efficiency was found decreased with age in individuals with ASD (Rudie et al., 2013; Ouyang et al., 2017a), indicating the network efficiency does not appropriately shift from a more local to a more distributed pattern during brain development of ASD. Such a more prominent local pattern of network efficiency may be due to the hyperconnectivity of short-range connections in individuals with ASD.

4.2 Atypical maturation of short-range connectivity in schizophrenia

SZ is a debilitating, psychiatric disorder characterized with mental impairments including hallucinations, delusions, avolition, apathy, anhedonia, and loss of cognitive functions across multiple domains (Tandon et al., 2009). It affects around 1% of the worldwide population, about 24 million people (Abi-Dargham, 2014). The onset of SZ usually falls in late adolescence, a time most critical in psychological development (Paus et al., 2008; Gogtay et

al., 2011). It has been suggested an aberrant brain developmental trajectory and dysconnectivity play important role in the pathophysiology of SZ (Murray et al., 1987; Weinberger, 1987). Opposite to the “hyperconnectivity” of ASD, a “hypoconnectivity” pattern of brain connections was suggested in individuals with SZ due to an exaggeration of the synaptic elimination or pruning (Feinberg, 1983; McGlashan and Hoffman, 2000; Paus et al., 2008), especially for those with childhood-onset or early-onset SZ (mean age of onset <10 years).

Inconsistent findings were reported in prior fMRI studies related to short-range FC in SZ patients (e.g. Alexander-Bloch et al., 2013; Guo et al 2014; Guo et al. 2015; Jiang et al. 2015; Repovs et al., 2011; Su et al., 2015; Wang et al., 2014). Increased short-range FC has been found in left superior medial frontal gyrus (Guo et al., 2015), right superior frontal gyrus (Jiang et al., 2015), DMN (Repovs et al., 2011), subcortical system and interhemispheric links (Guo et al., 2014) in patients with SZ. On the other hand, reduced short-range connectivity in the right postcentral gyrus, left middle occipital cortex (Jiang et al., 2015) or in a whole brain manner (Alexander-Bloch et al; 2013; Wang et al., 2014) has been shown. Interestingly, reduced short-range FC strength is more likely found in early-onset SZ than late-onset SZ (Alexander-Bloch et al., 2013; Jiang et al, 2015). Moreover, the symptom scores of SZ (i.e. Positive and Negative Syndrome Scale or PANSS) also correlated with the strength of short-range connections but not long-range connections in SZ (Jiang et al., 2015; Su et al., 2015), indicating an important role of short-range connections in the brain maturation of patients with SZ. Overall, it can be concluded that alterations of short-range connections take place in SZ, but it is not certain that “hypoconnectivity” is the alteration. The inconsistency might be related to varying factors including age of SZ onset, age range of the subjects with SZ, medication usage (i.e. minimally treated vs medication naive), methodological differences, as well as the different definition of short-range (or local) connectivity.

Short-range SC studies in SZ are relative fewer than FC studies, and several dMRI studies reported alterations of SWM microstructure in several brain areas in SZ patients compared with healthy controls (Phillips et al., 2011; Nazeri et al. 2013). Specifically, reduced SWM FA values of SZ patients have been found in left temporal, bilateral occipital regions (Phillips et al., 2011), left posterior parieto-occipital (including lateral occipital cortex, precuneus and posterior cingulate cortex) and left frontal regions (Nazeri et al., 2013). Also, the SWM FA in the left frontal region predicted attention, working memory and processing speed performance in healthy individuals, but not in patients with SZ (Nazeri et al., 2013).

Numerous topological alterations of structural and functional brain networks have been found in SZ with graph theory analysis. Reduced hierarchical organization (e.g. Bassett et al., 2008), reduced modularity (Alexander-Bloch et al., 2010 and 2013), less clustering and small-worldness (e.g. Liu et al., 2008; Lynall et al., 2010) were found in the brain network organization of individuals with SZ. These topological disruptions in SZ are predicted given the greater mean connection distance between the most strongly connected brain regions, and these abnormalities of network properties observed in SZ, like less clustering and less modularity, suggested an aberrant neurodevelopmental process favoring proportionally fewer short-range connections (Alexander-Bloch et al., 2013).

4.3 Summary of aberrant maturation of short-range connections in ASD and SZ

A pattern of short-range hyperconnectivity appears to occur in individuals with ASD, especially in early childhood (e.g Keown *et al.* 2013; Supekar *et al.* 2013; Rudie and Mapretto, 2013), while early-onset or childhood-onset SZ is associated with short-range hypoconnectivity (e.g. Alexander-Bloch et al., 2013; McGlashan and Hoffman, 2000), as suggested by sketch plot of Figure 5C. Since the pathogenic mechanisms for “hyper-” and “hypo-” short-range connections in ASD and SZ are not clear, these short-range connection patterns associated with ASD and SZ are possibly the consequence of atypical synaptic pruning during development (e.g. Feinberg, 1983; McGlashan and Hoffman, 2000; Tang et al., 2014). Although neuroimaging studies cannot immediately address the question of whether dysconnectivity in ASD or SZ is primarily synaptic or axonal pruning, these findings help to clarify the neuroimaging phenotype of alterations in short-range connectivity. Direct measurement of the elimination of short-range connections holds the key to filling an existing knowledge gap of developmental connectomics during typical and atypical brain maturation.

5. Future directions, methodological considerations and conclusion

In this review, we have consolidated findings on short-range connectivity in human brain during typical and atypical brain maturation. Several key attributes of short-range connectivity maturation were inferred from the studies. First, an inverted U-shaped developmental course was likely for both age-dependent short-range SC and FC, with maturation of short-range FC slightly behind that of short-range SC. Second, the maturation of short-range SC and FC is spatiotemporally heterogeneous, with the short-range connectivity in prefrontal lobe developing latest and that in primary sensorimotor brain areas earliest. Third, a suite of studies suggest that ASD or SZ are associated with aberrant maturation of short-range connections.

5.1 Future directions

Understanding short-range connections in typical and atypical developing brains is still in its infancy. Among a few important future directions, the mechanistic relationship between the short-range connection maturations and the developmental connectome requires further investigation. Neurogenesis, axonal growth, and synaptic pruning (Huttenlocher and Dabholkar, 1997; Innocenti and Price, 2005) have been considered as the major factors for reshaping the developmental networks. Such cellular processes are precisely regulated by spatiotemporal transcriptomic profiles (Silbereis et al., 2016). However, accurate and reliable measurements of these cellular processes are at microscale levels. The bridge between these microscale neuronal processes and macroscale connectome reconfiguration has not been established and, obviously, even the ~1mm resolution of modern neuroimaging does not approach cellular scales. Contemporary noninvasive neuroimaging techniques can be only used to “infer” these cellular processes. The existing literature has jointly suggested the maturational sequence from primary sensorimotor to higher-order cognitive brain functions. The emergence of a specific brain function is typically associated with rapid growth and subsequent pruning of short-range connections from certain brain regions characterized with this function. Nevertheless, the exact mechanism of short-range connections underlying

emerging primary or higher-order cognitive function is unknown. With cellular (e.g. Bourne et al., 2004; Rakic et al, 1986) and MR imaging (e.g. Belcher et al., 2013; Modha et al., 2010) approaches widely used in non-human primate models including marmoset and macaque, integrating information from both approaches may reveal the spatiotemporal relationship between the microscale cellular processes and macroscale short-range connections. Ultra-high-resolution optical methods such as CLARITY (Chung et al., 2013) may provide insights into the mechanistic relationship among the short-range connection maturation, developmental connectome and emerging brain functions in animal models.

Another important direction is to delineate how developmental changes in short-range SC reconfigure brain structural networks. A few studies have been conducted to understand the role of short-range FC in reshaping brain functional networks. Specifically, it has been revealed that the maturation of functional connectome is through the process of integration by increasing long-range FC and segregation by decreasing short-range FC (Cohen et al. 2008; Fair, et al. 2007; Fair et al. 2008, Cao et al., 2016), using rs-fMRI and graph theory. Similarly, further studies can be conducted using dMRI to investigate the role of short-range SC in reconfiguring developmental structural connectome. By integrating short-range FC and SC, knowledge on how short-range SC maturational processes underlie those of short-range FC in typical and atypical (e.g. ASD and SZ) human brain development is also needed. Other important future directions include investigating the relationship between short-range connectivity and cognitive development, and the relationship between short-range connectivity and behavioral maturation. All these studies on brain maturation would particularly benefit from longitudinal studies that would allow tracking of developmental trajectories of short-range connectivity within individuals. Elucidating the relationship between developmental trajectories of short-range connectivity and those of network organization, and the relationship of developmental trajectories of short-range connectivity and those of cognitive or behavioral characteristics of an individual may lead to early identification of biomarkers and subsequent early intervention for neurodevelopmental disorders.

Short-range WM fibers constituting short-range SC are not well delineated by dMRI tractography at various developmental periods, while long-range WM fibers have been systematically characterized in fetal stage (e.g. Huang et al., 2009; Takahashi et al., 2012; Mitter et al., 2015), infancy (e.g. Huang et al, 2006; Dubois et al. 2008; Jeon et al., 2015; Mishra, et al., 2013; Yu et al., 2014), childhood and adolescence (e.g. Lebel et al., 2012), and adulthood (e.g. Catani and de Schotten, 2008; Wakana et al., 2004; Huang et al, 2011). The definitions of short-range connectivity are still varying across different studies. As discussed in the previous section (see details in *Section 2.1 and 2.2*), without a common definition of short-range FC and SC (see details in Table 1 and 2), it becomes more complicated to integrate or compare findings from different studies on short-range connectivity. A clear well-defined short-range SC and FC across different ages and brain regions proposed in this review will facilitate systematic research in understanding short-range connections in developmental connectome.

5.2 Methodological considerations

The major methodological consideration is lack of analytic platforms dedicated to quantification of short-range FC and SC. Most of the approaches in rs-fMRI are developed for adult brain studies, while analyzing short-range FC of developmental brains needs age-specific brain templates and parcellation for image processing such as seeded region of interest (ROI) selection. For those early developing brains, the ROIs of higher-order brain functions in adult brains do not exist. With relatively small brain sizes, higher resolution is also required to delineate the short-range connections in local regions for the developmental brains. Since fMRI data is usually acquired at comparatively lower resolution and for longer duration (scan time) than structural imaging such as T_1-weighted or dMRI imaging, the registration to structural images and removal of motion artifacts across the imaging series forms an important step. Errors in this step are especially more prominent in studying developmental brains with the smaller brain sizes. The situation becomes more complicated in larger group studies where the fMRI data is averaged across the spatial and temporal domains. The seed-based (ROI) analysis of rs-fMRI is not very robust in identifying the temporal similarities of time series in structurally close regions (Sepulcre et al., 2010). In addition, it is important to acknowledge that the potential effect of head motion on FC measurements may lead to erroneous conclusions, especially when populations with different levels of head motion during fMRI acquisition are compared (e.g. Deen and Pelphrey, 2012 for head motion in ASD study). For short-range SC, while dMRI is relatively superior in resolution compared to fMRI studies, it also relies heavily on the computer-based methods using prior information about the WM tracts (deterministic tractography or probabilistic tractography). Current available dMRI-based tractography algorithms are known to suffer from false positives, especially in periventricular regions (e.g. Maier-Hein et al., 2016). All these challenges are further amplified in studies that involve developmental brains as there is no reliable way to check the accuracy of the trajectories due to lack of comprehensive and longitudinal dMRI atlas for developing brain. Recently the brain connectome studies have led to well developed software tools to understood DWM trajectories. However, significant improvements in the tools for tracking and visualizing the short-range connections in developmental human brain are still needed. For example, dMRI-based tractography tends to oversimplify the underlying neuroanatomy, which may lead to inaccurate estimation of the fiber orientations in complicated brain regions like SWM (Reveley et al., 2015; Zhang et al., 2010a).

5.3 Conclusion

Despite technical challenges in delineating the spatiotemporal patterns of short-range connections in brain development, recent neuroimaging advances have ushered a new era in which short-range FC and SC could be quantitatively characterized. As a major component of information transfer inside the human brain, short-range connectivity in typical brain development is characterized by unique and spatiotemporally heterogeneous dynamics throughout infancy to adulthood. Numerous studies suggest an inverted U-shaped pattern in the number of short-range connections across development, with functional trajectory slightly lagging behind structural trajectory and earlier maturation in primary sensorimotor cortices as compared to association cortices. The balance of short- and long-range connections play a critical role in segregation and integration processes of developmental

connectome. Alterations in developmental maturation of short-range connections are associated with neuropsychiatric disorders such as ASD and SZ, which are respectively characterized “hyperconnectivity” and “hypoconnectivity”. With investigation of short-range connections still in its early stage, important questions remain to be answered to reveal mechanistic relationship among the short-range connection maturations, the developmental connectome and emerging primary or higher-order cognitive functions. Research in this area will benefit from further methodological improvements including developing an analytic platform tailored for quantification of short-range SC and FC in developmental brains.

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Highlight

- Short-range connectivity plays a key role in information transfer in human brain.
- It contributes to segregation and integration of developmental connectome.
- Its maturation is spatiotemporally unique and heterogeneous in typical development.
- Its maturation follows the sequence from primary to higher-order brain regions.
- Alterations of short-range connections are associated with autism and schizophrenia.

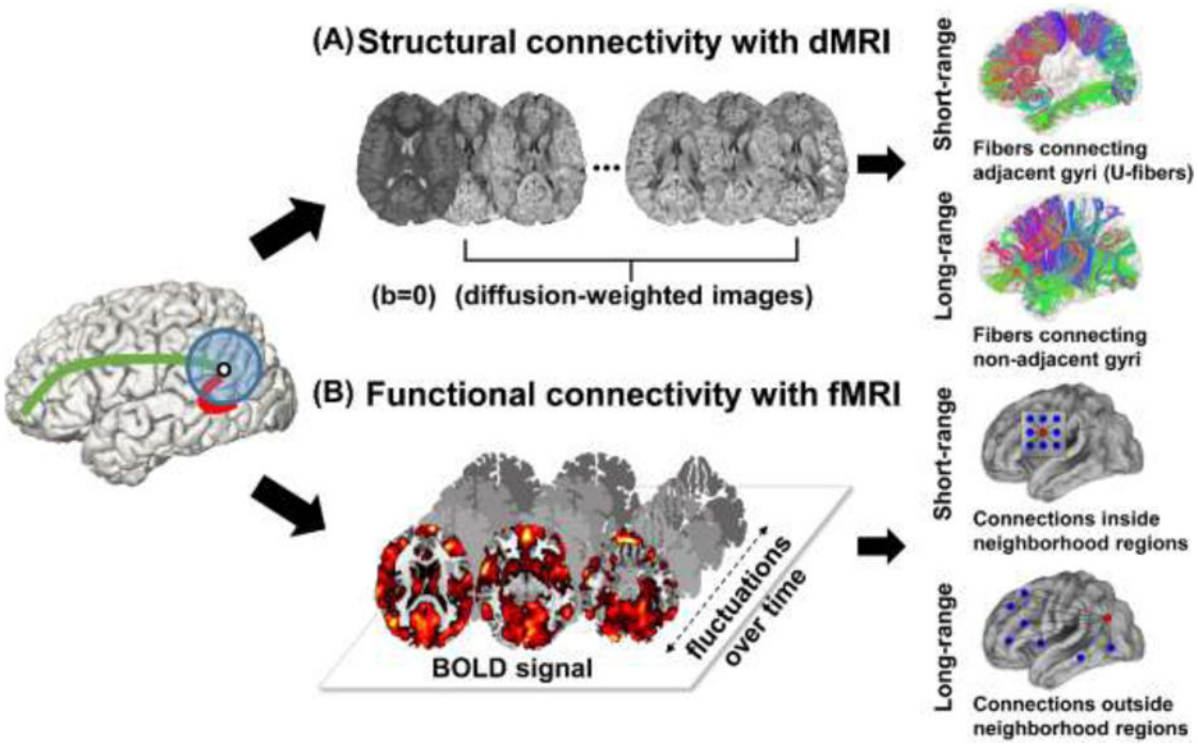

Figure 1.

Short-range structural and functional connectivity from diffusion MRI (dMRI) and functional MRI (fMRI), respectively. (A) With dMRI-based tractography, the fibers traced from a specific cortical gyrus and connected to its adjacent gyri, also called U-fibers, constitute short-range structural connectivity (SC) of the gyrus. The traced from a specific cortical gyrus and connected to its non-adjacent gyri constitute long-range SC of the gyrus. (B) Based on correlation of intrinsic blood-oxygen-level-dependent (BOLD) signal fluctuations between brain regions, short-range functional connectivity (FC) is represented by the functional connections inside the neighborhood brain regions, usually measured by Euclidean distance (Adapted from Sepulcre et al., 2010, with permission). Long-range FC is represented by the connections from outside the neighborhood brain regions.

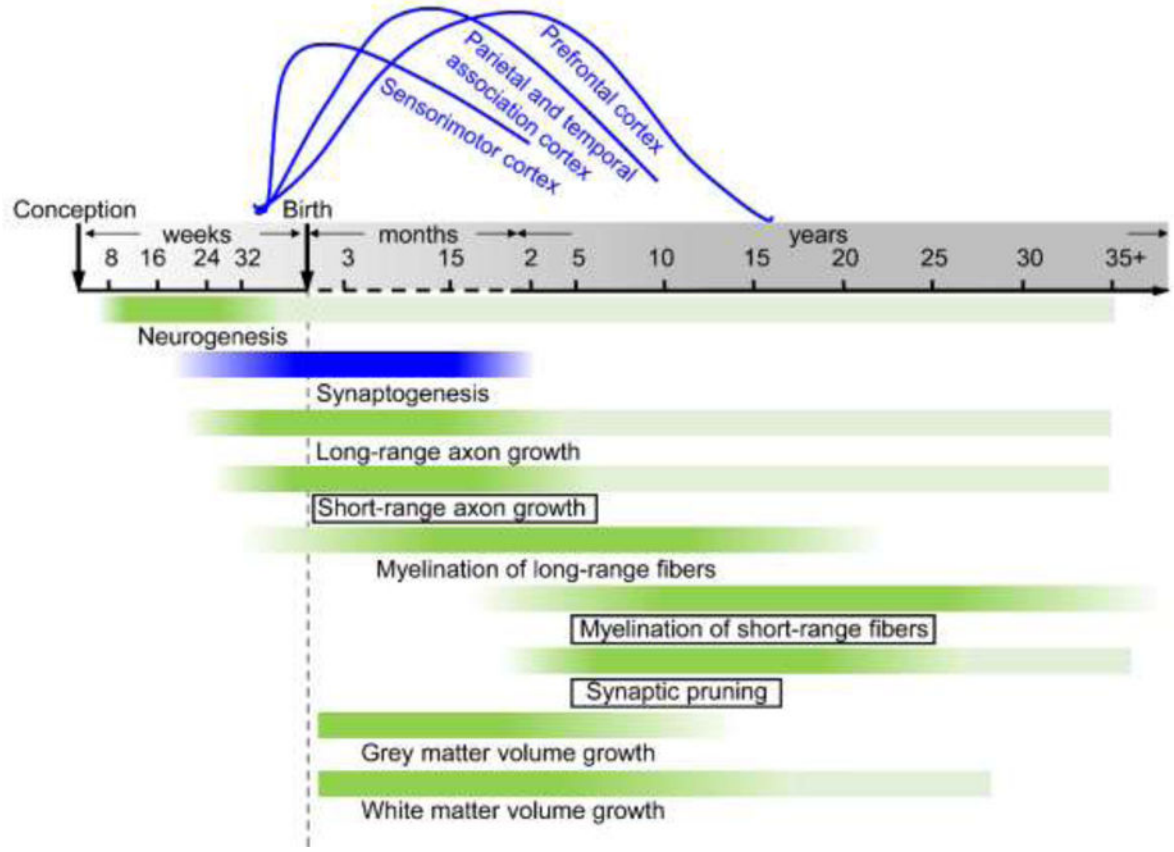

Figure 2.

Timeline of spatiotemporally distinctive human brain maturational processes, including neurogenesis, synaptogenesis, long-range and short-range axon growth, myelination of long-range and short-range fibers, synaptic pruning, and gray and white matter volume growth. Time axis is in post-conceptional weeks (before birth), postnatal months (until 24 months), and postnatal years (after 2 years). Processes related to maturation of short-range connections are highlighted with black boxes. The color intensity in each bar corresponds to the rate of developmental changes (Adapted from Giedd, 1999 with permission). The spatial progression is illustrated using synaptogenesis as an example. Besides temporal information, the spatial progression from primary sensorimotor cortex to higher-order prefrontal cortex of synaptogenesis (blue bar) is illustrated by the curves in corresponding color above the time axis.

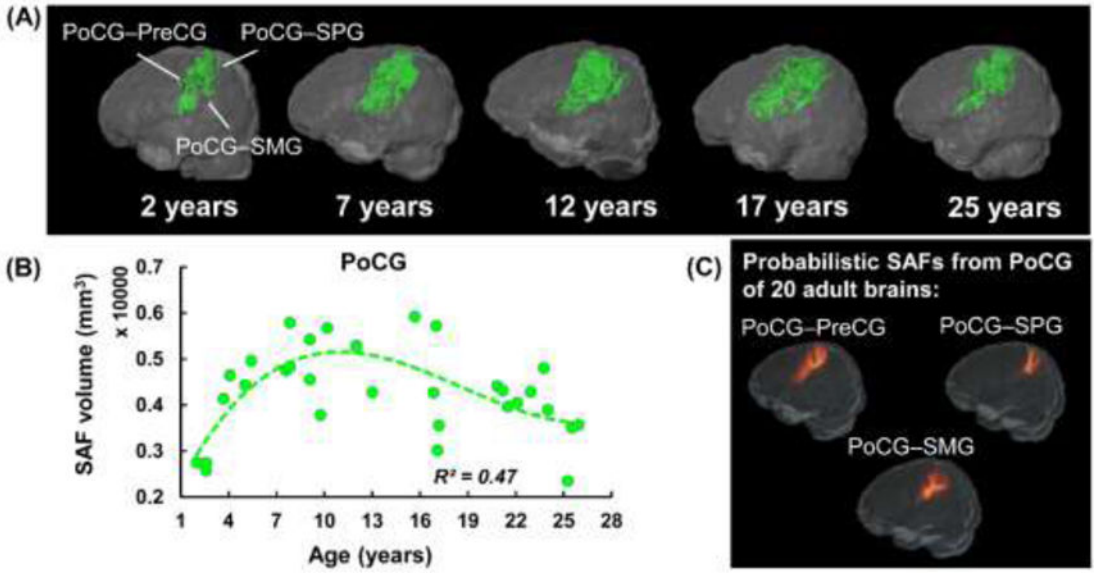

Figure 3.

Example of short-range SC changes of postcentral gyrus (PoCG) in typical brain maturation from 2 to 25 years. (A) Short-range association fibers (SAFs) traced from PoCG in five representative developmental brains from 2 to 25 years with dMRI-based tractography. Three SAFs between PoCG and its adjacent gyri, namely PoCG-precentral gyrus (PreCG), PoCG-superior parietal gyrus (SPG) and PoCG-supra marginal gyrus (SMG) are shown in each panel. (B) The age-dependent change of the volume of SAFs traced from PoCG is characterized with an initial increase from 2 to 12 years and later decrease from 12 to 25 years. (C) Three SAFs traced from PoCG shown in (A) have also been reproducibly identified in 20 adult brains, as shown in probabilistic maps. (Adapted from Ouyang et al., 2016a and Zhang et al., 2010, with permission)

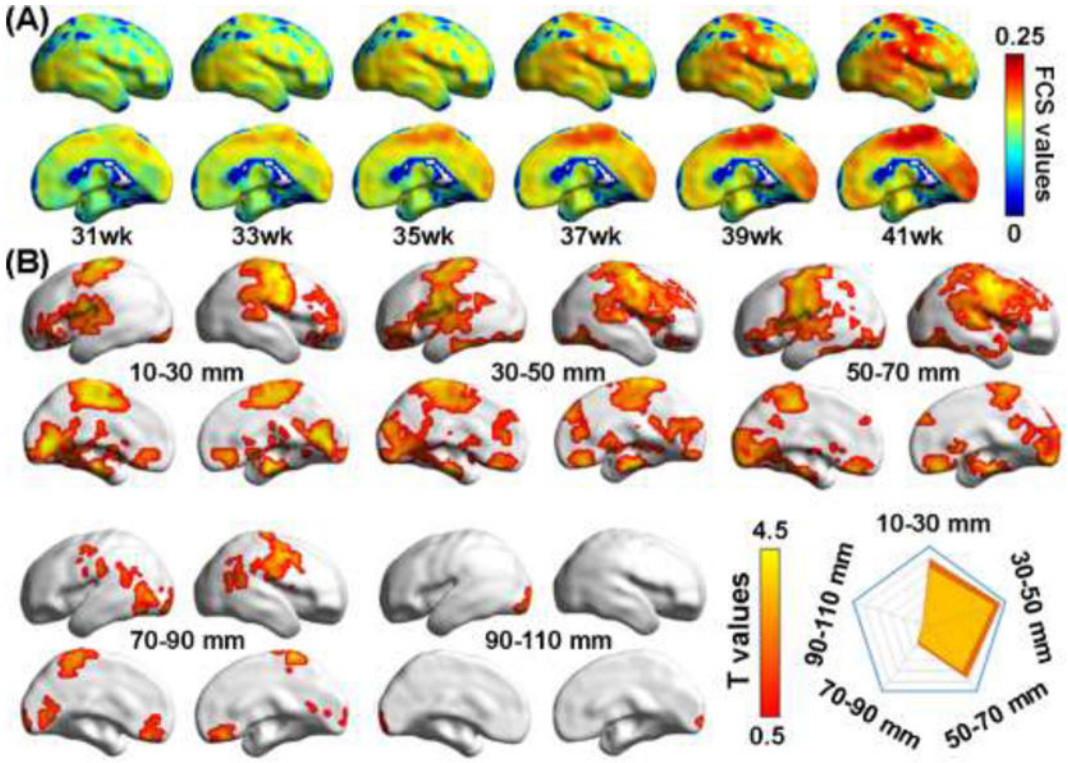

Figure 4.

Example of short-range FC changes during early brain development from 31 to 41 postmenstrual weeks (PMW). (A) Developing cortical FC strength from 31 to 41 PMW demonstrating age-dependent gradual increases of FC strength. (B) Age effects on cortical FC strength were differentiated with different distant bins. From 31–41 PMW, the age-related FC strength increases were found primarily in the short to middle distance connections. (Adapted from Cao, et al. 2016, with permission).

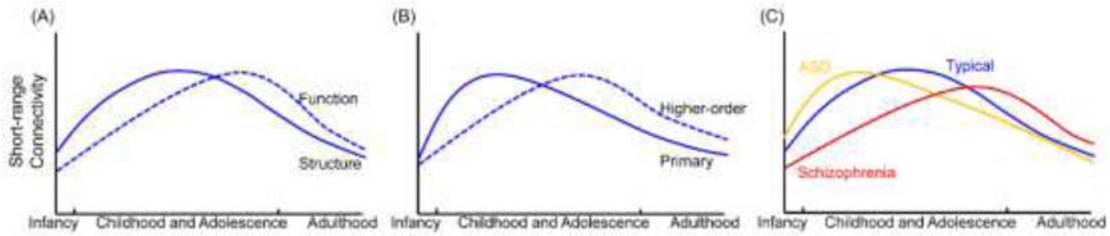

Figure 5.

Sketch plots showing age-dependent short-range connectivity changes. (A) Age-dependent short-range SC (solid line) and FC (dashed line) changes in typically maturational brain (TD) with FC maturation lagging behind SC maturation. (B) Age-dependent changes of short-range connection of primary (solid line) and higher-order association regions (dashed line) in TD brain. (C) Age-dependent changes of short-range connection in brain with TD (blue line), brain with autism spectrum disorder (ASD, orange line) and brain with schizophrenia (SZ, red line).

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Table 1

List of studies on short-range structural connectivity (SC) with diffusion MRI (dMRI), including diffusion tensor imaging (DTI) and high angular resolution diffusion imaging (HARDI).

Study	Modality	Subjects (N, age)	Topic	Analysis	Definition of short-range SC
Wakana et al. 2004	DTI	4 TD, 21–29 yrs	Atlas	Tractography	SAFs connecting adjacent gyri (U-fibers) locating in superficial WM regions
Oishi et al. 2008	DTI	81 TD, 18–59 yrs	Atlas	Tractography	SAFs connecting adjacent gyri (U-fibers) locating in superficial WM regions
Sundaram et al. 2008	DTI	16 TD, 6.8±3.5 yrs 50 ASD, 4.8±2.4 yrs	WM microstructure in frontal LAF and SAF	Tractography, DTI-derived metrics	Intra-lobe fibers
Zhang et al. 2010a	DTI	20 TD, 36.4±13.3 yrs	Atlas	Tractography	SAFs connecting adjacent gyri (U-fibers)
Oishi et al. 2011	DTI	1 rhesus monkey	Cross-species delineation of SAFs	Tractography	SAFs connecting adjacent gyri (U-fibers)
Phillips et al. 2011	DTI	26 SZ, 19–46 yrs 49 relatives to SZ, 17–72 yrs 75 TD, 18–70 yrs	Cortico-cortical structural integrity in SZ	DTI-derived metrics	SWM directly beneath the cortex containing a mixture of SAFs that include intra-cortical axons, which extend directly from GM, and subcortical fibers, that arch through the cortical sulci to connect adjacent gyri
Shukla et al. 2011	DTI	24 TD, 9–19 yrs 26 ASD, 9–18 yrs	Microstructural abnormalities of short-distance fibers in ASD	DTI-derived metrics	Short-distance WM fibers with a maximum length of 35 mm, and adjacent to the cortical boundary
Catani et al. 2012	HARDI	1 TD, 29 yrs	Anatomical description of U-fiber	Tractography, Post-mortem dissection	Local connectivity including U-shaped connections between adjacent gyri and longer intralobar fibres connecting distant areas within the same lobe
Guevara et al. 2012	HARDI	12 TD	Semi-automatic fiber segmentation	Tractography	SAFs with a length range between 35mm and 100mm
Magro et al. 2012	DTI	20 TD, 18–47 yrs		Tractography	SAFs defined as fibers with both ends within the same lobe
Nazeri et al. 2013	DTI	44TD, 18–55 yrs 45 SZ,18–55 yrs	Alteration of SWM microstructure in SZ	DTI-derived metrics	SWM was defined in MNI space as a part of WM that is both adjacent to the cortex and is not included in any of the DWM of ICBM-DTI- 81 atlas
Phillips et al. 2013	DTI	65 TD, 18–74 yrs	Microstructural properties in SWM	DTI-derived metrics	Superficially located WM, or SWM
Im et al. 2014	DTI	25 TD, 2–17 yrs 14 PMG, 2-20yrs	Altered brain network in PMG	Graph theory	Short U-shaped fibers, connecting a given gyrus to other adjacent gyri
Wu et al. 2014	DTI	133 TD, 14.3±2.2 yrs	Development of SWM microstructure	DTI-derived metrics Cortical thickness	SWM lying immediately beneath cortical GM and consists primarily of SAFs

Study	Modality	Subjects (N, age)	Topic	Analysis	Definition of short-range SC
Reveley et al. 2015	dMRI	Brain specimens from 3 macaque	SWM impede detection of long fibers	Probabilistic tractography	SWM beneath the cortex and composing SAFs
Im et al. 2015	DTI	20 TD, 3–23 yrs 20 TSC, 3–24 yrs	Altered brain network in TSC	Graph theory	First neighboring gyral connections based on gyral segment parcellation
Ouyang et al. 2016a	DTI	21 TD, 2–25 yrs	SAFs in developmental brain	Tractography	SAFs connecting adjacent gyri (U-fibers)
Philips et al. 2016a	DTI	47 TD, 69.2±4.5 yrs 44 AD, 71.0±5.8 yrs	SWM in AD	DTI-derived metrics	Superficially located WM
Philips et al. 2016b	DTI	49 TD, 42.4±12.2 yrs 24 HD, 27.5±14.7 yrs	SWM microstructure abnormality in HD	DTI-derived metrics	SAFs laying at the interface between the cortical GM and WM
Smyser et al. 2016	DTI	22 VPT without WMI 19 VPT with WMI 12 term infants	Microstructural properties in GM and adjacent WM	DTI-derived metrics	SWM immediately adjacent subcortical WM
Wen et al. 2016	DTI	27 TD, 6–17 yrs, 27 TS, 3–16 yrs	Microstructural in SWM in TS	DTI-derived metrics	SWM ROI from Type II WM parcellation map based on Oishi et al., 2008
Ouyang et al. 2017a	DTI	19 TD, 2–7 yrs 30 ASD, 2–7 yrs	SAFs underlie brain network reconfiguration	Tractography, Graph theory	SAFs connecting adjacent gyri (U-fibers)
Ouyang et al. 2017b	DTI	19 TD, 2–7 yrs 30 ASD, 2–7 yrs	Atypical maturation of SAFs in ASD	Tractography	SAFs connecting adjacent gyri (U-fibers)
Guevara et al. 2017	HARDI	79 TD, 23.6±5.2 yrs	Reproducibility of SWM fibers with dMRI	Tractography	SAFs with a length range between 20mm and 80mm

GM: gray matter; WM: white matter; DWM: deep white matter; SWM: superficial white matter; SAF: short-range association fiber; LAF: long-range association fiber; TD: typically developing; ASD: autism spectrum disorder; SZ: schizophrenia; AD: Alzheimer's disease; HD: Huntington's disease; PMG: polymicrogyris; TSC: Tuberous sclerosis complex; TS: Tourette syndrome; VPT: very preterm infant; WMI: white matter injury;

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Table 2

List of studies on short-range functional connectivity (FC) with functional MRI (fMRI), electroencephalography (EEG) and magnetoencephalography (MEG).

Study	Modality	Subjects (nr, age)	Topic	Analysis	Definition of short-range FC
Fair et al. 2007	rs-fMRI	210 TD, 7–32 yrs	Network integration and segregation	Graph theory	Short-range defined as connection between regions close in space
Fair et al. 2009	rs-fMRI	210 TD, 7–31 yrs	Brain network development	Graph theory	–
Kelly et al. 2009	rs-fMRI	40 TD, 8.7–24	Development of anterior cingulate FC	ROI-based FC	Short-range FC distances from seed ROI less than 40mm
Supekar et al. 2009	rs-fMRI,	45 TD, 7–22 yrs	Development of functional brain networks	Graph theory,	Short-range FC between more proximal anatomical regions
Dosenbach et al. 2010	rs-fMRI	238 TD, 7–30 yrs	Prediction of individual brain maturity	FC multivariate pattern analysis	–
Sepulcre et al. 2010	rs-fMRI	100 TD, 22.2±3.0 yrs	Organization of local and distant FC in brain	Graph theory	Short-range FC within 14 mm of a neighborhood brain regions
Shukla et al. 2010	rs-fMRI	29 TD, 13.8±0.6 yrs 26 ASD, 13.7±0.6yrs	ReHo in ASD	ReHo	KCC assigned to the center voxel calculated with time-series of its 6 nearest neighboring voxels
Smyser et al. 2010	rs-fMRI	90 TD, 26 week-term infants	Neural network development	Seed-based FC	–
Lopez-Larson et al. 2011	rs-fMRI	58 TD 11–35 yrs	Effects of age and gender on local FC	ReHo	KCC assigned to the center voxel calculated with time-series of its 26 nearest neighboring voxels
Repovs et al. 2011	rs-fMRI	15 TD, 23.4±2.9 yrs 18 TD SIB, 22.2±2.9 yrs 40 SZ, 24.4±3.1 yrs 31 SZ SIB,24.3±3.7 yrs	Brain network in SZ and their siblings	ROI-based FC	Short-range FC defined as connection within the same lobe
Alexander- Bloch et al. 2013	rs-fMRI	20 TD, 19.4±4.9 yrs 19 SZ, 18.7±4.9 yrs	FC distance predicts network topology	Graph theory	Short-range FC with a distance less than 50 mm
Mueller et al. 2013	rs-fMRI	25 TD, 51.8±6.9 yrs	Individual variability in FC	ROI-based network analysis	Short-range FC define as the connection within 12 mm
Maximo et al. 2013	rs-fMRI	29 TD, 13.8±2.4 yrs 29 ASD, 13.5±2.2 yrs	Local connectivity in ASD	ReHo	KCC assigned to the center voxel calculated with time-series of its 7, 19 or 27 nearest neighboring voxels
Keown et al. 2013	rs-fMRI	29 TD, 13.5±2.2yrs 29 ASD, 13.8±2.4yrs	Local hyperconnectivit y in ASD	Graph theory	Short-range connection for each voxel defined as the number of connected neighboring voxels within a 14 mm radius to the reference voxel

Study	Modality	Subjects (nr, age)	Topic	Analysis	Definition of short-range FC
Lee et al. 2013	rs-fMRI	Longitudinal study: 36 TD at preterm 30 TD at term 21 TD at 2yrs 22 TD at 4yrs	Development of regional FC in preterm infants into early childhood	ROI-based FC	–
Liang et al. 2013	rs-fMRI	48 TD, 27.4±7.1 yrs	Relationship between FC and cerebral blood flow	ROI-based FC	Short-range FC with a distance less than 75 mm
Supekar et al. 2013	rs-fMRI	35 TD, 7–13yrs 35 ASD, 7–13yrs	Brain hyperconnectivit y and social deficits in ASD	ROI-based FC, ALFF	Within certain Euclidean distance, with no specific range provided for short-rang FC
Guo et al. 2014	rs-fMRI	28 SZ, 25.35±5.8 yrs 28 TD SIB, 25.78±6.4 yrs 60 TD, 27.16±6.6 yrs	Anatomical distance affects FC in SZ and their siblings	ROI-based FC	Short-range FC with a distance less than 75.5 mm
Jakab et al. 2014	rs-fMRI	32 fetus, 21–38 weeks	Emerging fetal brain connectivity patterns	ROI-based FC; Graph theory	Short-range FC defined as connection with the lowest 25th percentile of the ROI-to-ROI distance matrix
Wang et al. 2014	rs-fMRI	20 TD, 35.0 ± 7.9 yrs 21 SZ, 35.5 ± 7.1 yrs	Disrupted FC in minimally treated SZ	ROI-based FC	Short-range FC with a distance less than 75 mm
Anderson et al. 2014	rs-fMRI	1079 TD, 7–30yrs	BOLD fluctuations and local FC	ReHo	KCC assigned to the center voxel calculated with time-series of its 26 nearest neighboring voxels
Sala-Llonch et al. 2014	rs-fMRI	98 TD, 64.87±11.8yrs	Functional networks and memory performance	Graph theory,	Short-range FC defined as connection within the same lobe
Washington et al. 2014	task-fMRI rs-fMRI	24 TD, 6–17 yrs 24 ASD, 6–17 yrs	Dysmaturation of DMN in ASD	ICA analysis; ROI-based FC	–
Guo et al 2015	rs-fMRI	49 SZ, 22.69±4.62 yrs 50 TD, 23.48±2.49 yrs	Alteration of DMN FC in SZ	Seed-based FC	Short-range FC with a distances less than 75 mm
Jiang et al. 2015	rs-fMRI	26 EOS, 14.5±1.94 yrs 25 TD, 14.37±2.97 yrs 20 AOS, 26.4±8.0yrs 17 HAC, 30.3±11.0 yrs	Local to remote connectivity in SZ	ReHo Seed-based FC	–
Su et al. 2015	rs-fMRI	28 TD, 36.3± 11.9 yrs 49 SZ, 38.4±13.4 yrs	SZ symptoms and brain network efficiency	Graph theory	Short-range FC with distance less than 40 mm
Cao et al. 2016	rs-fMRI	52 neoante, 31.3–41.7 weeks	Early development of functional network segregation	Seed-based FC, Graph theory	Short to middle FC with distance of 10–70 mm
Dajani and Uddin, 2016	rs-fMRI	53 TD, 11–18 yrs 53 ASD, 11–18 yrs	Local FC across development in ASD	ReHo	KCC assigned to the center voxel calculated with time-series of its 26 nearest neighboring voxels
Long et al. 2016	rs-fMRI	64 TD, 8–30 yrs 64 ASD, 8–31 yrs	Alteration of FC in ASD	Voxel-based FC	FC with a distance between 10 to 30 mm
Barttfeld et al. 2010	rs-EEG	10 TD, 25.3±6.54 yrs 10 ASD, 23.8±7.6 yrs	Alteration of FC in ASD	Delta band FC, Graph theory	Short-range FC defined as connection within the same lobe
Khan et al. 2013	task-MEG	20 TD, 16.5±2.5 yrs 17 ASD, 16.8±2.0 yrs	Reduced local and long-range FC in ASD	Phase-amplitude coupling, ROI-based FC	Short-range FC of regions on a spatial scale of roughly range from 1 cm to a few cm

Study	Modality	Subjects (nr, age)	Topic	Analysis	Definition of short-range FC
Ye et al. 2014	rs-MEG	15 TD, 12–15 yrs 20 ASD, 12–15 yrs	Atypical resting synchrony in ASD	Graph theory	–
Ghanbari et al. 2015	rs- MEG	22 TD, 10.9±2.5 yrs 26 ASD, 10.1±2.3 yrs	Resting state brain activity in ASD	Band-specific FC, Multi-scale entropy	Short-range FC defined as connection within the same lobe
Khan et al. 2015	rs- MEG	20 TD, 8–18 yrs 15 ASD, 8–18 yrs	Imbalanced local and directed connectivity in ASD	Phase locking, Granger causality	Short-range FC of regions on a spatial scale roughly ranging from 1 cm to a few cm

rs-fMRI: resting state functional magnetic resonance imaging; rs-EEG: resting state electroencephalography; rs-MEG: resting state magnetoencephalography; FC: functional connectivity; ROI: region of interest; ReHo: Regional Homogeneity; KCC: Kendall's coefficient concordance; BOLD: blood oxygen level dependence; ALFF: amplitude of low-frequency fluctuations; ICA: independent component analysis; DMN: default mode network; ASD: autism spectrum disorder; SZ: schizophrenia; TD: typical developing; SIB: sibling; EOS: early-onset schizophrenia; AOS: adulthood-onset schizophrenia; HAC: healthy adult control;