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Future directions for examination of brain networks in neurodevelopmental disorders

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Abstract

Neurodevelopmental disorders are associated with atypical development and maturation of brain networks. A recent focus on human connectomics research and the growing popularity of open science initiatives has created the ideal climate in which to make real progress towards understanding the neurobiology of disorders affecting youth. Here we outline future directions for neuroscience researchers examining brain networks in neurodevelopmental disorders, highlighting gaps in the current literature. We emphasize the importance of leveraging large neuroimaging and phenotypic datasets recently made available to the research community, and suggest specific novel methodological approaches, including analysis of brain dynamics and structural connectivity, that have the potential to produce the greatest clinical insight. Transdiagnostic approaches will also become increasingly necessary as the Research Domain Criteria (RDoc) framework put forth by the National Institute of Mental Health (NIMH) permeates scientific discourse. During this exciting era of big data and increased computational sophistication of analytic tools, the possibilities for significant advancement in understanding neurodevelopmental disorders are limitless.

Keywords

human connectomics; network neuroscience; resting state fMRI; dynamic functional connectivity; diffusion weighted imaging

What are brain networks and why should we focus on them?

Over the past decade we have witnessed the emergence of a new subspecialization within cognitive neuroscience, often referred to as "human connectomics" or "network neuroscience". This new theoretical framework originated from observations that cognitive

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processes rely on interactions among distributed brain regions (Mesulam, 1990), and encourages the examination of brain connectivity as a means for exploring the biology of complex behaviors (Sporns, 2014). Concepts from network science and complex systems are increasingly being used in this nascent field (Bassett & Sporns, 2017).

A network is any system that can be represented by a graph consisting of nodes and edges. In cognitive neuroscience, nodes are often thought of as discrete brain regions and edges as the links or connections between them (Bressler & Menon, 2010; Wig, Schlaggar, & Petersen, 2011). Connectivity in this context is typically defined as functional (e.g. temporal correlations between remote neurophysiogical events (Friston, 1994) or structural (e.g. anatomical links between brain regions). For the purposes of the current review, a brain network will be considered a neural system with characteristic functional and/or structural connectivity patterns among brain regions that constitute it. One example of a well-studied brain network that has been implicated in multiple mental disorders (Buckner, Andrews-Hanna, & Schacter, 2008) is the default mode network (DMN) (Raichle, 2015). The DMN is comprised of key nodes in medial prefrontal and posterior cingulate cortices (Greicius, Krasnow, Reiss, & Menon, 2003), and is thought to be involved in internally-oriented, evaluative cognitive processes (Uddin, Iacoboni, Lange, & Keenan, 2007).

In the context of clinical child and adolescent psychology, a focus on connectomics has yet to become mainstream. There are however, reasons to believe that such studies will become increasingly important for the future of the field. Researchers, clinicians, and policy makers are beginning to move towards more biologically-based models in their conceptualizations of disorders emerging in early childhood. The most prominent example of this shift is the Research Domain Criteria (RDoC) framework put forth by the National Institute of Mental Health. The RDoC integrates genomics, neural circuit, and behavioral data in an attempt to understand mental health in terms of *degrees* of function and dysfunction in psychological and biological systems (Insel, 2014). A recent comprehensive review highlights how the RDoC approach compares with traditional models such as those guiding the Diagnostic and Statistical Manual of Mental Disorders (DSM) and International Classification of Diseases (ICD) with respect to understanding and classifying mental disorders. The authors identify key challenges for the field, including understanding etiology and multiple causality, the description of phenomena as categorical or dimensional, thresholds for setting boundaries between disorder and nondisorder, and comorbidity among conditions (Clark, Cuthbert, Lewis-Fernandez, Narrow, & Reed, 2017). Network neuroscience can make subtle distinctions about neural function and dysfunction that may vary both along symptom spectrums as well as across development. As such, network neuroscience is poised to make significant contributions to each of the growth areas highlighted by Clark and colleagues, and to lead the field towards more data-driven, objective approaches for disease classification and treatment. Quantification of brain networks provides biologically-grounded metics that can be used to discriminate disordered from non-disordered populations, parse heterogeneity within disorders, and evaluate the effectiveness of treatment strategies.

Brain networks in neurodevelopmental disorders

Several reviews have summarized how network neuroscience approaches have informed studies of typical and atypical development (Di Martino et al., 2014; Uddin, Supekar, & Menon, 2010). Key themes that have emerged from these investigations include an emphasis on the evolution of segregation and integration of brain networks across development (Fair et al., 2007; Grayson & Fair, 2017). To date, the neurodevelopmental disorders that have been most thoroughly investigated using neuroimaging approaches are autism spectrum disorder (ASD) (Ecker, 2017; Uddin, Supekar, & Menon, 2013) and attention-deficit/hyperactivity disorder (ADHD) (Castellanos & Aoki, 2016). Considerable progress has also been made towards characterizing brain network abnormalities that emerge across adolescence in disorders including schizophrenia (Fornito & Bullmore, 2015), anxiety (Tovote, Fadok, & Luthi, 2015), and depression (Hamilton, Farmer, Fogelman, & Gotlib, 2015). While the DMN has received the most attention from clinical neuroscientists (Mohan et al., 2016), it is worth noting that several large-scale brain networks, and interactions among them, have increasingly been implicated in disorders with early life onset. One key finding emerging from studies of brain networks is that dysfunction of densely interconnected brain regions ("hubs"), such as the insula, is a common feature of multiple disorders including ASD, schizophrenia, and frontotemporal dementia (Uddin, 2015). Meta-analyses examining schizophrenia, bipolar disorder, depression, addiction, obsessive-compulisve disorder, and anxiety reveal common gray matter volume loss in the insula, suggesting that this region may be a common neurobiological substrate for mental illness (Goodkind et al., 2015). Unresolved big questions for the field include understanding whether and to what extent different clinical phenomena map on to distinct neurobiological signatures and how this might change across development. If it turns out to be the case that the majority of disorders result from atypical functional and structural connectivity within and among circumscribed brain networks, the implications for clinical psychology are widespread. Recent advances in neuroimaging data analytic approaches now permit such investigations.

Future Directions: Advanced neuroimaging data analytic approaches

Analysis of brain dynamics

Much of what is currently known regarding the development of brain networks comes from studies assessing functional connectivity using resting-state fMRI. Resting-state fMRI involves collection of functional neuroimaging data from participants who are not engaged in task performance. Participants are instructed to lay still in the MRI and either close their eyes or fixate on a cross-hair during data collection, which typically lasts five minutes or longer. Functional connectivity analyses use resting-state fMRI data to quantify spontaneous, synchronized fluctuations in the blood oxygen level dependent (BOLD) signal and identify "intrinsic" functional brain networks. Since the initial discovery that coherent, spontaneous low-frequency fluctuations in the BOLD signal can delineate functional brain networks even in the absence of task performance (Biswal, Yetkin, Haughton, & Hyde, 1995), it has become widely accepted that so-called "resting state networks" (De Luca, Beckmann, De Stefano, Matthews, & Smith, 2006) or "intrinsic connectivity networks" (Seeley et al., 2007) recapitulate the range of brain networks observable during task

performance (Bolt, Nomi, Rubinov, & Uddin, 2017; Cole, Bassett, Power, Braver, & Petersen, 2014; Smith et al., 2009).

To date, the majority of resting-state fMRI studies have averaged correlation values across the duration of data collection to create an overall index of functional connectivity strength between brain regions. A novel approach termed "dynamic functional connectivity" challenges the assumption that such an analysis strategy adequately indexes brain function. This new approach provides a means for quantification of brain dynamics from fMRI data by enabling the study of moment-to-moment (time-varying) changes in functional coupling between brain regions (C. Chang & Glover, 2010). Rather than assuming that functional relationships between brain regions remain stable over time, dynamic functional connectivity approaches aim to determine the frequency and duration of specific recurring "functional network connectivity states" in the brain. One approach for computing dynamic functional connectivity is the "sliding-window approach" (Figure 1)(Allen et al., 2014). This approach computes functional connectivity strength on the order of seconds rather than the more traditional practice of averaging across minutes, and permits the quantification of metrics including "dwell time" (the amount of time spent in a particular functional network connectivity state) and "frequency of occurrence" (the number of times a particular functional network connectivity state occurs). Another approach for computing dynamic functional connectivity relies on the identification of critical timepoints when the signal intensity surpasses a certain threshold, giving rise to multiple stable spatial patterns or co-activation patterns (CAPs) that can be obtained by clustering of critical time frames. The CAP approach relies on fewer model assumptions than the sliding window approach, and allows for the examination of state alterations closer to the temporal resolution of individual time frames (J. E. Chen, Chang, Greicius, & Glover, 2015). A review of these and other approaches for quantifying brain dynamics from fMRI data has recently been published (Preti, Bolton, & Van De Ville, 2016). It should be noted that the field of functional connectivity dynamics is very new and rapidly evolving, and debates surrounding appropriate methodology and conceptualization are ongoing. Recent controversies regarding how to properly measure and interpret dynamics in fMRI data have yet to be resolved (Abrol et al., 2017; Glomb, Ponce-Alvarez, Gilson, Ritter, & Deco, 2017; Liegeois, Laumann, Snyder, Zhou, & Yeo). Research groups actively working in this area are encouraged to participate in the Time Varying Working Group (https://groups.google.com/forum/#!forum/time-varying-working-group) that was formed at the 2017 Annual Meeting of the Organization for Human Brain Mapping in Vancouver.

Notwithstanding, studies of brain dynamics have already produced novel insights into typical brain development and maturation. Hutchison and Morton found that increasing age is associated with greater variability of functional connection strengths across time during resting states (Hutchison & Morton, 2015). It is currently unknown how atypical brain dynamics contribute to the emergence of symptoms characteristic of most neurodevelopmental disorders. A few studies have investigated functional brain dynamics in autism. Watanabe and Rees report that high-functioning adults with ASD show fewer transitions between brain states, a finding that is linked with symptom severity (Watanabe & Rees, 2017). Others have begun to explore brain dynamics as they relate to psychotic symptoms, and report not only that clinical high-risk individuals show intermediatate

dynamic functional connectivity patterns between healthy controls and individuals with schizophrenia (Du et al., 2017), but that otherwise healthy individuals experiencing subclinical symptoms show alterations in dynamic connectivity that correlate with executive function (Barber, Lindquist, DeRosse, & Karlsgodt).

Analysis of brain dynamics from resting-state fMRI data, while in its early stages, promises to be a fruitful avenue for exploring individual differences in functioning levels across neurodevelopmental disorders (Hutchison & Morton, 2016). In particular, functional connectivity dynamics can reveal more nuanced patterns of dysfunction within neural circuits than traditional static connectivity analyses. Individual differences in brain dynamics correlate with self-control (Steimke et al., 2017) and executive function abilities (Nomi et al., 2017), and can explain twice the variance in behavior across domains (alertness, cognition, emotion, personality) compared with traditional functional connectivity metrics (Jia, Hu, & Deshpande, 2014). The increased sensitivity to detect brain network abnormalities afforded by dynamic functional connectivity analyses will provide utility in future studies attempting to tease apart affects of comorbidity and heterogeneity on mental health outcomes in clinical populations.

Analysis of structural connectivity

Diffusion weighted imaging (DWI) is a powerful non-invasive tool for examining structural connectivity, specifically white matter microstructure, based on patterns of water diffusion. By observing how and in what directions diffusion is constrained, information about the surrounding tissue can be inferred. In the DWI field, the diffusion tensor model (DTI model) is most commonly employed, and yields the frequently used fractional anisotropy (FA) measure, which indirectly indexes "neuronal integrity", putatively reflecting both myelination and organization of the white matter tracts. In addition, the secondary measures of radial (RD) and axial diffusivity (AD) are believed to more specifically index myelination and axonal organization, respectively (Beaulieu & Allen, 1994; Song et al., 2003; Wozniak & Lim, 2006). With these capabilities, coupled with the ability to perform the technique in a standard MRI scanner over relatively short scan periods, DTI has become a very practical way to investigate structural connectivity, and has been shown to be sensitive to neurodevelopmental change (Asato, Terwilliger, Woo, & Luna, 2010; De Bellis et al., 2001; Giorgio et al., 2010; Kochunov et al.; Schmithorst & Yuan, 2010; Westlye et al., 2010).

However, despite these assets, DTI has limitations that are important for developmental researchers to consider. For example, the DTI model measures only extracellular space between myelinated axons, and thus cannot differentiate signal changes from myelin thickness, axonal girth, tract spacing, or organization. Accordingly, FA and other measures are always carefully referred to as indexing "WM integrity" rather than "myelination". Given the importance of myelin development in childhood and adolescence, it is important to understand strengths and limitations in measuring it. Currently, diffusion imaging is undergoing a period of rapid change, as the field tries to address and understand these limitations. For example, RD is generally considered the best DTI measure of myelination, however recent evidence shows that other factors may contribute more to RD than previously thought (E. H. Chang et al., 2017). In addition, it has become apparent that neural

tissue structure may be too complex to be accurately described by a single tensor. One voxel may contain fibers in multiple orientations, which is a particular problem in areas where tracts intersect and there are crossing fibers. In addition, there can be intracellular and extracellular compartments within the tissue, which may have different diffusion properties as well as different biological significance and different patterns of developmental change. Thus, there has been recent movement towards employment of non-FA measures that go beyond simple tensor models. First, when using DTI it is now common to report secondary tensor measures of RD, AD, and MD along with FA. In addition, with the recent widespread adoption of Human Connectome Project (HCP)-based sequences, and the broader availability of multi-shell sequences (e.g. diffusion sequences with multiple b-values), a wider range of available techniques are moving into the mainstream. For example, there is continuing development of alternatives to FA, such as quantitative anisotropy (QA) (Yeh, Verstynen, Wang, Fernandez-Miranda, & Tseng, 2013) which may provide a better basis for tractography and shows less interference from confounding factors such as crossing fibers.

Unfortunately, although we know that there are challenges in using DTI to measure myelination, the methods that might remedy this are rarely implemented in developmental research. One such technique is diffusion kurtosis imaging (DKI), which uses a different mathematical approach to modeling diffusion (Jensen & Helpern, 2010). Only a few studies have employed DKI developmentally, with two studies showing that kurtosis was more sensitive to microstructural changes than FA (Grinberg et al., 2017; Paydar et al., 2014), and another finding that DKI showed maturational differences in children with ADHD (Adisetiyo et al., 2014). Techniques such as DKI may not necessary supplant FA, but can be complementary. Relatedly, diffusion spectrum imaging (DSI) has been able to reveal entirely new features of the organization of the white matter (Wedeen, Hagmann, Tseng, Reese, & Weisskoff, 2005; Wedeen et al., 2012; Wedeen et al., 2008), but while it has been more widely employed than DKI, it is rarely used in developmental samples. Specifically, DSI has been used to demonstrate differences in ADHD youth and controls (Chiang, Chen, Lo, Tseng, & Gau, 2015; Chiang, Chen, Shang, Tseng, & Gau, 2016; Gau, Tseng, Tseng, Wu, & Lo, 2015; Lin et al., 2014) and in ASD (Lo, Chen, Hsu, Tseng, & Gau, 2017; Lo et al., 2011) showing it is sensitive to the kinds of differences we would expect in neurodevelopmental disorders. Still, work characterizing overall developmental changes in DSI measures is needed.

Another promising DWI method is neurite orientation dispersion and density imaging (NODDI) (Zhang, Schneider, Wheeler-Kingshott, & Alexander, 2012). This technique uses multi-shell DWI data and allows us to make better estimates of microstructural architecture (Figure 2). In particular, NODDI provides for the estimation of three factors relevant to development: neurite orientation, which reflects dendritic density and the complexity of dendritic branching (Jespersen, Leigland, Cornea, & Kroenke, 2012), neurite density, which is highly correlated with myelination (Jespersen et al., 2010), and cellular density (Sepehrband et al.). Measures of pruning and myelination have clear relevance to both healthy and disordered neurodevelopment, particularly in adolescence, and yet only a few developmental studies have employed NODDI thus far (Batalle et al., 2017; Eaton-Rosen et al., 2015; Genc, Malpas, Holland, Beare, & Silk, 2017; Jelescu et al., 2015; Kansagra et al., 2016; Kunz et al., 2014), primarily in neonates. One limitation in employing many of these

analytic strategies is that very few of the large publically available data sets include multi-shell data, which is necessary for the majority of these new techniques. It is thus imperative, moving forward, that developmental researchers not only obtain multi-shell data, but also explore the power of these newly developed techniques and translate them to developmental samples.

Machine learning for classification, prediction, and parsing heterogeneity

In computer science, the term 'machine learning' is used to refer to algorithms that can learn from and make predictions from data. In addition to using neuroimaging to identify neural correlates of neurodevelopmental disorders, researchers have recently begun to use features derived from functional and structural MRI data to discriminate between clinical and non-clinical populations, or to predict treatment response or other outcomes in patients. Identification of reliable brain-based biomarkers for neurodevelopmental disorders using machine learning can in principle help provide mechanistic explanations of etiology and symptomatology, and contribute to earlier identification and targeted treatment.

While the application of machine learning to the study of neurodevelopmental disorders is still in its infancy, the availability of large datasets has significantly accelerated the pace of this research. In one recent example using the Autism Brain Imaging Data Exchange (ABIDE) dataset, resting-state fMRI features were used to discriminate autism from typical development with 67% accuracy (Abraham et al., 2017). Importantly, this study performed both intra-site and inter-site cross-validation to validate the robustness of their approach. Such careful characterization of the effects of site-specific as well as more generalizable effects will be important for future work aimed at increasing the potential translational impact of classification studies.

A critical distinction in machine learning is that between supervised and unsupervised methods. Most neuroimaging classification studies have used supervised methods, where presumed labels (eg. ASD vs. control) are used to first train a classifier to find patterns of brain connectivity associated with the distinct labels. With unsupervised methods, on the other hand, the classifier explores population samples for patterns in the brain data which may be associated with a clinical population. With unsupervised approaches, subjectivity involved in label selection is thus avoided. A recent study using the ABIDE dataset achieved 70% accuracy in classifying ASD vs. control participants using deep learning algorithms, which have the added advantage of using unsupervised learning methods for extracting relevant neuroimaging features (Heinsfeld, Franco, Craddock, Buchweitz, & Meneguzzi, 2018).

Of note, several challenges inherent to using machine learning in clinical neuroscience have recently been noted. These include limited sample sizes, inconsistent approaches towards application of classification algorithms, and ascertainment bias due to the common practice of including equal numbers of patients and controls in studies (Uddin, Dajani, Voorhies, Bednarz, & Kana, 2017). On a more optimistic note, the issues regarding small sample sizes are now beginning to be addressed with the availability of the multi-site, large databases described below.

Future directions include expansion of the use of unsupervised learning methods to parse heterogeneity across neurodevelopmental disorders. Consistent with the RDoC framework (Casey et al., 2013; Insel, 2014), future work may go beyond traditional DSM-based diagnoses to identify aspects of cognitive dysfunction that cut across diagnostic categories (Dajani, Llabre, Nebel, Mostofsky, & Uddin, 2016). We envision that both supervised and unsupervised machine learning will continue to be important tools for discovering sources and consequences of comorbidity among neurodevelopmental disorders.

Future Directions: Harmonization of data acquisition protocols

As we enter an era of "big data", one growing focus is on the harmonization of neuroimaging, cognitive, and clinical measures across institutions, research groups, and samples. One important goal is increasing our understanding of the manner in which brain network connectivity supports cognitive processes, however our ability to pool data across samples to carry out big-data style analyses is limited if the method for assessing cognition is not standardized across studies. With growing acceptance of the RDoC approach, efforts have been made to identify specific neurocognitive tasks that probe cognitive domains of interest (for example, cognitive control, reward learning). This, in theory, should make it more likely that different groups, interested in different clinical populations, may select overlapping measures enabling data sharing across sites. However, for developmental studies it is not just important that measures allow for valid or parallel comparisons across sites, but also that they allow valid comparisons across age groups. Ongoing efforts have been made in this direction, for instance, the Penn's Computerized Neurocognitive Battery (CNB) has been psychometrically described in individuals aged 8–21, allowing for fairly broad developmental analyses. Likewise, the NIH Toolbox Cognition Battery (CB) is meant to be able to measure cognition from childhood up into old age (Weintraub et al., 2013). As the field moves forward, it would be helpful for researchers across areas to adopt these standardized measures in new studies to facilitiate data sharing and comparison.

Recent large-scale initiatives can provide examples for researchers of how harmonization of neuroimaging approaches can be accomplished in future studies. In one example focused on analytic techniques, the ENIGMA consortium (enigma.ini.usc.edu) has compiled very large neuroimaging samples by providing structured processing pipelines for investigators to employ in their laboratories, resulting in region-of-interest based data that can be shared, for example, to examine development of brain structure or structural connectivity across the lifespan (Jahanshad & Thompson, 2017). The benefit of this approach is that it is able to take advantage of data that investigators have already collected, whether the initial protocols were harmonized or not. Alternatively, on the side of acquisition approaches, the HCP has had a substantial impact on imaging practices. The HCP sequences have become broadly available, and scanners with features like multiband capabilities that allow the collection of high resolution data in shorter amounts of time (important for studies in children and adolescents as well as patient populations) have become more widespread. As a result, more groups have worked to try to implement the same neuroimaging sequences across sites, thus enabling both *a priori* and post-hoc collaborations. These approaches represent promising strides, and efforts are ongoing to determine the best methods for compilation and comparison of multi-site data (Jovicich et al., 2016; Mirzaalian et al., 2015).

Future Directions: Integration with biological measures

Biological factors may have a profound impact on developmental studies, and it is important to consider how they can be included in future studies of children and adolescents (De Los Reyes & Aldao, 2015). Importantly, some of these factors may differ or be more pronounced in patient populations. A key consideration for many developmental brain connectivity studies is the inherent variability in levels of maturity even among children of the same chronological age, particularly in peri-pubertal individuals where, for example, the differences between two twelve year olds can be substantial. One approach to this issue, which is still fairly uncommon in the literature, is to either incorporate questionnaire based measures of pubertal stage, or to measure hormonal markers of puberty (Blakemore, Burnett, & Dahl, 2010). As attention to this issue grows, and data from large scale studies become available, enough imaging data with puberty measures may accumulate to make these analyses more common (Di Martino et al., 2014; Herting et al., 2017; Nguyen et al., 2013; Satterthwaite et al., 2016; Satterthwaite et al.). However, an important limitation of such measures is that the age-range in which pubertal changes may occur, typically around early adolescence (Blakemore et al., 2010), is narrower than our current understanding of neural and cognitive development, which can continue up into the third decade of life (Casey, Heller, Gee, & Cohen, 2017; Dennis et al.; Karlsgodt et al., 2015; Peters et al., 2014). More research is needed to clarify whether pubertal changes serve as a driving force impacting neural connectivity changes.

In addition, body mass index (BMI) has been associated with differences in structural brain connectivity in both adults and adolescents (Alarcon, Ray, & Nagel, 2016; Gupta et al., 2015; Kennedy, Collins, & Luciana, 2016). The importance of this in young samples is twofold. First, there has been a nationwide increase in obesity, with 30% of children in North America being qualified as either overweight or obese (Tyson & Frank, 2017), which would of course be associated with an increased BMI. However, in addition, adolescence is a risk period for eating disorders such as anorexia, which may be associated with lower BMI, and which has also been shown to be associated with both functional and structural brain connectivity changes (Ehrlich et al., 2015; Gaudio et al., 2017; Scaife, Godier, Filippini, Harmer, & Park, 2017). Furthermore, some patient populations may have differences in BMI associated with medication or other factors (Ventriglio, Gentile, Stella, & Bellomo, 2015). As BMI is a relatively straightforward variable to acquire, often based on data already gathered as part of the imaging process, inclusion of BMI with other demographics may help with generalizability and comparisons between samples. BMI may also be used as a covariate to help better understand the basis of neural connectivity differences.

There is also growing evidence that sleep is an important variable, particularly for adolescents (Meltzer, 2017). Differences in sleep have been shown to impact functional connectivity measures (Nilsonne et al., 2017; Uy & Galvan, 2017; Zhou, Wu, Yu, & Lei, 2017) as well as functional activation patterns (Telzer, Fuligni, Lieberman, & Galvan, 2013). However, sleep duration, self-reported sleepiness, or sleep variability is rarely reported on as a part of standard imaging studies, nor is it often included as a covariate. This variable is particularly important to consider in clinical samples, as there are a number of developmental disorders that have been associated with sleep disruption (Meltzer & Mindell,

2006). Finally, early life environmental influences, such as trauma, stress, or immune dysfunction can have profound impacts on later neural function or cognition (Ellman et al., 2010; Fareri & Tottenham, 2016; Hostinar, Nusslock, & Miller, 2018). These factors may be relatively more difficult to measure, but studies that are focused on elucidating the effects of such early factors may have important ramifications for our understanding of development.

An important consideration for future research is that while there have been efforts to investigate biological variables that might contribute to structural and functional brain connectivity changes, as described above, the majority of these efforts are cross-sectional. Moving forward, it will be important to look not only at how such variables impact neuroimaging measures in the moment, but also how they longitudinally impact developmental trajectories.

Future Directions: Considerations for translational neuroscience

With a growing emphasis in the field on translational research that can take us from 'bench to bedside', it is important to consider how measures of brain networks can bridge across different levels of analysis, and how that may impact our thinking about developmental disorders. Indeed, some of our earliest notions that brain regions can function as a network originated from studies in animal models (Fuster & Alexander, 1971; Quintana, Fuster, & Yajeya, 1989). The power that neuroimaging analyses derive from being non-invasive, easy to integrate with behavior, and possible to do longitudinally cannot be understated, but many neuroimaging measures are limited by their inferential nature. As new analytic methods develop, it is important to continue thinking of ways in which translational work may serve as a validation or extension of more standard analytic approaches. As one example of the potential for translational validation of current structural connectivity methods, there have been efforts to use neuroimaging and histological techniques in animal models to validate our assumptions about what aspects of cellular architecture DTI techniques are measuring (E. H. Chang et al., 2017; Sepehrband et al., 2015). In addition, with recent advances in small bore imaging, it has also become possible to measure functional connectivity in rodent models (Bergmann, Zur, Bershadsky, & Kahn, 2016; Gorges et al., 2017), expanding the range of possibility for genetic investigations or assessments of animal models of neuropsychiatric disorders. By continuing to pursue translational approaches that take the new developments from cognitive neuroscience and neuroimaging fields, and translate them both to basic science models of cellular and neural function, as well as to relevant clinical populations, we will greatly enhance our ability to gain traction on the neural bases of developmental disorders.

Future Directions: Leveraging the power of existing data collection and sharing initiatives

One of the most exciting developments over the past several years has been the emphasis, both from funding agencies and from grassroots initiatives, on making large neuroimaging datasets publicly available to researchers. These "open science" data sharing initiatives permit unprecedented access to neuroimaging and phenotypic information, and have already been leveraged by researchers across fields to provide unique insights into typical and

atypical brain development. A list of currently available datasets curated by the authors and the larger community is available at https://sites.google.com/site/publicdatadatabase/. Below we highlight some of these datasets that we anticipate will continue to contribute to discovery science in developmental populations for years to come (Table 1). We note where some of the future directions outlined above can already be addressed using existing datasets.

Philadelphia Neurodevelopmental Cohort

The Philadelphia Neurodevelopmental Cohort (PNC, http://www.med.upenn.edu/bbl/philadelphianeurodevelopmentalcohort.html) is a research initiative funded by NIMH that focuses on characterizing brain and behavior interaction with genetics (Satterthwaite et al., 2016). Data have been collected from over 9,500 individuals age 8–21 from the greater Philadelphia area, with functional and structural neuroimaging data available from a subset of these participants. These data permit analyses of the impact of genetic variation on brain network organization and function in children and adolescents. As this dataset is based on a community sample, it is also well-suited to allow investigations of not just diagnosed disorders, but of a range of subclinical symptoms, for instance, attention disorders, psychosis spectrum disorders, and mood disorders, consistent with the RDoC approach.

Adolescent Brain Cognitive Development

The Adolescent Brain Cognitive Development (ABCD, https://abcdstudy.org/) is the largest concerted effort in the United States to study brain development and factors that influence child health. Supported by NIH, ABCD funds 21 research sites across the US to collect neuroimaging, behavioral, and other biological data from approximately 10,000 children ages 9–10 years longitudinally. This ambitious project aims to determine how childhood experiences interact with biological changes to affect brain development and social, behavioral, academic, and health outcomes. This study will be releasing data that will potentially allow researchers to predict biological factors that contribute to the development of substance abuse and other psychiatric outcomes. Further, the longitudinal design will provide neuroimaging data suitable for answering questions regarding developmental trajectories of brain networks and relationships with adolescent mental health. The inclusion of sleep measures collected using wearable sensors makes this dataset particularly promising with respect to answering open questions about how sleep quality influences the developing brain. An inaugural, fast track data release occurred in July 2017, with plans to release curated data annually starting February 12, 2018.

Lifespan Human Connectome - Development

The Lifespan Human Connectome Project Development (HCP-D) (https://www.humanconnectome.org/study/hcp-lifespan-development) is associated with the broader HCP initiative, which is focused on assessing adults age 21–35 using high quality multi-modal neuroimaging measures (https://www.humanconnectome.org/). HCP-D is an NIH funded project that will enroll approximately 1350 healthy children, adolescents, and young adults age 5–21 across four institutions. Importantly for developmental analyses, a subset of peri-pubertal participants return for longitudinal data acquisition at 1.5 and 3 years. This multimodal data set is particularly well-suited for future investigations of not just how

individual neural features, such as grey matter and white matter, mature independently, but how their developmental processes may interact, something which is currently not well understood. The high quality of the functional and structural neuroimaging data collected under this project will permit the advanced types of analyses discussed above, including analysis of brain dynamics and microstructural architecture.

IMAGEN

IMAGEN is a European consortium following 2000 participants across 8 sites longitudinally, with assessments at ages 14, 16, 19, and 22. This project is focused on elucidating neural and genetic risk factors for psychiatric illnesses as well as the basis of variability in specific traits associated with psychiatric symptomatology, including sensitivity to reward and punishment, impulsivity, and emotional response (Schumann et al., 2010). The longitudinal design with multiple timepoints of data collection provides unprecedented resources for clinical neuroscience researchers to explore questions surrounding brain network maturation and socioemotional development. Further, this dataset will be ideal for those interested in using machine learning applied to neuroimaging data to predict which individuals will go on to develop neuropsychiatric disorders.

ABIDE I and II

The Autism Brain Imaging Data Exchange (ABIDE, http://fcon_1000.projects.nitrc.org/indi/abide/) is a grassroots initiative founded with the understanding that single laboratories typically are unable to obtain sufficiently large datasets to reveal the brain mechanisms underlying a heterogeneous disorder like ASD. The curators of ABIDE have released two large-scale collections (ABIDE I and ABIDE II), each created through the aggregation of datasets independently collected across more than 24 international laboratories. ABIDE I was openly released in August of 2012 (Di Martino, 2014) and ABIDE II was released to the scientific community in June 2016 (Di Martino, 2017). These datasets are already starting to be used by researchers using machine learning to conduct classification analyses, and will continue to provide utility for those interested in understanding the multiple neurobiological manifestations of ASD. The wide age range of participants included in these datasets permits investigation of brain atypicalities in ASD as a function of developmental stage (Uddin et al., 2013).

ADHD-200

The ADHD-200 Sample (http://fcon_1000.projects.nitrc.org/indi/adhd200/) is another grassroots initiative that orchestrated the unrestricted public release of 776 anonymized resting-state fMRI, structural MRI, and phenotypic datasets across 8 independent sites (Consortium, 2012). In combination with ABIDE, ADHD-200 data may contribute to a clearer undestanding of ASD/ADHD comorbidity and its neural substrates. Further, as the ADHD-200 contains data from different ADHD subtypes, it will be possible to explore whether these distinct clinical categories map onto distinct patterns of brain network abnormalities.

SchizConnect

SchizConnect (http://schizconnect.org/) is a database that allows researchers to search for and download publicly available neuroimaging data collected from individuals with schizophrenia (Ambite et al., 2015). SchizConnect provides data integration across several multi-site consortia including the Functional Biomedical Informatics Research Network (FBIRN) (Glover et al., 2012) and the Mind Clinical Imaging Consorium (MCIC) (King et al., 2014). With a current user count of 502 since its initial release in 2014, this tool continues to provide schizophrenia researchers with the means to access previously collected neuroimaging data to conduct replication studies or test novel machine learning algorithms on large samples.

NKI-Rockland

The Enhanced Nathan Kline Institute-Rockland Sample, funded by an NIMH award, (http://fcon_1000.projects.nitrc.org/indi/enhanced/) is a large-scale community sample of individuals across the lifespan, and includes a host of neuroimaging, physiological, and phenotypic information (Nooner et al., 2012). This well-characterized sample spans ages 6–85, and includes detailed information regarding psychiatric diagnoses and scores on a battery of widely-used neurocognitive measures. Similar to the PNC sample, this community sample includes a broad range subclinical symptoms, making RDoC style investigations possible.

Pediatric Imaging, Neurocognition, and Genetics

The Pediatric Imaging, Neurocognition, and Genetics (PING) data resource is a multi-site project which includes neurodevelopmental histories, information regarding developing mental and emotional functions, multimodal brain imaging data, and genotypes for over 1000 chidren and adolescents ages 3–20 (http://pingstudy.ucsd.edu/). Funded by the National Instute of Drug Abuse (NIDA) and the National Institute of Child Health and Human Development (NICHD), this initiative has already resulted in a number of discoveries surrounding development of self-regulation (Fjell et al., 2012) and the genetic organization of brain areas (C. H. Chen et al., 2012).

Conclusions

At this juncture, the field of child and adolescent psychology has the potential to draw inspiration and resources from network neuroscience to make dramatic progress towards understanding the neurobiology of mental disorders affecting youth. Collaborations between cognitive neuroscientists, clinical psychologists, engineers and computer scientists will result in the expertise necessary for leveraging the power of large datasets to further our understanding of typical and atypical brain network development.

Acknowledgments

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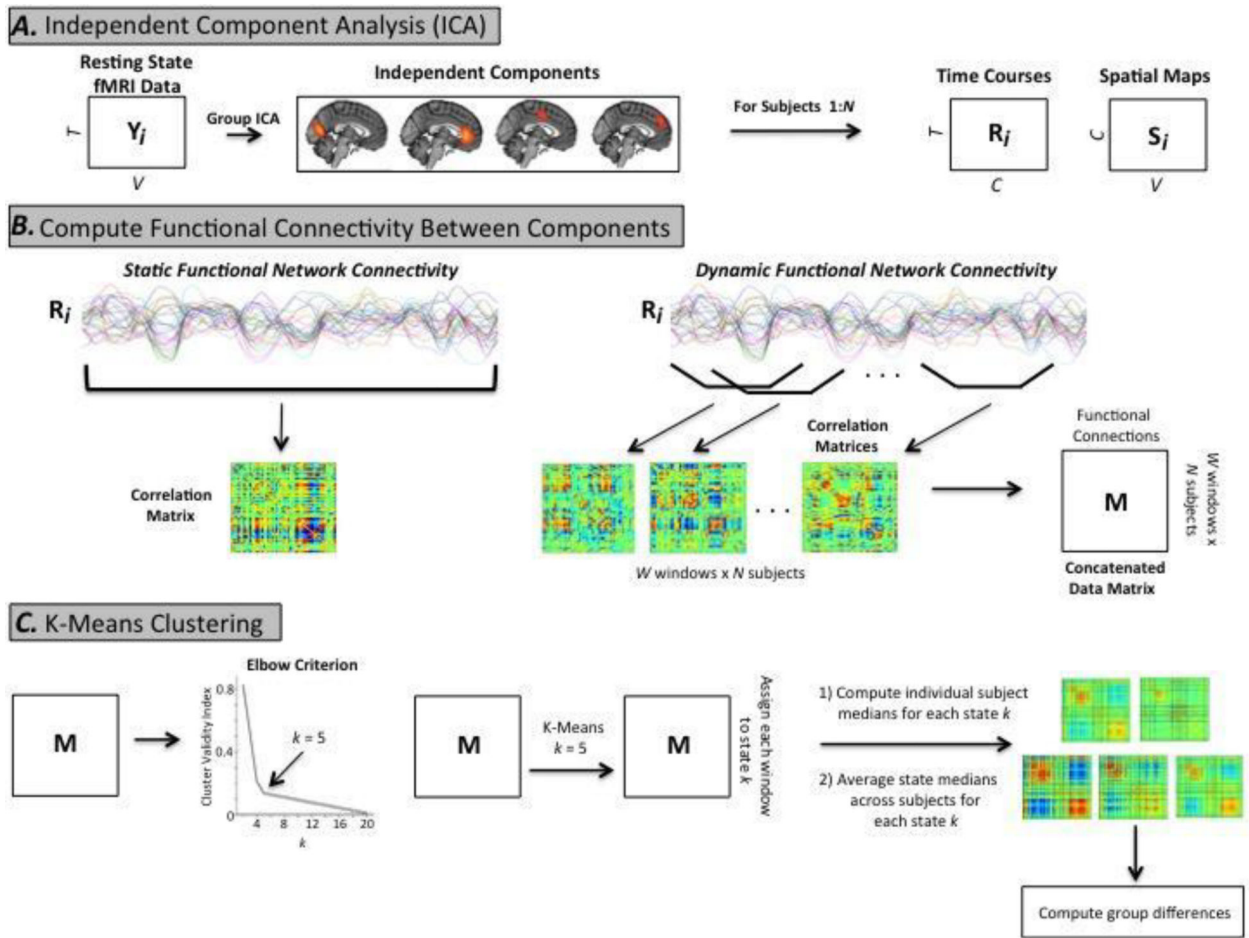
Figure 1. Analysis of brain dynamics.

Example sliding window approach for computing dynamic functional network connectivity (dFNC). A) High-model order ICA creates functional parcellation of the brain, resulting in several independent components. B) Subject-specific timecourses are used to compute functional connectivity between pairwise components. Traditional static FNC analysis entails computing correlations across the entire duration of a scan per subject. Dynamic FNC analysis utilizes sliding windows (eg. 45 seconds in duration) to produce multiple correlation matrices for each subject (one per window). C) A concatenated data matrix is then subjected to *k*-means clustering, and the optimal *k* is identified using the elbow criterion (*k*=5 in this example). Each window is assigned to a dynamic state *k* regardless of subject assignment. Subject-specific medians are then back-reconstructed for each state *k* before they are averaged together to produce the final *k* dynamic states. Finally, group differences in dFNC can be computed.
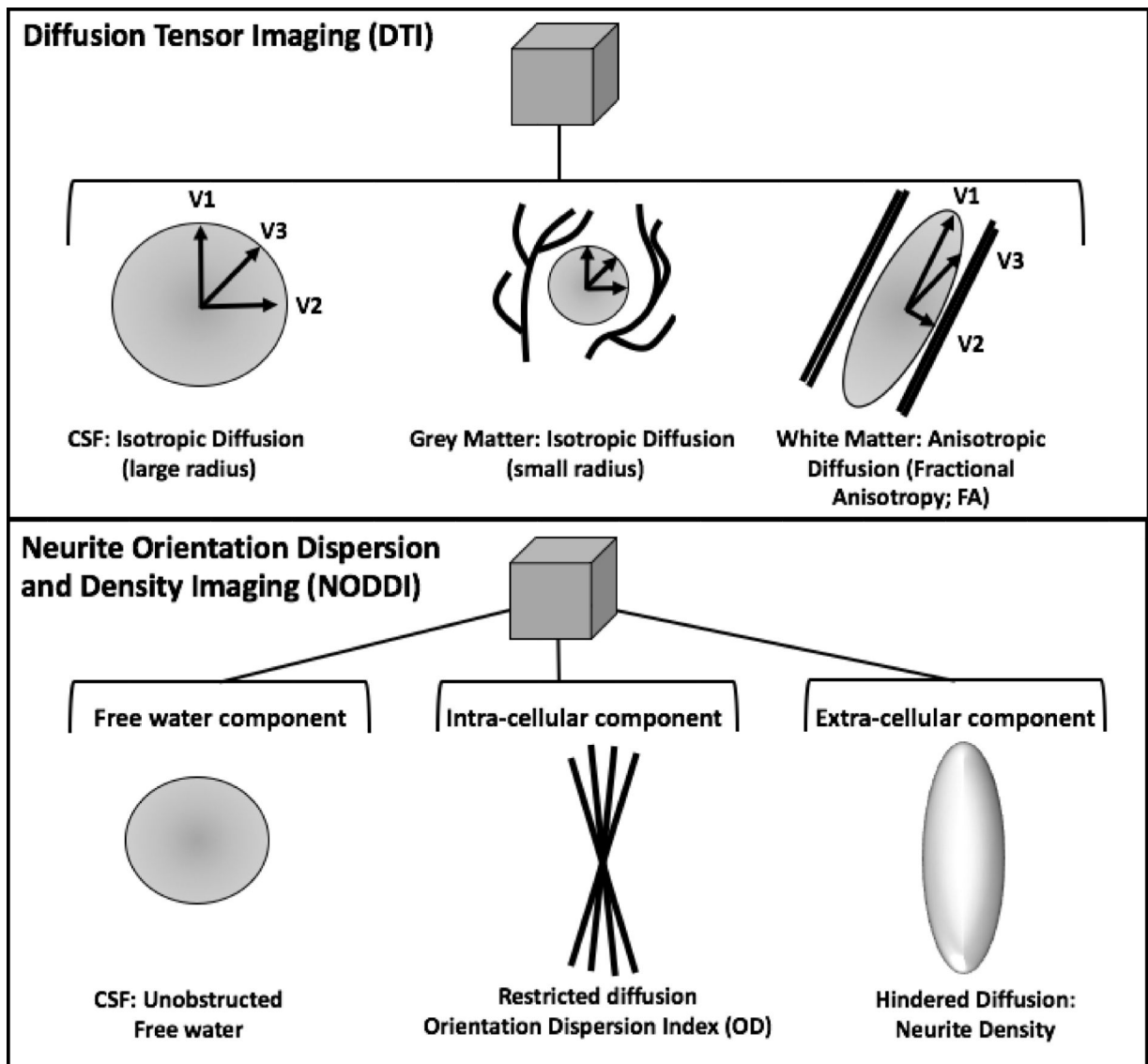
Figure 2. Analysis of structural connectivity.
Top panel: Diffusion tensor imaging (DTI), measures are all based on different ratios of diffusion restriction, leading to relatively isotropic or anisotropic tensors. Both CSF and grey matter show isotropic diffusion, while white matter shows anisotropic diffusion. In DTI each voxel is modeled with a single tensor. Lower panel; Neurite orientation dispersion and density imaging (NODDI) models tissue as three separate compartments, allowing determination of separate contributions of free water (CSF), neurite density (axons and dendrites), and orientation dispersion (myelination).

Table 1.

Existing pediatric neuroimaging data collection and sharing initiatives

	Datasets currently available	Age Range (years)	Variables Collected	Strengths	Limitations
Philadelphia Neurodevelopmental Cohort (PNC)	TD: 1,445	8–21	Neuroimaging: sMRI, DWI, ASL, tfMRI, rsfMRI Other: Kiddie-SADS; Penn CNB	All data acquired on same scanner platform. Genotype available.	rsfMRI collected with relatively long TR (3000ms).
Adolescent Brain Cognitive Development (ABCD)	TD: 4,010 (inaugural data release)	9–10	Neuroimaging: sMRI, DWI, tfMRI, rsfMRI Other: Kiddie-SADS and other clinical measures, NIH toolbox, physical, cultural, biological measures	Uses harmonized HCP protocol. Genotype, longitudinal and sleep data will be available.	Data collection ongoing. Data collection on different scanner platforms.
Human Connectome Project (HCP) Lifespan Development	TD: 1,350	5–21	Neuroimaging: sMRI, multishell DWI, tfMRI, rsfMRI Other: extensive battery of social, behavioral, and neurocognitive measures	Uses harmonized HCP protocol. rsfMRI collected with short TR (720ms). Genotype, sleep data, and pubertal status will be available. Longitudinal data available for subset.	Data collection ongoing.
IMAGEN	TD: > 2,000	14, follow up at 16, 19, 22	Neuroimaging: sMRI, DWI, tfMRI, rsfMRI Other: extensive battery of social, behavioral, and neurocognitive measures	Longitudinal data collected at multiple timepoints will be available. Genotype and pubertal status available. Collaboration with ENIGMA.	Data collection on different scanner platforms. Recruitment emphasized ethnic homogeneity.
Autism Brain Imaging Data Exchange (ABIDE) I and II	ABIDE I ASD: 539, TD: 573 ABIDE II ASD: 521, TD: 593	5–64	Neuroimaging: sMRI, rsfMRI Other: some clinical assessments	Wide age ranges available. Preprocessed neuroimaging data available.	Data collection on different scanner platforms. Limited phenotypic information.
ADHD-200	ADHD: 285 TD: 491	7–21	Neuroimaging: sMRI, rsfMRI Other: some clinical assessments	Wide age ranges available.	Data collection on different scanner platforms. Limited phenotypic information.
SchizConnect	Schizophrenia: 384 TD: 632	0–67	Neuroimaging: sMRI, tfMRI, rsfMRI Other: some clinical assessments	Wide age ranges available.	Data collection on different scanner platforms. Phenotypic information varies by dataset.
NKI-Rockland	TD: > 1000	6–85	Neuroimaging: sMRI, DWI, tfMRI, rsfMRI Other: extensive battery of social, behavioral, and neurocognitive measures	rsfMRI data collected at to different TRs (645 and 1400ms) available. All data acquired on same scanner platform.	Limited task fMRI data available.
Pediatric Imaging, Neurocognition, and Genetics (PING)	TD: > 1000	3–20	Neuroimaging: sMRI, DWI, rsfMRI Other: extensive battery of social, behavioral, and neurocognitive measures	Genotype available.	Data collection on different scanner platforms.

ASD = Autism Spectrum Disorder; ADHD = Attention-Deficit/Hyperactivity Disorder; TD = Typically Developing; sMRI = structural MRI; DWI = Diffusion Weighted Imaging; ASL = Arterial Spin Labeling; tfMRI = task fMRI; rsfMRI = resting state fMRI; Kiddie-SADS = Kiddie-Schedule for Affective Disorders and Schizophrenia; Penn CNB = Computerized Neurocognitive Battery; ENIGMA = Enhancing Neuro Imaging Genetics through Meta Analysis; TR = repetition time