A Network Neuroscience Approach to Typical and Atypical Brain Development

Sarah E. Morgan,
Behavioural and Clinical Neuroscience Institute, University of Cambridge, Cambridge

Simon R. White,
Department of Psychiatry, University of Cambridge, Cambridge; MRC Biostatistics Unit, University of Cambridge, Cambridge

Edward T. Bullmore,
Behavioural and Clinical Neuroscience Institute, University of Cambridge, Cambridge; Cambridgeshire and Peterborough NHS Foundation Trust, Huntingdon; ImmunoPsychiatry, Immuno-Inflammation Therapeutic Area Unit, GlaxoSmithKline R&D, Stevenage, United Kingdom

Petra E. Vértes
Behavioural and Clinical Neuroscience Institute, University of Cambridge, Cambridge

Abstract

Human brain networks based on neuroimaging data have already proven useful in characterizing both normal and abnormal brain structure and function. However, many brain disorders are neurodevelopmental in origin, highlighting the need to go beyond characterizing brain organization in terms of static networks. Here, we review the fast-growing literature shedding light on developmental changes in network phenotypes. We begin with an overview of recent large-scale efforts to map healthy brain development, and we describe the key role played by longitudinal data including repeated measurements over a long period of follow-up. We also discuss the subtle ways in which healthy brain network development can inform our understanding of disorders, including work bridging the gap between macroscopic neuroimaging results and the microscopic level. Finally, we turn to studies of three specific neurodevelopmental disorders that first manifest primarily in childhood and adolescence/early adulthood, namely psychotic disorders, attention-deficit/hyperactivity disorder, and autism spectrum disorder. In each case we discuss recent progress in understanding the atypical features of brain network development associated with the disorder, and we conclude the review with some suggestions for future directions.

Keywords

ADHD; Autism spectrum disorder; Development; MRI; Network neuroscience; Schizophrenia

Childhood and adolescence are critical periods during which several brain disorders develop. Characterizing how atypical developmental trajectories diverge from normal brain development is essential to understand and ultimately treat these disorders. Network models of neuroimaging data have already highlighted key drivers in brain organization (1–3), for example, the role of hubs in coordinating information transfer (4) and the economic trade-off brain networks navigate between the cost of long-distance connections and their topological benefits, enabling efficient information processing by connecting distant brain regions (5). Figure 1 summarizes commonly used graph metrics. However, owing to the difficulty and cost of recruiting and scanning large cohorts, historically many network studies of neurodevelopmental disorders have focused on static patient/control differences, disregarding the changing structure of brain networks over time. What can network models tell us about healthy brain development and how developmental trajectories differ in disease? Several neuroimaging studies have begun to tackle this question, including the Human Connectome Project Development study (6), the Developing Human Connectome Project (7), the NeuroScience in Psychiatry Network (8), and the Philadelphia Neurodevelopmental Cohort (9), among others. These collaborative projects benefit from large sample sizes with several hundred participants, which is crucial to obtain enough power to detect statistically significant, potentially nonlinear changes with age. Perhaps the most exciting feature of some of these projects is the longitudinal neuroimaging data being acquired (Box 1). While cross-sectional data can provide important insights into average group changes, longitudinal data are essential to study development at an individual level because significant individual differences exist even between healthy individuals of similar ages (10,11), which may confound cross-sectional analyses (12). In atypical development, the trajectory of changes in an individual's brain network may be a more useful biomarker than the absolute values (13).

Here, we build on previous reviews (14–20), with particular emphasis on how healthy development can provide insights into abnormal development and the importance of longitudinal data. We begin by reviewing cross-sectional and longitudinal studies of healthy brain network development and their implications for understanding neurodevelopmental disorders. We then turn to studies of three specific neurodevelopmental disorders that first manifest primarily in childhood and adolescence/early adulthood, namely psychotic disorders, attention-deficit/hyperactivity disorder (ADHD), and autism spectrum disorder (ASD). We conclude with suggestions for future directions.

Healthy Development

The human brain undergoes extraordinary changes during development, from conception to birth and throughout childhood. Before birth, neurogenesis is largely completed by week 20 after conception; axons begin to grow and synapses start to form between neurons (19,21). After birth, a further proliferation phase in which the number of synapses continues to increase is followed by a consolidation phase characterized by cell loss, synaptic pruning, and myelination of axons, which is thought to continue into adolescence (22). Neuroimaging provides a noninvasive, albeit indirect, way to study these developmental changes. Table 1 lists cross-sectional and longitudinal studies performed in healthy children and adolescents,

using structural magnetic resonance imaging (sMRI), diffusion-weighted imaging (DWI), and functional MRI (fMRI).

Structural MRI

sMRI provides several metrics characterizing brain morphology, for example, gray and white matter volumes and cortical thickness (CT). The first longitudinal pediatric neuroimaging study was performed in 1999 and showed that gray matter volume increases in early childhood before decreasing in later childhood/adolescence, forming an inverted U–shaped trajectory, which peaks at different ages in different brain regions (23). These peaks occur later than expected from cross-sectional studies (13), although recent longitudinal studies have suggested that methodological issues might have confounded these results and CT may decrease from earlier in childhood (24–26). For example, Mills *et al.* (25) found that gray matter volume decreased from 8 to 30 years of age in four longitudinal samples. One potential confound is that in-scanner movement can lead to reduced CT and volume estimates (27,28), which can bias developmental trajectories. A recent multisample study analyzed longitudinal changes in cortical volume, surface area, and thickness from 7 to 29 years of age and found that cortical thinning is the dominant contributor to volume reductions during adolescence (29). In Giedd *et al.* (23), white matter volumes increased from 4 to 20 years of age, in agreement with recent results (24). Microscopically, these changes are thought to be driven by the pruning of synapses, dendrites, or cell bodies and the myelination of axons. Several studies have shown that lower-order somatosensory and visual cortices mature first, followed by higher-order association cortices (30–34), in line with the order of cognitive and behavioral changes during childhood. These studies used a variety of developmental benchmarks, e.g., age at attainment of adult brain volume or at other inflection points.

To study the relationships between brain regions, morphological metrics can be correlated between regions across subjects to create one structural covariance network per subject group (35). The network's nodes correspond to brain regions and the edges represent cross-correlations of morphological metrics between pairs of regions taken across subjects. While this approach cannot elucidate intersubject differences, it can provide insights into average developmental changes. For example, volumetric covariance networks suggest that small-world, modular topology is already present at 1 month (36). Later work found that network measures follow nonlinear trajectories (37,38); for example, in a longitudinal study, global efficiency and CT peak at 7 years of age, and at the same time local efficiency is lowest and cortical folding becomes stable (38). Correlations between fractional anisotropy (FA) (see below for details) and CT covariance matrices suggest that white and gray matter development is synchronized (39).

Like individual morphometric measures, in structural covariance networks different brain regions follow different developmental trajectories (37,40–42). Several studies have shown early maturation of primary regions followed by protracted development of high-order regions (37,40,41). One study of 108 adolescents with three to six longitudinal scans per participant created both structural and maturational covariance networks, in which maturational networks were derived from the rate of change of CT in different regions (42).

Structural and maturational covariance networks exhibited similar topological properties and spatial organization, suggesting that correlated anatomical structure between brain regions results from similarities in maturational trajectories. In other words, brain regions with high structural covariance might have developed in similar ways.

Other work has highlighted the importance of hub regions (37,43,44). Khundrakpam *et al.* (37) found that both the number and the distribution of hubs change over development; the number of hubs peaks in late childhood, then the distribution of hubs shifts toward frontal regions during adolescence. Whitaker *et al.* (43) also pointed to a key role for hubs in association cortices during adolescence, showing that they are less myelinated at 14 years of age than other regions, but have faster rates of myelination and cortical shrinkage between 14 and 24 years of age. These results are consistent with the idea that primary sensory and motor regions develop early on, while hub regions of the association cortex that are responsible for more complex integrative function mature more slowly.

Recently Seidlitz *et al.* (45) proposed a new approach for calculating sMRI networks at the individual level, based on interregional similarity of several morphological metrics such as CT, gray matter volumes, surface area, and curvature. Future studies based on these morphometric similarity networks could enable a deeper understanding of how individual sMRI connectivity develops.

Diffusion-Weighted Imaging

DWI exploits the diffusion of water molecules to generate contrast between different types of brain tissue. It can be used to measure mean diffusivity, axial diffusivity, or radial diffusivity, and FA, which is believed to reflect fiber density, axonal diameter, and myelination. Finally, white matter fibers can be tracked to create a tractography (diffusion tensor imaging [DTI]) network where predefined gray matter regions of interest are connected by an edge if white matter fibers are inferred between them (46). As in sMRI, DWI is susceptible to motion artifacts, particularly DTI networks, due to their long acquisition times (47,48).

During development, diffusivity decreases with age while anisotropy increases (19). These changes are believed to reflect increasing myelination. Changes occur most rapidly up to 2 years, then continue throughout childhood and adolescence, until at least 18 years of age and possibly into early adulthood (49,50).

Many global topological properties of DTI networks are already established at birth, including small-worldness and the presence of hubs (46,49). However, several studies report substantial reorganization of DTI networks during childhood and adolescence, including monotonic increases in integration and global efficiency and decreases in clustering (46,49,51–53). The studies use several approaches to calculate edge weights, including binarization, radial diffusivity, and mean diffusivity values, and span age ranges from birth to 30 years of age. The monotonic changes are consistent with increasing white matter volume. Recently, Baum *et al.* (54) observed that while global efficiency increases with age, surprisingly both participation coefficient and between-module connectivity decrease, suggesting that networks become both more modular and more integrated. These changes

were driven by strengthening of network hub edges. Other studies agree that connectivity between hubs or association regions changes disproportionately to other regions, particularly in adolescence (52,55). Recently, Wierenga *et al.* (56) also showed increases in connectivity between rich-club nodes and peripheral nodes. We note that some studies observe decreasing global efficiency with age (57,58). These different results may be due to using different measures, as Lim *et al.* (57) used networks weighted by streamline count, while Baum *et al.* (54) used FA. In line with these results, in Koenis *et al.* (58) networks weighted by streamline count showed decreasing global efficiency with age, while FA-weighted networks showed increasing global efficiency. In Lim *et al.* (57), the proportion of intermodule connections increased with age, again unlike Baum *et al.* (54), and possibly owing to differences in network construction.

Functional MRI

In fMRI brain images, each voxel is associated with a time series. There are several approaches to analyzing fMRI networks, including 1) independent component analysis, a data-driven approach that identifies components that group voxels into regions with similar response patterns; 2) seed-based maps, which study correlations between a particular seed region and other areas of the brain; 3) regional maps, which study correlations between brain regions selected a priori; and 4) whole-brain network analysis, in which an atlas is used to parcellate the brain into regions and correlations are studied between regions. We note that there are still questions about how to preprocess fMRI data. As for other modalities, movement can bias estimates of functional connectivity (59–61). Several authors have proposed methods to address this problem (61–64); however, older studies may still be affected. The role of intersubject differences in mean connectivity and whether to perform global signal regression are also topics of debate (65,66).

In contrast to structural networks, in fMRI networks global topological metrics including efficiency and clustering generally remain stable across development (67–69), although Gao *et al.* (70) observed some changes in global efficiency between neonates and 1-year-olds, and Gao *et al.* (71) and Wu *et al.* (72) observed some changes in clustering at later stages of development.

Despite these broadly constant global topological properties, several authors have shown that long-range connections strengthen during development and short-range connections weaken (67,69,70,73,74). Although this result may be exaggerated by motion artifacts in early studies, the effect remains significant after motion correction (74).

Consistent with structural results, several developmental changes focus on hub regions (71,75,76), and intermodular integration also increases with development (67,77). Recent evidence from 780 subjects from 8 to 22 years of age suggests that different modules follow distinct developmental trajectories: for example, the default mode system shows increasing inter- and intrasystem connectivity, while sensorimotor systems become increasingly segregated from other systems (78).

Finally, recent work found that subjects develop more stable, individual functional connectomes during adolescence (79). In particular, for 797 subjects from 8 to 22 years of

age, the identification accuracy of one resting-state fMRI (rs-fMRI) or task fMRI scan from a subject based on other fMRI scans from the same subject (termed connectome distinctiveness) increases with age (see Figure 2). Machine-learning approaches like this one offer an alternative, individual-centric perspective on development.

A Window into Atypical Development

Developmental studies on healthy subjects provide a crucial benchmark for neurodevelopmental disorders. They can also provide further insights, e.g., by 1) studying individuals from a general population with disorder-like traits or (subclinical) symptoms; 2) highlighting which network properties/regions change at which stages of development and linking them to the disorders separately shown to affect the same network properties/regions; and 3) associating brain development with genes that are known to be implicated in disorders.

Here, we discuss studies that take these approaches to explore what large healthy developmental cohorts can teach us about brain disorders. Above, we discussed work by Kaufmann *et al.* (79), which showed that connectome distinctiveness increases from 8 to 22 years of age. The authors also showed that this increase is delayed in subjects from the general population with increased clinical symptom scores for a range of disorders. This delay in connectome distinctiveness reflects both a delay in stabilization of an individual's brain network over time and a delay in the individualization of the subject's brain network with respect to the other subjects.

Healthy subjects can also inform our understanding of disorders by highlighting the network features that change during development and are therefore particularly vulnerable to abnormal development. As discussed above, one of the main results from several healthy developmental studies, across multiple modalities, is that developmental changes often focus on hub regions. For example, Whitaker *et al.* (43) showed that the greatest rates of myelination and cortical shrinking during adolescence are focused on hub regions of the association cortex. Disruptions to hub connectivity have been observed in patients: for example, a meta-analysis showed that hub regions are more likely to be anatomically abnormal than nonhub regions in nine different brain disorders, including Alzheimer's disease and schizophrenia (80). Together, these results suggest that disorders may be linked to abnormal development of these key regions. In Whitaker *et al.* (43), the authors combined neuroimaging with the Allen Institute for Brain Science dataset on brainwide gene expression (81) (see Figure 3). The hub regions with greatest rates of myelination and cortical shrinkage from 14 to 24 years of age show overexpression of a set of genes enriched for both synaptic processes and schizophrenia risk-genes. The involvement of these risk genes in normal maturational processes during adolescence could explain why this period is particularly vulnerable to the onset of schizophrenia. The study provides an example of the way in which genetic and genomic datasets can link the brain development of healthy individuals and disorders for which there is a known set of risk genes (82). It also shows how macroscopic brain imaging results can be linked to a microscopic understanding of the brain (83–88). Similar methods are currently being applied to other disorders, including autism (89) and Huntington's disease (90).

Abnormal Development

Despite the significant insights that can be gained from healthy developmental studies, ultimately building a comprehensive picture of disorders requires longitudinal studies of patients. Below we review longitudinal and cross-sectional studies on ASD, ADHD, and psychosis, which are listed in Tables 2, 3, and 4, respectively.

Autism Spectrum Disorder

ASD manifests in the first few years of childhood and strongly impacts subsequent development. Zielinski *et al.* (91) found that CT development in boys with ASD undergoes three phases: in childhood cortical expansion is accelerated compared with control subjects; in late childhood/adolescence cortical thinning is accelerated; and in early adulthood cortical thinning is decelerated. The wide age range studied, from 3 to 36 years of age, was made possible by an accelerated longitudinal design (see Box 1). Topologically, studies comparing adult ASD patients and control subjects have found evidence for reduced efficiency and long-range connections in patients' fMRI and DTI networks (92,93), although increased local connectivity has also been observed (93,94). Network changes may be state dependent (e.g., sustained attention vs. at rest) (95). Disruption has also been observed in hub regions and regions related to social interaction, which is abnormal in ASD (96,97).

In DTI networks, reduced local efficiencies in low-level sensory processing regions have been observed in high-risk infants as young as 6 months of age and correlate significantly with 24-month symptom severity (98). Later in development, ASD patients fail to show the increases in rich-club organization observed in typically developing subjects (99). Nonnegative matrix factorization can be used to identify developmental subnetworks in ASD and subnetworks that discriminate between patients and control subjects. For example, Ghanbari *et al.* (100) identified one subnetwork with reduced interhemispheric subcortical connections that can discriminate groups but does not correlate with age, and another subnetwork involving frontal regions that is both discriminative and developmental. In contrast, other work taking a similar approach found increases in local connectivity in the cingulate cortex in ASD (101). Functional resting-state networks show a similarly complex picture. One study showed decreased default mode network (DMN) connectivity in independent component analysis networks of ASD children and adolescents, which normalizes by adulthood (102). Chen *et al.* (103) also observed reduced connectivity in some network edges, although other edges showed increased connectivity. A recent study suggested that rs-fMRI can predict whether 6-month-old infants develop autism at 24 months, although the sample size was relatively modest (59 infants, including 11 with ASD) (104). Further work is needed to clarify how connectivity develops in ASD.

Attention-Deficit/Hyperactivity Disorder

ADHD is one of the most common neurodevelopmental disorders and is often diagnosed between 6 and 12 years of age. Adult patients' rs-fMRI networks show reduced integration and increased segregation compared with control subjects (105,106), and a DTI study observed local reductions in efficiency and increases in clustering (107). Several authors have highlighted the importance of development in ADHD. Patients exhibit reduced brain

volumes, which normalize in some regions during development but not in others (108). There is also a delay in the age at which ADHD patients' CT peaks, which was first established by Shaw *et al.* (109) using a mixed longitudinal and cross-sectional design.

Most work to date on brain network development in ADHD has focused on rs-fMRI networks, which exhibit higher clustering and lower global efficiency in children with ADHD than in age-matched control subjects (110,111), in line with results in adults. These measures correlate with behavioral symptoms including inattention and hyperactivity/ impulsivity symptoms and differ between clinical subtypes (110). Early results showed that the rs-fMRI connectivity of the DMN is reduced in 23 ADHD patients compared with age-matched control subjects (112). Based on previous work on healthy development, this suggested a delay or disruption to development in ADHD patients. Later, Sripada *et al.* (113) showed that the connectivity within the DMN and between the DMN and task-positive networks in ADHD patients does indeed lag behind control subjects in a large cross-sectional sample from 7 to 22 years of age. Recently, Kessler *et al.* (114) used an independent component analysis approach to chart the development of brain connectivity networks in 519 subjects from 8 to 22 years of age, including 25 with ADHD. They found evidence for disrupted maturation in ADHD patients' functional networks, which involves the DMN, although interestingly maturation is reduced (downshifted) in patients rather than delayed. It would be interesting to see if these results could be replicated in a larger, longitudinal sample and related to structural network changes.

Psychosis

Psychotic disorders are often associated with brain dysconnectivity. sMRI studies show reduced CT and volume in adults with schizophrenia (115), DTI network connectivity is often reduced (116), and patients' rs-fMRI networks exhibit lower mean correlations and more randomized topologies (117). Psychotic disorders normally manifest in late adolescence/early adulthood, although earlier developmental changes could be valuable to identify individuals at risk.

Longitudinal studies show greater volume reductions in patients than in control subjects during adolescence, particularly in the frontal and temporal regions (118). Similarly, CT shows exaggerated thinning in patients (119). Alexander-Bloch *et al.* (120) found both age-constant deficits of CT and faster cortical thinning in childhood-onset schizophrenia patients compared with control subjects. They used structural covariance to derive five brain development modules with similar maturational trajectories in normal subjects and found that deviations in patients are primarily in the cingulofrontotemporal module. Other longitudinal work using CT structural covariance networks observed that left hemisphere occipitotemporal connectivity is significantly reduced in patients and siblings at 12 years of age compared with control subjects (121). By 17 years, siblings catch up with control subjects, but patients exhibit further delayed development, reminiscent of other disorders (79,114). Few DWI studies have focused on brain network development in psychosis, although in older subjects (19 to 54 years) longitudinal results show decreasing global efficiency over a 5-year period in patients with schizophrenia, compared with increases in the same period in control subjects (122).

There are few functional brain network studies of schizophrenia patients during childhood/ adolescence. One study found that local degree, local clustering, and local path length are reduced in most cortical regions in adults compared with children/adolescents, and reduced in adults with schizophrenia compared with control subjects in the thalamus and midbrain regions (123). However not all healthy development studies show similar trends, as discussed previously. Other work has found a complex pattern of increases and decreases in local connectivity in early-onset schizophrenia patients (124). Further studies are required to resolve these differences. A recent rs-fMRI study of at-risk mental state subjects found that those who transitioned to psychosis exhibited less segregated networks and disrupted network communities (125).

An alternative approach to studying developmental disorders is using generative models (126,127), algorithms that generate synthetic networks with certain topological properties. Vértes *et al.* (126) proposed a generative model incorporating a term that penalizes long-distance connections and a topological term that favors connections between nodes with shared nearest neighbors. The model reproduces several topological properties of healthy rs-fMRI brain networks. Simulations of schizophrenia patients' networks required a reduced distance penalization parameter, which increased the probability of long-distance connections, producing more randomized networks. Generative models could shed light on microscopic changes during disease. For example, increased probability of long-distance connections in disease could be related to the dysregulation of normal maturational processes such as pruning and myelination (43).

Conclusions and Future Directions

Larger sample sizes and the availability of longitudinal data are enabling more accurate assessments of the developmental changes of healthy children and adolescents across modalities. Healthy brain connectivity evolves during development, with evidence for stronger long-distance connections with age (74), more integration (52,67,128), and increasing connectome distinctiveness (79). Certain results have been observed across modalities, for example, the importance of hubs during brain network development (37,43,55), although other results vary by modality in ways that are not always clearly understood, for example, the changes in global efficiency with age observed in sMRI results are often not replicated in fMRI networks (38,67). Overall, healthy studies provide an important benchmark for neurodevelopmental disorders, for which atypical developmental trajectories may be a key biomarker.

Patient developmental studies are important to understand precisely how and when network properties change in disorders. Many results point toward delayed or disrupted development in patients (68,102,109) and to changes in network hubs and rich-club nodes, which are known to be vulnerable during development. Characteristics of specific disorders are likely to be related to their developmental timing. ASD patients exhibit a mixture of increased/ decreased connectivity in different brain regions from childhood, which may be age and/or state dependent. ADHD patients show a clearer pattern of reduced local efficiency, which lags behind control subjects. In psychosis, patients exhibit increased cortical thinning during

adolescence, which is likely coupled to functional changes although more work is required to elucidate this relationship.

Large, longitudinal datasets are essential to build a clearer picture, and making data openly accessible is an important step toward more reproducible research. Table 5 lists large open datasets for typical and atypical development. There are noticeable gaps, e.g., a paucity of developmental rs-fMRI data from patients with schizophrenia. Several ongoing psychosis projects will go some way to address this problem [e.g., (9,129–131)]. Similar initiatives are underway for other disorders (132,133).

Another advantage of large collaborative projects is that they often collect data from multiple modalities, enabling the relationships between modalities to be assessed. Networks provide an excellent framework to compare or combine different data types across temporal and spatial scales, for example, by using multilayer networks. Combining neuroimaging results with nonneuroimaging data also represents an exciting avenue for future research. For example, gene expression data from the Allen Institute for Brain Science has already provided a link between the developmental changes in hub regions during adolescence and genes implicated in schizophrenia (43). Ultimately, using networks to bridge the gap between macroscopic neuroimaging results and the microscopic level could open the door to a new depth of understanding and treatments for neurodevelopmental disorders.

Acknowledgments

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Box 1

From Cross-Sectional to Longitudinal Analysis

To understand developmental change, it is crucial to distinguish individual age-related changes from subject heterogeneity. Cross-sectional studies only contain a single observation per individual in a cohort of varying age and therefore cannot make this distinction (135,136). In contrast, longitudinal studies incorporate repeat measurements of the same individuals at multiple time points. Longitudinal studies increase the complexity of design and analysis, but the scientific benefits to understanding developmental changes are substantial.

Mixed-effects models are an established approach to analyzing longitudinal data (24,137–139) and include (as special cases) other well-known techniques such as change-score regression and repeated-measures analysis of variance. However, standard mixed-effects models are not without issues, notably, assumptions of Gaussian errors and the need to specify the random-effects structure (139). Longitudinal data also bring issues of attrition, which if associated with a biomarker or outcome of interest may lead to differential missingness, also known as missing not at random (140). Another challenge is the so-called age-period-cohort problem (141)—including the difficulty of separating changes owing to aging from changes due to external factors at different calendar periods, which is especially pertinent for long-term studies.

Study design is particularly important for longitudinal studies and requires balancing robust and reliable inferences against recruitment and costs to determine not only how many participants, but also how many visits per subject are needed. A classical longitudinal design follows a single cohort of subjects for the duration of interest, observing each subject multiple times. However, this makes the duration of many developmental studies untenable.

An alternative is the accelerated longitudinal design (142), also called the cohort-sequential design (143), in which multiple cohorts are followed with overlapping follow-up. This introduces two new design considerations, the number of cohorts and the overlap, which affect the acceleration of the design. An accelerated longitudinal design with sufficient overlap can disentangle age-period-cohort effects and the number of observations per subject is the primary determinant of power to detect an age-related trajectory (144).
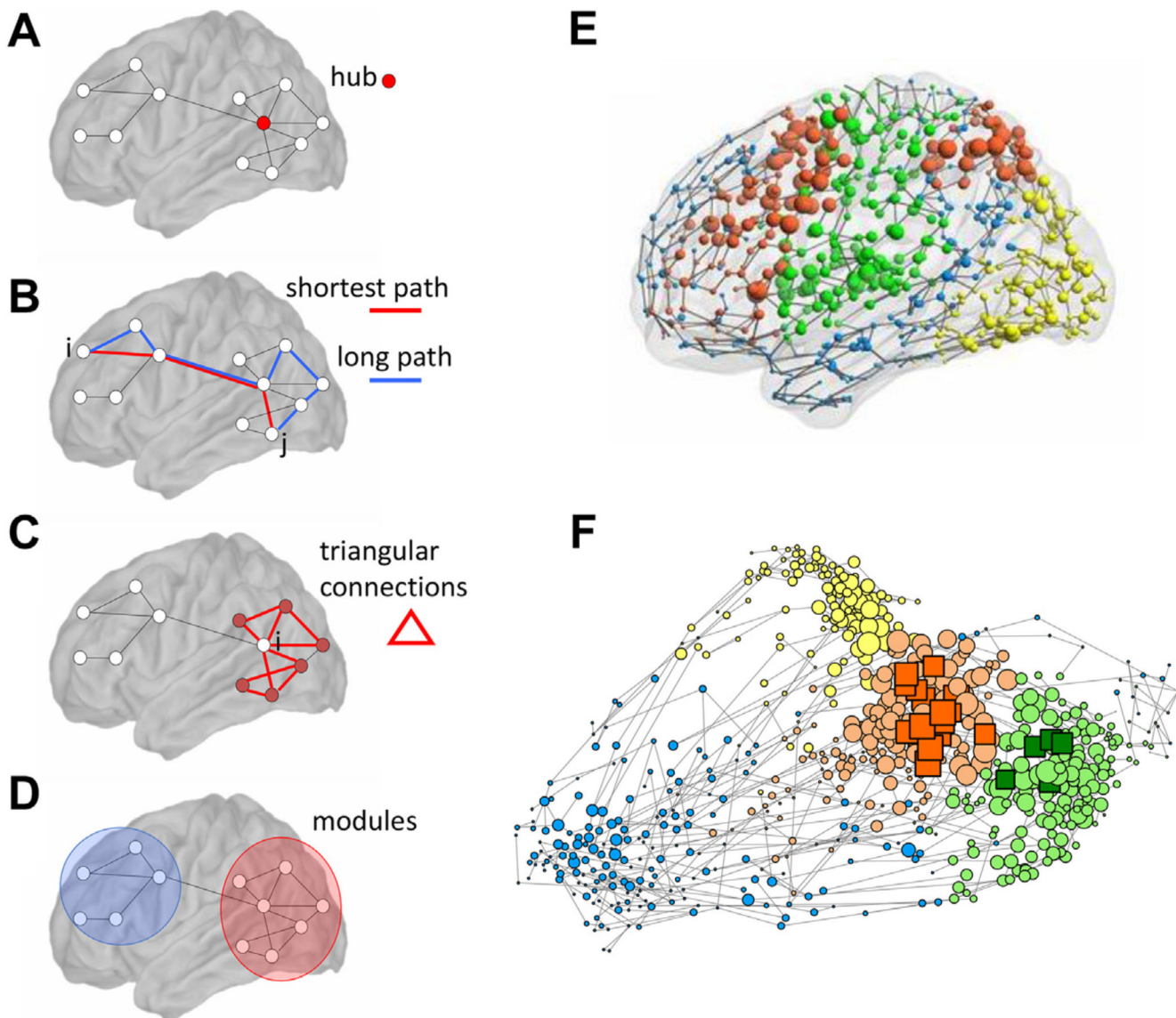
Figure 1.

An illustration of commonly used network metrics. **(A)** Degree, hubs, and rich clubs: The degree of a node is the number of links or connections it makes. Hubs are nodes with a significantly higher degree than other nodes in the network. In many networks, these nodes preferentially connect to one another, forming an elite group of nodes called a rich club. **(B)** Path length and efficiency: the minimum path length between two nodes i and j is the minimum number of edges that need to be traversed to go from one node to another, and efficiency is inversely related to path length. **(C)** Clustering and local efficiency: the clustering coefficient measures the number of connections that exist between the first neighbors of a node i as a proportion of the maximum possible number of such connections. These edges form triangular connections around the node i, which increases the local efficiency by decreasing the path length locally between the node's neighbors. **(D)** Modularity: Many complex networks have a modular community structure, whereby they

contain subsets of highly interconnected nodes called modules. Many of these features are highlighted in a brain functional network shown in both **(E)** anatomical space and **(F)** topological space. Node size is proportional to degree and rich-club nodes are highlighted as squares in panel **(F)**. The modular organization is highlighted by assigning different colors to nodes of different modules. Reproduced with permission from Vértes *et al.* (14) and Crossley *et al.* (134).
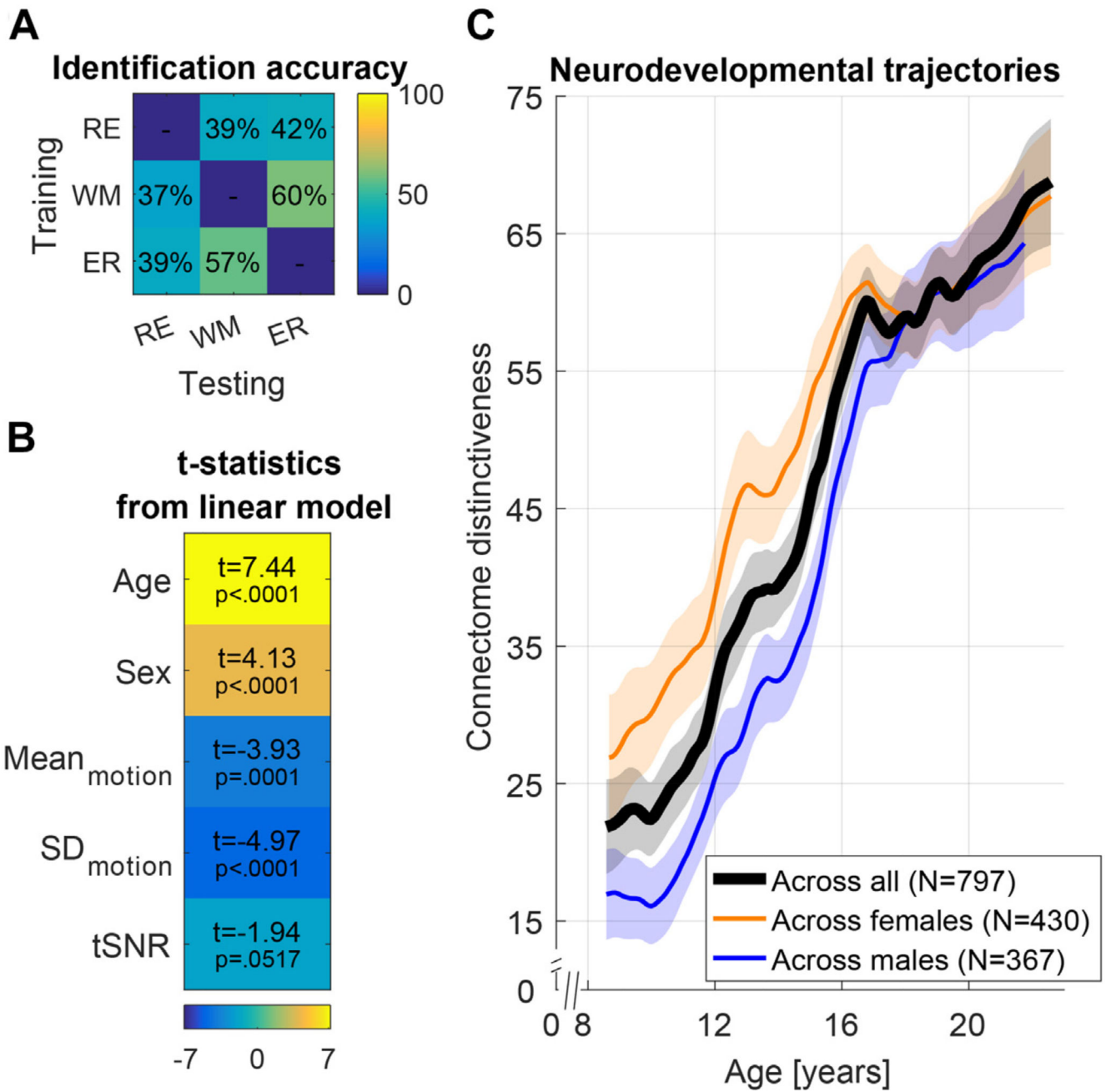
Figure 2.
(A) Average identification accuracy using testing and training functional magnetic resonance imaging scans from a working memory task (WM), emotion recognition task (ER), and resting state (RE). **(B)** Statistics from a linear model of connectome distinctiveness. **(C)** Changes in connectome distinctiveness with age. Male subjects developed later than female subjects. Similar results were obtained using independent component analysis. Reprinted with permission from Kaufmann *et al.* (79). tSNR, temporal signal-to-noise ratio.
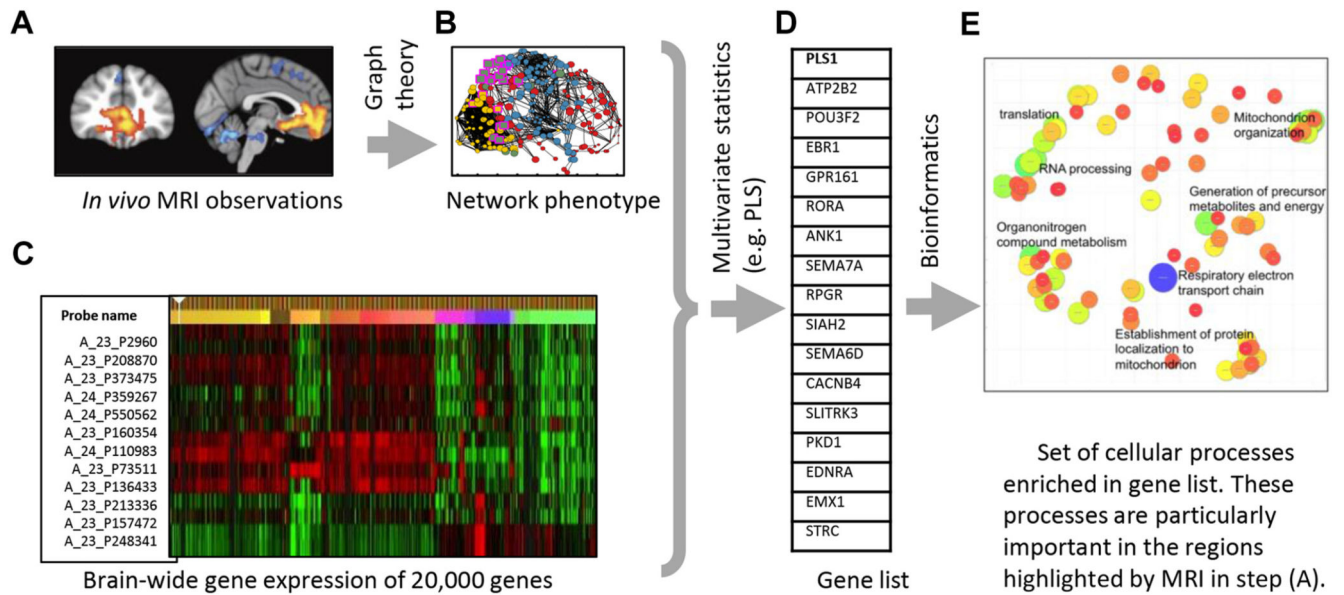
Figure 3.
Schematic of the methodology in Whitaker *et al.* (43). Gene expression data can be used to link magnetic resonance imaging (MRI) observations and network phenotypes to a microscopic understanding of the brain. **(A)** In vivo MRI observations are used to **(B)** identify network phenotypes. Multivariate statistical methods can then **(C)** combine this information with brainwide gene expression data and **(D)** identify genes that are associated with the network phenotype. **(E)** Cellular processes that are known to be enriched in those genes can provide information about the processes that are particularly important in the regions highlighted by MRI. PLS, partial least squares.

Table 1

Cross-Sectional and Longitudinal Neuroimaging Brain Network Studies Performed in Healthy Children and Adolescents, Using sMRI, DWI, and fMRI

Author	Date	No. of Subjects	Age	Longitudinal	Data Type
Alexander-Bloch *et al.* (42)	2013	108	9–22 years	Yes	sMRI, rs-fMRI
Fan *et al.* (36)	2011	28	0–2 years	Yes	sMRI
Khundrakpam *et al.* (37)	2013	203	5–18 years	No	sMRI
Moura *et al.* (39)	2017	249	7–14 years	No	sMRI
Nie *et al.* (38)	2013	445	3–20 years	Yes	sMRI
Váša *et al.* (44)	2018	297	14–24 years	No	sMRI
Whitaker *et al.* (43)	2016	297	14–24 years	No	sMRI
Zielinkski *et al.* (40)	2010	300	5–18 years	No	sMRI
Baker *et al.* (55)	2015	31	15–19 years	Yes	DWI
Baum *et al.* (54)	2017	882	8–22 years	No	DWI
Dennis *et al.* (53)	2013	439	12–30 years	No	DWI
Koenis *et al.* (58)	2015	162	9–15 years	Yes	DWI
Lim *et al.* (57)	2013	121	4–40 years	No	DWI
Tymofiyeva *et al.* (51)	2013	33	0–6 months	No	DWI
Wierenga *et al.* (52)	2016	85, 38	7–23 years	No	DWI
Wierenga *et al.* (56)	2017	146, 141	4–13 years, 8–13 years	Yes	DWI
Yap *et al.* (46)	2011	39	2 weeks to 2 years	Yes	DWI
Hagmann *et al.* (49)	2010	30	2–18 years	No	DWI/rs-fMRI
Uddin *et al.* (76)	2011	23 children, 22 adults	7–9 years, 19–22 years	No	DWI/rs-fMRI
Cao *et al.* (71)	2014	126	7–85 years	No	rs-fMRI
Fair *et al.* (67)	2009	210	7–31 years	No	rs-fMRI
Fair *et al.* (128)	2007	139	7–9 years, 10–15 years, 20–31 years	No	rs-fMRI
Fransson *et al.* (68)	2011	18 infants, 18 adults	39 weeks, 22–41 years	No	rs-fMRI
Gao *et al.* (70)	2011	147	2 weeks to 2 years	No	rs-fMRI
Gu *et al.* (78)	2015	780	8–22 years	No	rs-fMRI
Hwang *et al.* (75)	2013	99	10–20 years	No	rs-fMRI
Marek *et al.* (77)	2015	192	10–26 years	No	rs-fMRI
Satterthwaite *et al.* (74)	2013	780	8–22 years	No	rs-fMRI
Supekar *et al.* (69)	2009	23 children, 22 adults	7–9 years, 19–22 years	No	rs-fMRI
Wu *et al.* (72)	2013	51	6–18 years	No	rs-fMRI
Dosenbach *et al.* (73)	2010	115	7–30 years	No	fMRI
Kaufmann *et al.* (79)	2017	797	8–22 years	No	fMRI

Studies were identified using the PubMed search terms: *brain*, *network*, or *graph theory*, *longitudinal* or *cross-sectional* or *development*, *image* or *imaging* or *MRI* or *DTI* or *scan*, and *healthy* or *normal*. Studies were only included if they included subjects below 21 years of age, discussed network or graph theoretical properties, and were either cross-sectional (studying changes in age across a population) or longitudinal.

DTI, diffusion tensor imaging; DWI, diffusion-weighted imaging; fMRI, functional magnetic resonance imaging; rs-fMRI, resting-state functional magnetic resonance imaging; sMRI, structural magnetic resonance imaging.

Table 2

Cross-Sectional and Longitudinal Neuroimaging Brain Network Studies Performed in Patients With ASD

Author	Date	No. of Subjects	Age	Longitudinal	Data Type
Chen *et al.* (103)	2015	735	6–40 years	No	rs-fMRI
Nomi and Uddin (102)	2015	26 children, 28 adolescents, 18 adults	7–39 years	No	rs-fMRI
Ball *et al.* (101)	2017	196, 51	5–86 years, 8–18 years	No	DWI
Ghanbari *et al.* (100)	2014	24 ASD, 59 control subjects	6–18 years	No	DWI
Lewis *et al.* (98)	2017	260	6 months, 12 months	Yes	DWI
Watanabe and Rees (99)	2015	45 ASD, 36 control subjects	9–18 years	No	DWI

Inclusion criteria were the same as for Table 1, except the search terms *ASD* and *autism* were used instead of *healthy* or *normal*.

ASD, autism spectrum disorder; DTI, diffusion tensor imaging; DWI, diffusion-weighted imaging; rs-fMRI, resting-state functional magnetic resonance imaging.

Table 3

Cross-Sectional and Longitudinal Neuroimaging Brain Network Studies Performed in Patients With ADHD

Author	Date	No. of Subjects	Age, Years	Longitudinal	Data Type
Fair *et al.* (112)	2010	23 ADHD, 23 control subjects	7–16	No	rs-fMRI
Kessler *et al.* (114)	2016	519, including 25 ADHD	8–22	No	rs-fMRI
Sripada *et al.* (113)	2014	133 ADHD, 288 control subjects	7–22	No	rs-fMRI

Inclusion criteria were the same as for Table 1, except the search terms *ADHD* and *attention deficit disorder* were used instead of *healthy* or *normal*.

ADHD, attention-deficit/hyperactivity disorder; rs-fMRI, resting-state functional magnetic resonance imaging.

Table 4

Cross-Sectional and Longitudinal Neuroimaging Brain Network Studies Performed in Patients With Psychotic Disorders

Author	Date	No. of Subjects	Age, Years	Longitudinal	Data Type
Alexander-Bloch *et al.* (120)	2014	106 schizophrenia, 102 control subjects	8–30	Yes	sMRI
Zalesky *et al.* (121)	2015	109 COS, 86 siblings, 102 control subjects	12–24	Yes	sMRI
Sun *et al.* (122)	2016	31 schizophrenia, 28 control subjects	19–54	Yes	DWI
Jiang *et al.* (124)	2015	20 adult-onset/26 early-onset schizophrenia patients, 17/25 age-matched control subjects	26 ± 8, 15 ± 2, 30 ± 11, 14 ± 3	No	rs-fMRI
Tomasi and Volkow (123)	2014	40 children/adolescents, 69 schizophrenia, 74 control subjects	13 ± 4, 38 ± 14, 36 ± 12	No	rs-fMRI
Wang *et al.* (125)	2017	76 ARMS nontransition, 12 ARMS transition, 48 control subjects	21.7 ± 3.6, 19.7 ± 3.1, 21.5 ± 4.2	Yes	rs-fMRI

Inclusion criteria were the same as for Table 1, except the search terms *psychosis* and *schizophrenia* were used instead of *healthy* or *normal*. ARMS, at-risk mental state; COS, childhood-onset schizophrenia; rs-fMRI, resting-state functional magnetic resonance imaging; sMRI, magnetic resonance imaging.

Table 5

Some Example Large Open Datasets Relevant to Healthy and Atypical Development

Dataset	Disorder	No. of Subjects	Age, Years	Longitudinal Neuroimaging	Data Type	Availability
Child Mind Institute Healthy Brain Network (145)	Population	10,000	5–21	No	fMRI, sMRI, DWI, EEG	Ongoing, 664 subjects available in first release
IMAGEN (146)	Population	2000	14–22	Yes	fMRI, sMRI, DWI	Open to project proposals
NKI/Rockland Study (147)	Population	1000 expected	6–85	Yes	rs-fMRI, sMRI, DWI	Ongoing, some data available
PNC (9)	Population	1000	8–21	Obtained but not openly available at present	fMRI, sMRI, DWI	Available
ADHD-200 (148)	ADHD	491 HC, 285 ADHD	7–21	No	rs-fMRI, sMRI	Available
ABIDE I (149)	Autism	539 ASD, 573 HC	7–64	No	rs-fMRI, sMRI	Available
ABIDE II (132)	Autism	521 ASD, 593 HC	5–64	Partially ($n = 38$)	rs-fMRI, sMRI, DWI	Available
NUSDAST (150)	Schizophrenia	171 SCZ, 170 HC, 44 SCZ siblings, 66 HC siblings	13–67	Yes	sMRI	Available

Datasets were only included if they had large numbers of subjects ($N > 300$), with subjects from a range of ages, including significant numbers of subjects under 21 years of age, and are (or will be) openly available.

ABIDE, Autism Brain Imaging Data Exchange; ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; DTI, diffusion tensor imaging; DWI, diffusion-weighted imaging; EEG, electroencephalography; fMRI, functional magnetic resonance imaging; HC, healthy control; NKI, Nathan S. Kline Institute for Psychiatric Research; NUSDAST, Northwestern University Schizophrenia Data and Software Tool; PNC, Philadelphia Neurodevelopmental Cohort; rs-fMRI, resting-state functional magnetic resonance imaging; SCZ, schizophrenia; sMRI, structural magnetic resonance imaging.