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What have we really learned from functional connectivity in clinical populations?

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ABSTRACT

Functional connectivity (FC), or the statistical interdependence of blood-oxygen dependent level (BOLD) signals between brain regions using fMRI, has emerged as a widely used tool for probing functional abnormalities in clinical populations due to the promise of the approach across conceptual, technical, and practical levels. With an already vast and steadily accumulating neuroimaging literature on neurodevelopmental, psychiatric, and neurological diseases and disorders in which FC is a primary measure, we aim here to provide a high-level synthesis of major concepts that have arisen from FC findings in a manner that cuts across different clinical conditions and sheds light on overarching principles. We highlight that FC has allowed us to discover the ubiquity of intrinsic functional networks across virtually all brains and clarify typical patterns of neurodevelopment over the lifespan. This understanding of typical FC maturation with age has provided important benchmarks against which to evaluate divergent maturation in early life and degeneration in late life. This in turn has led to the important insight that many clinical conditions are associated with complex, distributed, network-level changes in the brain, as opposed to solely focal abnormalities. We further emphasize the important role that FC studies have played in supporting a dimensional approach to studying transdiagnostic clinical symptoms and in enhancing the multimodal characterization and prediction of the trajectory of symptom progression across conditions. We highlight the unprecedented opportunity offered by FC to probe functional abnormalities in clinical conditions where brain function could not be easily studied otherwise, such as in disorders of consciousness. Lastly, we suggest high priority areas for future research and acknowledge critical barriers associated with the use of FC methods, particularly those related to artifact removal, data denoising and feasibility in clinical contexts.

1. Introduction

Ever since scientists have appreciated that the brain is the organ of the mind, they have searched for the origins of diseases affecting mental function through analysis of brain structure and function. From phrenology to modern day neuroimaging, a countless variety of measures have been proposed-whether grounded in evidence or not-to explain mental dysfunctions affecting the global population. Before the widespread use of neuroimaging, the idea that the brain is an interconnected network, with functional systems distributed across the cortex, was gaining traction in behavioral neurology (Geschwind, 1965), neuropsychology (Mesulam, 1990), and cognitive science (Rumelhart et al., 1986; Rumelhart and McClelland, 1987). Within the last several decades, *functional connectivity* (FC)-or the statistical interdependence of blood-oxygen dependent level (BOLD) signals between different brain regions measured using functional magnetic resonance imaging (fMRI)-has emerged as an increasingly common method for investigating dysfunctions of brain networks in humans (Fig. 1). In the context of clin-

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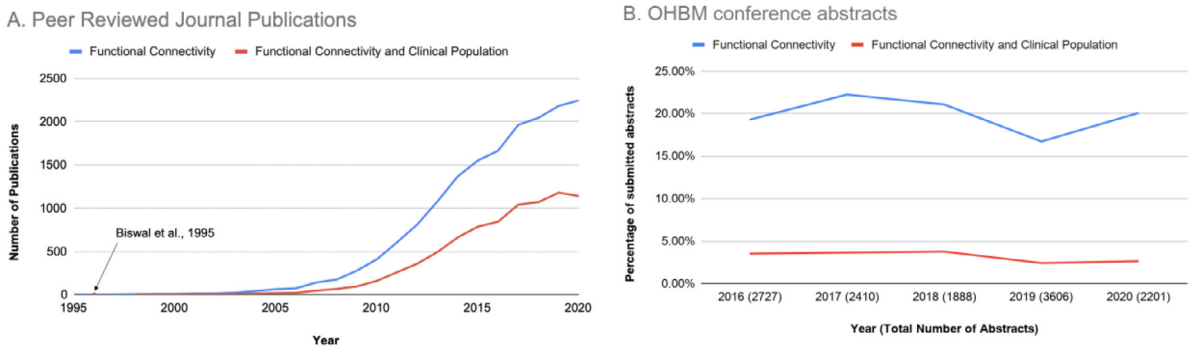

Fig. 1. Functional connectivity has become a widely used tool for probing brain dysfunction. (A) Since 1995, the number of publications including FC as a measure grew and in the last 10 years, about half of the FC publications studied clinical populations. This figure represents search results on PubMed (www.ncbi.nlm.nih.gov/pubmed) in April 2021 using advanced query ("fMRI AND "functional connectivity" OR "dynamic connectivity" OR "intrinsic connectivity fMRI" OR "spontaneous connectivity" NOT "connective tissue"). Criteria for literature on clinical population included additional keywords such as "disease" or "disorder". B) At Annual Meetings of the Organization for Human Brain Mapping (OHBM) between 2016–2020 (where abstract submission records are available by courtesy of the OHBM executive office), the number of abstracts using FC as a measure consistently comprised about 20% of total submitted abstracts, with 15–20% of those on diseases and disorders. Inclusion criteria keywords "intrinsic connectivity", "functional connectivity", "resting state connectivity", "connectivity + during rest", "dynamic connectivity", "functional network". Exclusion criteria included keywords "structural connectivity" and "white matter connectivity". Criteria for the clinical population included keywords such as "disease", "disorder", "Alzheimer's", "Parkinson's", etc.

ical disorders, FC is most commonly investigated in a wakeful 'resting state' condition (task-free, revealing 'intrinsic' or 'spontaneous' FC, (Biswal et al., 1995)), but can technically be investigated in a variety of contexts and brain states (*e.g.*, task, sleep, medication). In this paper, we therefore focus primarily on resting state FC.[1]

Currently, there is tremendous global excitement in the field surrounding the application of FC as a tool to identify clinical biomarkers, stratify patients into biologically-based subgroups, pinpoint treatment targets, track disease progression over time, and even predict future disease development, progression, and treatment outcome (Saggar and Uddin, 2019). Toward these goals, recently launched, large-scale national and international neuroimaging initiatives (A. Laird and D. Barch papers in this issue; Human Connectome Studies Related to Human disease) include resting state fMRI scans as a central component in their study designs, with the aim of facilitating data sharing and rigorous FC analyses in large, heterogeneous clinical cohorts.

The excitement surrounding examination of brain FC in clinical disorders is due to at least three factors. First, at a conceptual level, patterns of FC across the whole brain (also known as the 'functional connectome'; (Biswal et al., 2010)) are thought to reflect a given individual's *intrinsic* functional network organization that remains largely stable across different behavioral states (Fox and Raichle, 2007). As such, the functional connectome may be akin to a fingerprint (Finn et al., 2015) that encodes an individual's neurocognitive traits, including those specific traits that underlie disease and disorder (Castellanos et al., 2013). Second, at a technical level, despite issues associated with FC estimation from fMRI data, such as the impact of head motion and limitations of imaging resolution and signal-to-noise ratio (Power et al., 2015), spatial patterns of FC can be reliable within single individuals sampled at different times (Gratton et al., 2018; Taxali et al., 2021). Third, at a practical level, FC can be estimated from fMRI data while patients are 'at rest' (*i.e.*, are not instructed to perform a structured task), a condition that can easily be administered to most clinical populations and in a repeatable and reliable fashion (Zuo and Xing, 2014). This allows examination of functional neural architecture in patients who may not be able to easily engage in other functional tasks. Further, it is feasible to administer resting state scans at multiple timepoints and compare within-subject changes without the confound of repetition effects that come with many cognitive task paradigms.

As the field continues to grow, the scope of studies on FC and neurodevelopmental, psychiatric, and neurological diseases and disorders continues to broaden. Other than rare examples such as the adoption of FC as a tool for brain mapping before surgery or brain stimulation (H. Akram paper in this issue; (Castellanos et al., 2013; Fox and Greicius, 2010), FC applications are not currently standard in clinical settings. Major conceptual challenges (*e.g.*, disease heterogeneity and temporal dynamics of FC) and methodological barriers in clinical studies (*e.g.*, head motion, difficulty to acquire longer scans and larger sample sizes) still need to be overcome before FC can be reliably used as a clinical tool. With considerable continued global investment in this research, including the hope of using FC to guide clinical practice, it is timely to ask: what have we really learned from FC in clinical populations?

In earlier review articles on this topic, authors aimed to summarize findings from resting state fMRI in clinical contexts and synthesize how specific FC abnormalities may underlie distinct clinical conditions (Greicius et al., 2009; Whitfield-Gabrieli and Ford, 2012; Zhang and Raichle, 2010). Extensive meta-analyses within (*e.g.*, (Badhwar et al., 2017; Dong et al., 2018; Kaiser et al., 2015; Wolters et al., 2019)) and across conditions (*e.g.*, (Doucet et al., 2020; Makovac et al., 2020; Marusak et al., 2016; Sha et al., 2019)) have also been conducted. Here we do not attempt to perform a systematic review of this vast clinical neuroscience literature for two reasons: (1) pragmatically, this task has now become infeasible given the growth of literature, and (2) conceptually, the clinical field (especially psychiatry) has begun to move toward a dimensional, transdiagnostic approach that emphasizes overlapping symptoms and common neural mechanisms rather than distinct symptom-based classification of disorders (*e.g.*, Research Domain Criteria, or RDoC; (Insel et al., 2010)). Instead, we attempt to provide a high-level synthesis of major concepts that have arisen from FC findings in a manner that cuts across different clinical conditions and sheds light on overarching principles. We draw mainly from examples in well-studied clinical conditions that we, a group of co-authors with diverse interests and expertises, are most familiar with.

We first evaluate what major pieces of knowledge may have come from FC studies in clinical populations that could not, or have not, been otherwise obtained with other methods. After exploring what we have learned, we assess high priority areas for future research and identify barriers to gaining further knowledge.

[1] FC was first introduced to study task-related changes in inter-regional coupling in positron emission tomography (PET) and fMRI data (Friston et al., 1993) and can also be investigated based on directional interactions (effective connectivity; see review in Reid et al., 2019) and changes on shorter time scales (time-varying or dynamic connectivity; Lurie et al., 2020).

2. What have we learned from FC in human patients?

2.1. Virtually everyone has intrinsic functional networks

Intrinsic functional networks derived from BOLD FC at rest were first described within the healthy adult brain (Biswal et al., 1995; Cordes et al., 2000; Hampson et al., 2002; Lowe et al., 1998). Following the discovery that resting state FC can delineate and recapitulate different large-scale functional systems (*e.g.,* somatomotor, language and default mode networks) across the brain, a natural next question concerned whether altered spatial patterns of FC would emerge within clinical patients who present with deficits related to the putative functions of one or more of those systems. In early clinical studies of resting state FC, investigators largely used hypothesis-driven approaches to statistically compare FC between groups of patients and healthy adults (e.g., examining the default mode network, which is implicated in memory function, in Alzheimer's disease (AD) (Greicius et al., 2004)). Statistically significant FC alterations were reported within a wide variety of psychiatric and neurological conditions. However, sample sizes were small (typically 10–20 per group), and conflicting findings began to emerge across different studies, even when investigating the same clinical groups (see (Fornito and Bullmore, 2010; Zhang and Raichle, 2010) for review).

Yet one finding was consistent across all of these early studies: all patients *had* intrinsic networks. That is, the spatial topography of FC-or the 'functional architecture'-that had been described in the healthy brain was also found in virtually every clinical condition (though rare case reports describing 'absent' FC should be further confirmed (Boly et al., 2009; Salvador et al., 2005)). For example, resting FC between the major nodes of the default mode network was clearly present within patients with AD (Greicius et al., 2004), amyotrophic lateral sclerosis (Mohammadi et al., 2009), neuropathic pain (Cauda et al., 2009), autism spectrum disorder (ASD; (Cherkassky et al., 2006), schizophrenia (SZ; Zhou et al. 2007), and even in a patient in vegetative state (Boly et al., 2009). Recent work confirms that the similarities of intrinsic FC network organization between healthy and psychiatric populations are strikingly large and are much greater than any inter-group differences that are found (Spronk et al., 2021) (Fig. 2A).

In addition, this consistent functional architecture of intrinsic networks is preserved in several striking clinical examples. For example, canonical intrinsic networks are readily identifiable in presurgical patients facing severe clinical indications (*e.g.*, high grade glioma, refractory epilepsy) (Leuthardt et al., 2018), and the same spatial patterns of FC can be reliably confirmed within the same individuals from bedside recordings of intracranially implanted electrodes (Foster et al., 2015; Hacker et al., 2017; He et al., 2008; Keller et al., 2013; Kucyi et al., 2018a) (Fig. 2B). Intrinsic network organization can even be highly resilient to severe brain damage and developmental abnormalities. Following corpus callosotomy or commissurotomy, homotopic inter-hemispheric FC remains partially preserved (Roland et al., 2017; Uddin et al., 2008) (Fig. 2C). Following hemispherectomy, the organization of canonical intrinsic network is preserved within the intact hemisphere (Ivanova et al., 2017; Kliemann et al., 2019) (Fig. 2D). In developmental affectation of the frontal lobes resulting in near-absence of frontal structures, posterior default mode and visual network FC remains preserved (Ibáñez et al., 2018). An adolescent who suffered large bilateral perinatal strokes in intact tissue had proportionally preserved intrinsic network organization (Laumann et al., 2021).

In addition to correlated activity within intrinsic networks, a unique finding that arose from FC is anticorrelated resting state hemodynamic activity (especially between default mode and dorsal attention networks) (Buckner et al., 2013). The discovery of this intrinsic, antagonistic relationship within the healthy brain (Fox et al., 2005; Fransson, 2005) offered insight into a previously unknown, yet potentially fundamental feature of brain organization that has now been studied extensively in clinical populations (Whitfield-Gabrieli and Ford, 2012). Though the observation of anticorrelated activity has sparked important technical debates about their interpretation in fMRI data (Murphy and Fox, 2017), neurophysiological recordings in animals (Popa et al., 2009) and humans (Keller et al., 2013; Kucyi et al., 2020) have offered some validation of this phenomenon. Anticorrelated networks are typically also found in clinical populations, but a common finding is that the magnitude of anticorrelation is reduced in aging (Keller et al., 2015; Zhang et al., 2020) and various psychopathological states (Whitfield-Gabrieli and Ford, 2012).

Taken together, the study of FC in highly diverse clinical samples has taught us that intrinsic networks have ubiquitous, broad, organizational features that seem to generalize across the human population. At the global, whole-brain level, differences in spatial FC patterns across different diseases and disorders are typically emphasized in the clinical literature, but these differences tend to be very small relative to the clear, striking similarity of intrinsic network organization that is found reliably across diverse healthy and clinical populations. This knowledge has been (and could only have been) gained specifically from the broad, widespread study of FC across highly diverse clinical populations.

2.2. FC has clarified and extended principles of functional brain maturation and aging

Many clinical disorders are neurodevelopmental (*e.g.*, ASD, attention-deficit/hyperactivity disorder or ADHD, SZ) or neurodegenerative (*e.g.*, AD, Parkinson's) in nature. Therefore, characterizing the typical developmental trajectory of the brain across the lifespan is important for understanding these clinical disorders, as this characterization can provide a benchmark against which to examine deviations. The study of FC has contributed substantially in this domain, resulting in new applications and insights over-and-above what had been done with or known from other neuroimaging methods. In studies of typical maturation and aging, FC has clarified and in some cases extended principles of functional brain development previously derived from structural MRI and task-based fMRI studies. Below we list a few key developmental principles supported by FC and note clinical conditions associated with deviations from typical patterns.

Developmental changes in cortical folding and cortical thickness suggest that brain areas supporting visual, auditory, and somatosensory processing mature earlier than association areas supporting higher-order cognition (Sowell, 2004). FC has shown that sensory and motor networks appear most adult-like in infancy, though the precursors of all functional networks are present at birth (Gao et al., 2009; Smyser et al., 2011). In adolescence, FC studies have also shown earlier maturation of cortical areas involved in motor control compared to areas involved in social and emotional functions (Kelly et al., 2009). Experience-dependent pruning of local circuitry (Huttenlocher, 1979) and myelination of long-range connections (Paus et al., 2001) continue through early childhood and adolescence and has been observed with structural MRI (Casey et al., 2005; Lenroot and Giedd, 2006); these findings have since been extended using FC approaches (Di Martino et al., 2014; Uddin et al., 2010). While there has been concern that distance-related effects are inflated by head motion, it has been shown that some of these effects remain even when motion is strictly controlled, albeit reduced (Fair et al., 2012; Satterthwaite et al., 2013). Aberrant development of short- and long-range connections have been studied in ASD. Compared to age-matched controls, children and adolescents diagnosed with ASD have been found to have local hyperconnectivity in visual regions (Maximo et al., 2013), consistent with biases for local visual patterns in ASD. While long-range connections between the default mode network and other networks have been observed to increase in strength in typical development, the same does not occur in ASD (Padmanabhan et al., 2017), consistent with dysfunction in self-referential processing that is typical in ASD.

FC studies also recapitulate several developmental principles describing trajectories in early versus late life. Characterization of large-scale brain function with task-based fMRI has revealed a shift from dif-

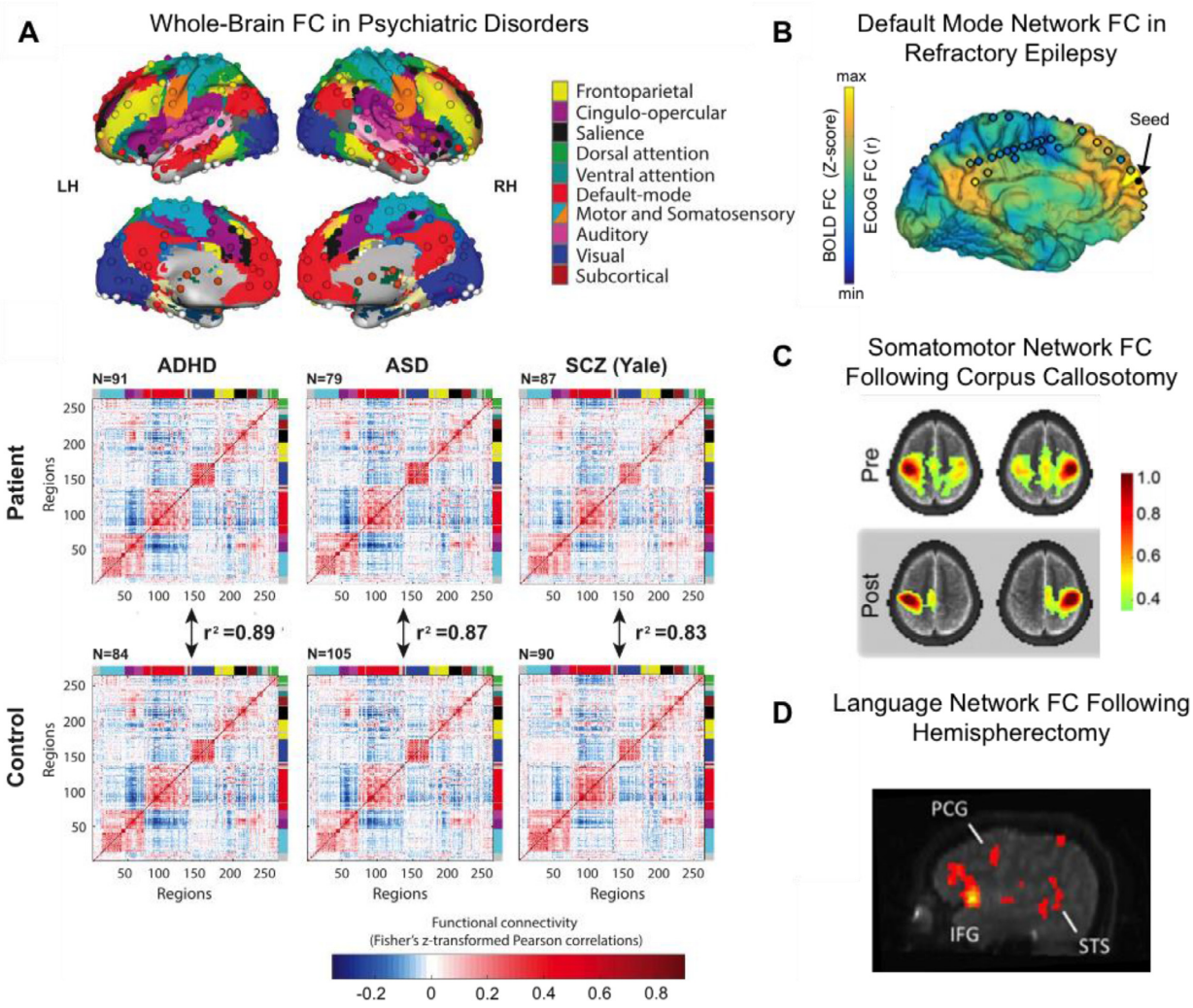

Fig. 2. Virtually everyone has intrinsic functional networks. (A) Across a healthy cohort and three cohorts of patients with distinct psychiatric diagnoses, whole-brain functional connectivity matrices are highly similar (reproduced from Spronk et al., 2021). Top: Brain regions (spheres) analyzed and their classification according to functional networks, shown on the inflated cortical surface (different colors indicate different networks; gray areas indicate no network assignment in the functional atlas (Power et al., 2011). Bottom: Mean resting state functional connectivity between all pairs of regions in the functional atlas within control (healthy) subjects and different patient groups. (B) In a patient with focal epilepsy, both presurgical FC from resting state fMRI (shown on cortical surface) and FC from subsequently implanted intracranial electrodes clearly show the topographic pattern of the default mode network (reproduced from Kucyi et al., 2018a). (C) In a patient undergoing corpus callosotomy, the sensorimotor network was intact bilaterally prior to surgery; following surgery, the network was still intact within a single hemisphere (reproduced from Roland et al., 2017)(Copyright 2017 National Academy of Sciences). (D) In a patient who underwent left hemispherectomy, the FC between regions resembling a language network in the right hemisphere remains intact (reproduced from Ivanova et al., 2017).

fuse to focal activation patterns during brain maturation (Durston and Casey, 2006; Rivera et al., 2005) and an apparent reversal in this pattern in aging (Davis et al., 2008; Park and Reuter-Lorenz, 2009). Task-based fMRI, however, is complicated by the fact that there are complex relationships between changes in brain activation related to performance and changes related to brain maturation or aging, as observed differences in brain activation can result from differences in strategy or cognitive effort (Casey et al., 2005; Schlaggar et al., 2002). Resting state FC sidesteps these issues and provides a useful framework for examining large-scale changes in brain function at the network level. The use of graph theoretical and other network neuroscience approaches (D. Bassett in this issue) has revealed that by late childhood (ages 7–10 years), the parcellation of cortex using FC (Barnes et al., 2012), the location of integrative hubs (Hwang et al., 2013), and the topography of functional networks (Cui et al., 2020; Marek et al., 2019) are largely mature. However, during development, patterns of FC across many functional networks in the cortex, subcortex, and cerebellum continue to change (*e.g.*, (Marek et al., 2015); Greene et al., 2014), such that FC can predict an individual's age (Dosenbach et al., 2010; Nielsen et al., 2019; Satterthwaite et al., 2013; Greene et al., 2014). Compared with typical age curves, adolescents with Tourette syndrome display immature FC in control networks (Church et al., 2009). Further, brain network modularity increases during childhood and adolescence (Gu et al., 2015), while the opposite pattern of decreasing modularity is reported in older adulthood (Cao et al., 2014; Geerligs et al., 2015). In preclinical AD, reduced modularity is associated with more severe dementia rating (Brier et al., 2014).

Interestingly, nuanced patterns of between-network connectivity changes across the lifespan are seen primarily among higher order cognitive networks. As an exemplar, one canonical network that appears to change with age in both development and aging is the default mode network (Damoiseaux, 2017). Studies consistently find default mode network connectivity with other networks to increase during development (Betzel et al., 2014; Gu et al., 2015; Vij et al., 2018), suggesting its role in functional integration strengthens with age. Aberrant default mode network connectivity has been used to evaluate risk for development of

Table 1
Select examples of disorders and diseases in which both focal and distributed (often FC-based) disruptions have been emphasized in the literature.

Condition	Focal disruption	Distributed disruption
Alzheimer's disease	Neurofibrillary tangles in the transentorhinal cortex and hippocampus (Van Hoesen and Hyman, 1990)	Altered FC in default mode network (Dickerson and Sperling, 2009); tau deposition via medial temporal lobe and default mode network to the entire brain (Jones et al., 2016)
Parkinson's disease	Depletion of dopamine cells in substantia nigra and ventral tegmental area (Lotharius and Brundin, 2002)	Altered FC in sensorimotor, thalamus, and cerebellum networks (Gratton et al., 2019; Tinaz et al., 2016)
Tourette syndrome	Altered morphometry and activity in striatum and striatal motor circuits (Albin and Mink, 2006)	Altered FC in control, sensorimotor, and default mode network (Greene et al., 2016; Nielsen et al., 2020b; Tinaz et al., 2015)
Chronic pain	Altered neurobiology, metabolism and morphometry in nociceptive targets, *e.g.*, cingulate, insula and somatosensory cortex (Apkarian et al., 2005; Tracey and Mantyh, 2007)	Altered FC across default mode and salience networks (Kucyi and Davis, 2015; Lee et al., 2021)
Schizophrenia with auditory hallucination	Altered morphometry, metabolism and activity in the auditory cortex (Allen et al., 2008)	Altered FC between auditory cortex and the default mode network (Northoff and Qin, 2011)
Depression	Altered neurobiology, metabolism and morphometry of the subgenual anterior cingulate cortex (sgACC) (Drevets et al., 2008)	Altered FC between sgACC and default mode and executive networks (Greicius et al., 2009; Hamilton et al., 2015)

AD in older adults (Badhwar et al., 2017; Viviano et al., 2019). On the other hand, anticorrelation between the default mode network and frontoparietal control network increases during development (Chai et al., 2014) and decreases during aging (Keller et al., 2015), mirroring the inverted U-shape of rise and decline in executive function. Reduced default mode network anticorrelation has been observed in neurodegenerative conditions such as SZ (Whitfield-Gabrieli et al., 2009) and AD (Weiler et al., 2017). Many regions that comprise the default mode network are considered a part of the connectome's 'rich club', i.e., brain regions that share denser anatomical connections (white matter tracts as assessed by diffusion imaging) with each other than is expected by chance (van den Heuvel et al., 2012; van den Heuvel and Sporns, 2011). Functional rich club organization is present, but varies across age, and follows an inverted U-shape pattern of a lower rich club coefficient in children and older adults and a maximum rich club coefficient around 40 years of age (Cao et al., 2014; Grayson et al., 2014). Accordingly, rich club FC is further reduced in mild cognitive impairment (Xue et al., 2020).

To summarize, developmental FC studies extend what was previously gleaned from structural and task-based MRI studies in important ways. FC studies on neurodevelopmental and neurodegenerative disorders further clarify that these clinical conditions often manifest in deviations from these typical FC trajectories. As fetal and infant imaging becomes more available and pubertal status taken into account in developmental FC studies, we can expect to gain a more nuanced understanding on these most active neurodevelopmental stages and therefore identify more precise patterns of aberrant FC in clinical populations (Di Martino et al., 2014; Uddin et al., 2010).

2.3. Many disorders and diseases are less 'focal' than previously believed

Prior to the development of whole-brain human neuroimaging techniques, clinical neuroscience historically placed greater emphasis on localizing dysfunction to specific, focal areas of the brain than on the significance of disconnection between brain regions. Beginning as early as Broca's work with aphasia, and continuing to 20th century research on patient H.M.'s anterograde amnesia, many brain disorders and diseases have been presumed to have focal origins (Catani and Ffytche, 2005; Eickhoff et al., 2018). Partially due to the limitations of the available neuroscientific tools, investigators traditionally often approached clinical problems affecting the brain via the study of localized brain regions with atypical structure or function (Table 1, 'Focal disruption'). With the emergence of whole-brain neuroimaging techniques and associated quantitative data analyses, clinical studies of structure (*e.g.,* voxel-based morphometry) and task-based activation (*e.g.,* observed in PET and fMRI) began to highlight the importance of distributed network dysfunctions within a wider range of diseases and disorders than had previously been considered (*e.g.*, (Apkarian et al., 2005; Goodkind et al., 2015; Larivière et al., 2020)). The introduction of FC was in part motivated by those findings and has built significantly on earlier neuroimaging foundations, propelling forward clinical research that focuses specifically on network-level dysfunctions. Clinical FC studies have significantly advanced knowledge of how distributed brain function across many regions within a network, or across multiple networks, can be impacted in disease and disorder (Table 1, 'Distributed disruption'). When combined with a cellular-level understanding of how pathologies spread throughout the brain, FC can offer mechanistic insight into the large-scale pathways by which focal origins lead to distributed dysfunction (Fornito et al., 2015).

FC has further revealed how even clinical conditions with well-studied and established focal mechanisms can be associated with much more distributed effects on brain function. For example, localized damage to brain tissue from ischemic stroke can yield distal changes in FC that are beyond the lesion, across hemispheres and across networks (He et al., 2007). The location of a lesion in the functional network architecture (*e.g.*, connector hub region vs. peripheral region) predicts how widespread the effects of the lesion are on total brain function (*i.e.*, modularity, (Gratton et al., 2012)) and on behavior (Warren et al., 2014). The "network degeneration hypothesis" accounts for this phenomenon by positing that focal dysfunction leads to disappearance or rewiring of synapses, which in turn impacts anatomically and functionally connected regions. This theory was significantly advanced by FC studies (especially on AD) showing disease progression through nonadjacent but networked regions (Seeley et al., 2009).

One major area where FC has shifted clinical thinking to go beyond focal mechanisms comes from research on AD, a neurodegenerative disorder with its earliest pathology (neurofibrillary tangles) confined to the transentorhinal cortex before spreading via medial temporal lobe and limbic regions throughout the entire cortex (Braak and Braak, 1991). Even though AD was recognized as a systems-level disorder, many neuroimaging studies in the 1990's and early 2000's focused on localization to specific brain regions, such as the hippocampus (Van Hoesen and Hyman, 1990). The rise of FC-based network approaches revived the systems-level focus and led to an increased understanding of the trajectory of brain changes in AD. A current theory suggests that the posterior default mode network, which serves as a central hub of the association cortex, plays an important role in the spread of pathology throughout the brain (Jones et al., 2016). In cognitively unimpaired older adults, connectivity between the entorhinal cortex, medial temporal lobe and the default mode network is positively associated with tau deposition, suggesting that tau spreads through this brain network. Because of the role of the default mode network as a central network hub, pathology will subsequently spread throughout the entire brain. Presence of amyloid in these regions may accelerate the spread and distinguish typical age-related tauopathy from AD (Adams et al., 2019).

Parkinson's disease is characterized by the depletion of dopaminergic cells in the substantia nigra and ventral tegmental area (Lotharius and Brundin, 2002). FC studies reveal distributed disruptions in the salience, frontoparietal, sensorimotor, thalamic, and cerebellar networks, which go well beyond the basal ganglia and other primary dopaminergic tar-

gets and better explain the wide range of neuropathological and clinical symptoms in Parkinson's disease (Gratton et al., 2019; Tinaz et al., 2016).

In addition, Tourette syndrome and its characteristic symptom, tics (abnormal, unwanted movements and/or vocalizations), have long been associated with abnormalities of the striatum (Albin and Mink, 2006). However, atypical FC in Tourette syndrome is not exclusive to the striatum or striatal motor circuits, but is also present among control networks, sensorimotor networks, and the default mode network (Greene et al., 2016; Nielsen et al., 2020b; Tinaz et al., 2015). This atypical FC observed across multiple functional networks in Tourette syndrome may reflect the complexity of the disorder, including symptoms and behavioral issues beyond tics (*e.g.*, attentional problems, obsessive-compulsive symptoms).

In chronic pain, research has traditionally focused primarily on brain regions to which nociceptive pathways directly project (*e.g.*, cingulate, insula, and somatosensory cortex) or in the brainstem descending modulatory system (Apkarian et al., 2005; Tracey and Mantyh, 2007). Yet FC has revealed the important roles of broader systems, such as the default mode, salience, and frontoparietal networks, in tonic pain and in the interplay between pain and other cognitive processes (Kucyi and Davis, 2015; Lee et al., 2021).

In SZ, abnormal volume, metabolism and activation in the auditory cortex has traditionally been thought to underlie auditory hallucinations (Allen et al., 2008), but theoretical advances inspired by FC suggest that interplay between the auditory cortex and default mode network is linked to erroneous attribution of self-generated voices as belonging to others (Northoff and Qin, 2011). Consistent with this hypothesis, a study in medication-resistant SZ patients has shown that, after a mindfulness-based neurofeedback intervention, more reduction in connectivity between the auditory cortex and default mode network was associated with more improvement in auditory hallucination (Bauer et al., 2020).

In depression, early neurobiology and morphometry work identified reduced glial cell count (Ongür et al., 1998), abnormal blood flow and metabolism (Drevets et al., 1997; Mayberg et al., 1999), as well as reduced cortical volume (Drevets et al., 1997; Ongür et al., 1998) in the subgenual anterior cingulate cortex (sgACC). Hyperconnectivity within the default mode network (including the sgACC) indexes symptom severity in patients (*e.g.*, Greicius et al., 2009; Hamilton et al., 2015) and at-risk children (Chai et al., 2016). More recently, transcranial magnetic stimulation (TMS) has emerged as a promising personalized treatment option by targeting the region in the patient's dorsolateral prefrontal cortex that is most anticorrelated to the sgACC by FC (*e.g.*, (Cash et al., 2019; Fox et al., 2013, 2012; Weigand et al., 2018)), which normalizes the default mode network hyperconnectivity (Liston et al., 2014; Hopman et al., 2021; Liston et al., 2014).

Taken together, though the relevance of connectivity to brain dysfunction had long been appreciated within the context of some clinical conditions (such as those labeled "disconnection syndromes" (Catani and Ffytche, 2005)), the emergence of FC approaches has played a key role in inspiring a recent mainstream focus on the role of large-scale, network-level pathologies within the context of virtually all brain diseases and disorders. The key examples that we have highlighted in this section illustrate how FC has inspired new theories about how symptoms arise from over-connected, under-connected, and abnormally anti-correlated functional brain networks. These examples additionally illustrate how FC may better characterize the neural underpinnings of the many complexities of a given disorder or disease and thus inspire new ways to therapeutically target functional network disturbances.

2.4. FC supports a dimensional approach for studying diseases

Candidate FC markers of clinical disorders and diseases were initially identified using case-control categorical approaches, which rely on comparisons between discrete groups (*e.g.*, patients vs. healthy controls). For example, it was previously proposed that individuals with ASD can be characterized by stronger or weaker FC across different points in development (Uddin et al., 2013). However, case-control approaches do not adequately describe heterogeneity within clinical disorders. The high comorbidity of certain disorders, along with a range of symptom types and severities, suggests the need to investigate FC across subgroups of clinical populations using approaches that examine a range of functions from normal to abnormal. Currently, psychiatry is moving toward a dimensional approach to neurobiological assessments of cognitive dysfunction, such as that delineated by the RDoC framework introduced by the National Institutes Mental Health (Insel, 2014). This trend has emerged concurrently with the rising popularity of FC applications in psychiatry. The analysis of FC across health and disease has provided supportive evidence for dimensional frameworks at the neural level (van den Heuvel and Sporns, 2019). The goal is often to identify subgroups of clinical populations by integrating multiple levels of information (from genomics to neural circuits to behavior) to explore dimensions of functioning spanning the full range of normal to abnormal behavior.

There are at least three types of applications of FC analyses that have supported a dimensional framework. The first type of application directly probes common neural markers underlying multiple, sometimes comorbid, conditions. For example, anxiety and depression co-occur with high frequency, and their comorbidity generally implicates parts of the limbic system (Oathes et al., 2015; Pannekoek et al., 2015). Another example is shared atypical default mode and salience network FC in ASD and SZ (Chen et al., 2017). The second type of application associates FC metrics with symptoms that cut across many traditional clinical categories using the RDoC framework. For example, executive function deficit has been associated with FC correlates in multiple neurodevelopmental disorders (Dajani et al., 2016) as well as mood disorders (Huang et al., 2020). Executive function deficit has also been more specifically indexed with aberrant FC between the medial prefrontal cortex and the dorsolateral prefrontal cortex (lack of anticorrelation), which has been observed in patients or at-risk populations for bipolar disorder and SZ (Chai et al., 2011; Whitfield-Gabrieli et al., 2018, 2009). Another example is indexing negative self-related rumination with default mode network hyperconnectivity, which has been observed in patients or at-risk populations for depression (Chai et al., 2016; Whitfield-Gabrieli et al., 2020), SZ (Whitfield-Gabrieli et al., 2009), and chronic pain (Kucyi et al., 2014). The third type of application involves identifying an FC marker of a specific psychological construct within the healthy brain and then examining more extreme expressions of that marker within patients who are characterized by that symptom. For example, FC-based predictive modeling suggests that patients with ADHD under-express and over-express FC markers of sustained attention (Rosenberg et al., 2016) and mind wandering (Kucyi et al., 2021), respectively. Analogously, patients with chronic back pain over-express an FC marker that tracks tonic pain within the healthy brain (Lee et al., 2021).

Generally, studies have either used a categorical or dimensional approach when characterizing FC in clinical disorders. Recently, some studies have attempted to combine categorical and dimensional approaches in a categorical-dimensional hybrid framework (Elton et al., 2016, 2014; Nomi, 2019; Pruim et al., 2019). Such analytical models attempt to identify case-control group differences alongside dimensional associations using clinical diagnosis and symptom severity in the same group of subjects. These studies can disentangle FC differences related to case-control categorical group differences alongside dimensional associations between FC and symptom severity. Hybrid categorical-dimensional analyses have suggested that both categorical and dimensional FC associations may be needed to thoroughly characterize clinical neurobiology.

Researchers are increasingly adopting FC for dimensional analyses. It is a standard and widely collected measure (i.e., not specifically designed for particular conditions) and therefore can easily enable combined analysis of separately collected datasets across clinical condi-

tions. This characteristic of FC is similar to other standard scan types, such as structural or diffusion MRI. But importantly, FC allows examination of functional neural architecture, or brain activity fluctuations over time. Further, FC uniquely potentiates investigation of early, brain-based biomarkers of transdiagnostic symptoms and their developmental trajectories because there are no behavioral confounds from task and pediatric clinical populations can more easily tolerate resting state scans than comply with task demands.

2.5. FC can be combined with other methods to enhance characterization of disorders

Currently, there is no clear evidence that FC outperforms other imaging approaches (*e.g.*, structural MRI, task fMRI, electroencephalography, magnetoencephalography, positron emission tomography, etc) at predicting risk or treatment response and FC is not yet a gold-standard clinical tool for diagnosis or prognosis. Nevertheless, there is substantial empirical evidence pointing towards its promise to *enhance* multimodal characterization of disorders and prediction of symptom progression. For example, correspondence between FC and structural connectivity (assessed with diffusion MRI) has been used to index functional rigidity in youths at-risk for SZ and bipolar disorder compared with controls (Collin et al., 2017). In other instances, FC has detected broader impacts on brain networks beyond those observed with other imaging modalities. Simultaneous PET-MR approaches are beginning to disentangle how neuroinflammatory markers and FC interact to jointly serve as markers of clinical symptoms (Albrecht et al., 2021). In traumatic brain injury, diffuse axonal injury has been associated with putatively compensatory increases in FC in addition to decreases related to the structural disconnection observable with diffusion imaging (Sharp et al., 2014). In Parkinson's disease, by combining FC with imaging modalities targeting dopaminergic and metabolic activities, a recent study (Ruppert et al., 2020) showed hypoconnectivity between dopamine-depleted striatal seed and sensorimotor cortical regions is associated with reduced metabolic activity in the cortical regions. As mentioned in Section 2.3, in AD, FC revealed additional insights for the mechanism of disease propagation by showing the networked nature of regions presenting tau and amyloid beta pathologies.

Another exciting clinical application is the potential to use FC 'on top' of other measures to prospectively predict symptom change. For example, (Whitfield-Gabrieli et al., 2016) has shown that FC, in addition to white matter integrity (as assessed by diffusion-weighted imaging), predicts treatment response in social anxiety disorder. FC has also been integrated with gray matter morphology to predict conversion from mild cognitive impairment to AD (Hojjati et al., 2019, 2018).

Beyond neuroimaging modalities, FC can be a mediator between behavior and genetic variation (Meyer-Lindenberg, 2009). Amygdala-prefrontal connectivity has been studied extensively in psychiatric disorders in conjunction with gene variations related to serotonin. For example, functional movement disorder patients who are *T* carriers of the (*TPH2*) gene polymorphism-G703T have an early age at onset, worse disease severity, and lower amygdala-frontal FC (Spagnolo et al., 2020). In AD, APOE genotype is associated with distinct default mode network FC profiles, which may help classify disease stages (Zhu et al., 2019). In other neurodegenerative disorders such as Huntington's disease and ayotrophic lateral sclerosis, pre-symptomatic carriers present FC alterations from controls and towards values observed in symptomatic carriers (Kronenbuerger et al., 2019; Shoukry et al., 2020). The study of pre-symptomatic carriers of known mutations might help predict the timing of disease onset.

The aforementioned examples of multimodal characterization demonstrate that diseases and disorders with complex etiology manifest at different levels, including disruption in functional neural architecture. Importantly, in many clinical conditions, FC tells us unique information in addition to other knowledge domains. Therefore, studying clinical populations using FC as a tool may yield a fuller understanding of disease and disorder mechanisms and subsequently facilitate more precise treatments.

2.6. FC permits characterization of functional abnormalities in conditions where the study of brain function was previously limited

Task fMRI requires patient cooperation, rendering it unreliable in the presence of severely impaired verbal, motor, or cognitive abilities to follow commands. Resting state FC overcomes this limitation, as it probes brain network function without requiring patients' active participation. Thanks to this technique, we have learned that default mode network FC may be reflective of level of consciousness. Long-range default mode network connections can be absent in severe disorders of consciousness, can reappear in minimally conscious states, and are intact in locked-in patients (Boly et al., 2009; Vanhaudenhuyse et al., 2010). These connections are more variable during the vegetative state, and probably reflective of whether recovery is already taking place, even while patients are not able to communicate. In these cases, further clarification can be obtained with a multi-network approach (Demertzi et al., 2015).

Resting state FC has also allowed major innovations in the exploration of functional brain development in utero (Turk et al., 2019; van den Heuvel and Thomason, 2016), shedding light on the effects of maternal stress in brain development and in infancy (Fransson et al., 2009, 2007). This raises the possibility of early diagnosis and interventions prior to overt disease manifestation. A confounding factor that needs to be considered in these studies is the sleep-wake cycle in these populations (Zhang et al., 2019).

3. Long-term goals for potential clinical applications

Based on the progress made so far by FC studies, several goals can be identified for the use of FC in clinical settings in the future. First, in line with a movement within psychiatry away from DSM-type diagnostic manuals, FC has the potential to be a neural system level biomarker for diagnosing and monitoring progression of disorders and diseases (Sui et al., 2020). Second, baseline FC assessment could be used to prospectively predict longitudinal clinical outcomes for individual patients (e.g., conversion to illness, future symptom change or treatment response). Predictive FC markers could be based on fMRI scans conducted before initiation of treatment or based on the malleability of FC immediately after treatment onset (*e.g.,* assessing how FC changes after the first pharmacotherapy dose of a treatment regimen). Analytic strategies such as carefully designed cross-validation within and between datasets (Gabrieli et al., 2015; Poldrack et al., 2020; Scheinost et al., 2019; Woo et al., 2017) and the use of machine learning (Hahn et al., 2017; Nielsen et al., 2020a) show promise for making these types of prospective predictions.

Third, given known FC mechanisms in certain disorders, FC itself can be a treatment target for neuromodulation techniques like TMS (*e.g.*, Brady et al. 2019) or real-time neurofeedback (*e.g.*, Bauer et al., 2020; Ramot et al., 2017). Substantial progress has already been made in the use of baseline resting FC measurement to optimize TMS targeting, with some evidence suggesting that an FC-guided approach can serve to enhance clinical outcome in major depressive disorder (Cash et al., 2021, 2019; Fox et al., 2013). Though real-time fMRI neurofeedback was traditionally based on regional activity, FC has inspired new applications in which subjects aim to regulate inter-regional interactions, for example between two regions (Ramot et al., 2017; Yamashita et al., 2017; Zich et al., 2020), or two networks (Bauer et al., 2020; Pamplona et al., 2020), or based on whole-brain FC patterns (Scheinost et al., 2020). It remains an open question whether these network-based neurofeedback training approaches can successfully normalize aberrant FC across broad patient populations.

Fourth, knowing the typical developmental trajectory of FC could make it possible to generate a growth-chart like index based on FC (Castellanos et al., 2013), where patients get measured and compared to

Box 1
What have we learned indirectly (*i.e.* mechanisms and applications) from the study of FC in disease?

In this paper, we have focused on what we may have learned directly from the results of FC studies that enrolled clinical patients. We speculate that beyond those studies themselves, the drive to understand FC in clinical disorders has strongly motivated many other complementary research directions that may not have otherwise been pursued (nor funded by granting agencies). For example, it is likely that the study of FC in disorders has indirectly led to major discoveries regarding the evolutionary origins of FC (Buckner and Krienen, 2013), the computational mechanisms of FC (Cabral et al., 2017), the role of the vascular (Drew et al., 2020) and neurotransmitter (Zerbi et al., 2019) systems in generating FC, the electrophysiological basis of FC in human (Nir et al., 2008) and non-human (Thompson et al., 2013) brains, effect of targeted lesions on FC (O'Reilly et al., 2013), and the relationship between FC and the causal impact of brain stimulation on propagation of signals through networks (Chen et al., 2013; Keller et al., 2011; Shine et al., 2017). These, and other advances, are discussed in other articles in this issue (M. Bright, C. Chang and S.Keilholz papers in this issue).

a standard chart. This may eventually be helpful in early detection and intervention of diseases and disorders. Early progress has been made on this front where a measure of 'brain age' can be calculated based on FC and compared against chronological age to detect atypical development or aging (Cole and Franke, 2017; Dosenbach et al., 2010; Liem et al., 2017). Fifth, FC may serve as a surrogate outcome measure for treatment efficacy during drug development. For example, randomized controlled trials have been conducted to test FC change in response to antidepressant drugs (Capitão et al., 2020; Klöbl et al., 2020; McCabe and Mishor, 2011; Wagner et al., 2017). As the scope of clinical applications widens, ethical, legal and social implications will become more complex and should be continuously considered to ensure responsible implementations of FC-based biomarkers (Davis et al., 2017).

The field is currently grappling with how specific benchmarks should be set to evaluate whether these neuroimaging applications can achieve their clinical promise, an issue that is not specific to FC (Castellanos et al., 2013). In addition to the collection of large, clinically heterogeneous datasets, several other milestones would need to be reached for FC to achieve its promise. Among these include improving replication and reliability of metrics through harmonized data collection and standardized data processing workflows, deep phenotyping, and consideration of ways to reduce the cost of neuroimaging (Saggar and Uddin, 2019). Additional conceptual, methodological, and technical barriers that likely must be overcome are discussed next.

4. Barriers to learning more about clinical disorders from FC

4.1. Conceptual barriers

Several critical barriers still exist before FC can be successfully adopted into common clinical use. First, the detailed neurophysiological mechanisms that generate FC observed in fMRI remain unknown, limiting the interpretability of FC alterations found in clinical populations. Importantly, the momentum in the field surrounding understanding clinical disorders has motivated basic neuroscientific studies that have generated fundamental knowledge about the mechanisms of FC (Box 1).

Another significant conceptual barrier is the heterogeneity in disease and the factors that limit our ability to reliably capture this variability with FC. Two patients diagnosed with the same disorder can exhibit very different symptomatology (*i.e.*, type, severity of symptoms), potentially indicating the presence of subtypes within disorders. Incorporating FC and assessing the contribution of different brain networks may help explain and better predict this heterogeneity (Feczko et al., 2019; Sylvester et al., 2012). There has been some success incorporating FC to aid in subtyping in depression (Drysdale et al., 2017), ADHD (Fair et al., 2012), ASD (Dajani et al., 2019), and posttraumatic stress disorder (PTSD) (Etkin et al., 2019), but these efforts have been met with significant challenges related to the stability and reliability of FC measurements as well as heterogeneous characteristics of patient cohorts recruited at distinct clinical sites (Uddin et al., 2017). For example, FC-based subtypes of depression (Dinga et al., 2019) and PTSD (Esterman et al., 2020) were not fully replicated in independent datasets.

A major conceptual barrier concerns uncertainty over the degree to which FC captures dynamic states (*i.e.*, changes within individuals) versus traits (*i.e.*, stable features that reliably characterize differences between individuals). Currently, FC is commonly analyzed in clinical populations with the aim of finding biomarkers of traits, rather than states. The effect of state (*e.g.*, cognitive task performance vs. rest) on whole-brain spatial organization of BOLD FC has been estimated to be much smaller than the trait component (Cole et al., 2014; Gratton et al., 2018; Laumann et al., 2017), a finding also supported by scalp (Chu et al., 2012; Nentwich et al., 2020) and intracranial (Kramer et al., 2011; Kucyi et al., 2018a; Mostame and Sadaghiani, 2021) EEG showing high similarity of FC patterns across rest, task, and sleep states. However, growing evidence suggests that more subtle, yet significant within-individual changes in resting state networks across multiple time scales may reflect fluctuations in arousal (Laumann et al., 2017), physiological state (Chang et al., 2013; Schneider et al., 2016), spontaneous memory replay (Tambini and Davachi, 2019), and ongoing conscious experiences (Gonzalez-Castillo et al., 2021; Kucyi et al., 2018b). Functional connectivity even changes systematically as a function of time of day (Orban et al., 2020) and across different phases of the menstrual cycle (Andreano et al., 2018; Pritschet et al., 2020). Further studies involving dense sampling of single individuals and analyses of FC fluctuations over short and long time scales (Rosenberg et al., 2020; Shine et al., 2016) will help to clarify in what contexts FC serves as a marker of state, trait, or both. This critical conceptual issue was acknowledged during early applications of FC in clinical populations (Fornito and Bullmore, 2010) but has not yet been resolved.

Since the initial report by Chang and colleagues that time-varying or dynamic changes in FC between brain regions can be quantified in resting state fMRI (Chang and Glover, 2010), an emerging literature on FC dynamics has attempted to refine these theoretical approaches and methods (see Calhoun et al., 2014; Hutchison et al., 2013). Static and dynamic FC appear to make differential contributions to behavior (Kucyi and Davis, 2014; Liégeois et al., 2019; Vidaurre et al., 2021), for example with dynamic measures better reflecting behavioral variability (Eichenbaum et al., 2021). Dynamic FC approaches have been used to characterize typical aging (*e.g.*, Viviano et al., 2017) and neurodevelopmental disorders including ASD, where there is already evidence that diagnosed individuals exhibit altered transitions between brain states (Uddin, 2021). Distinct contributions of dynamic versus static FC to a wide range of clinical conditions have also been reported, for example in Alzheimer's disease (Fu et al., 2019), stroke (Bonkhoff et al., 2020), and chronic pain (Cheng et al., 2018). Analyses of time-varying FC have also revealed how disorders of consciousness are associated with altered temporal dynamics that generalize across multiple datasets and conditions (Demertzi et al., 2019; Huang et al., 2020). There are many unresolved issues with respect to the nature and interpretation of dynamic metrics (Lurie et al., 2020), and the contribution of sampling variability and head motion artifacts to these findings have been noted (Laumann et al., 2017). New dynamic FC analysis techniques are continuing to be developed and validated to offer whole-brain analyses of FC on fine time scales (Xie et al., 2019; Zamani Esfahlani et al., 2020). As mechanisms of dynamic FC (and how they relate to static FC) are more clearly understood, we are likely to gain additional insights into how altered brain network dynamics contribute to cognitive and behavioral impairments associated with clinical conditions (Cohen, 2018).

Relatedly, a specific concern for resting state fMRI dynamics is the possible presence of sleep states during scans. As subjects lie in the scanner for a task-free experiment, micro-sleep and sleep can occur within the session (Fukunaga et al., 2006). About 30 percent of healthy sub-

jects may present microsleeps during resting FC scan (Tagliazucchi and Laufs, 2014). Daytime sleepiness may be present for disorders with sleep disturbances, including Parkinson's disease (Mantovani et al., 2018), AD (Lloret et al., 2020), ADHD (Hvolby, 2015), and pain (Mathias et al., 2018). The amount and depth of sleep can vary depending on the subject's sleep drive and circadian rhythm, the time of the day, and scan duration. Wake FC patterns differ from those during the transition to sleep or during sleep. While changes are subtle in the early sleep, deep levels of sleep are associated with decoupling of frontal-parietal connections to the midline components of the default mode network (Horovitz et al., 2009, 2008; Larson-Prior et al., 2011; Sämann et al., 2011) and thalamocortical connections (Picchioni et al., 2014). These factors should be considered when interpreting FC findings before the impact of sleep on FC can be accurately quantified.

Another conceptual barrier to progress in the field has been the lack of consensus surrounding terminology and naming conventions for brain networks. For example, we have referred to large-scale brain networks throughout this review such as the default mode network and salience network. However, this terminology is not universally adopted, and these neural systems go by different names in different literatures, such as social neuroscience and psychiatry. To facilitate communication amongst researchers in psychology, cognitive neuroscience, psychiatry and other human neuroimaging fields, some have suggested that a standard taxonomy of functional brain networks should be adopted (Uddin et al., 2019). In addition to standardizing taxonomy, a conceptually complementary method that also circumvents idiosyncrasies in naming conventions is gradient-based FC approaches (Guell et al., 2018; Margulies et al., 2016; Tian et al., 2020; Zhang et al., 2019), which use dimension-reduction techniques to show the relationship between brain topology and FC organization. Gradient-based approaches offer a framework to unite findings that may be considered separate under the network parcellation approach and are becoming adopted in studies involving clinical patients as well (Bayrak et al., 2019; Dong et al., 2020).

4.2. Methodological and technical barriers

There are several outstanding methodological challenges in the field. Small, single-site studies continue to be common in the clinical FC literature, especially within highly specialized populations that may be difficult to recruit for study participation. Within small studies, data preprocessing and analysis strategies vary drastically across laboratories/institutions and are often selected based on the investigators' expertise or preferences. Thus, combining results across studies, and determining generalizability, remains highly challenging. The availability of dedicated softwares and computational pipelines for FC preprocessing and analysis has played an important role in encouraging more standardized approaches across studies (Esteban et al., 2019; Singh and Mathey, 2020; Whitfield-Gabrieli and Nieto-Castanon, 2012) but may not always be flexible enough to accommodate users' needs. Due to continually evolving best practices in handling FC and other types of neuroimaging data (Nichols et al., 2017), these public resources, as well as custom pipelines preferred by some investigators, must be updated regularly to maintain consensus. Future potential applications in clinical settings will require efficient, user-friendly tools (*e.g.,* for clinician use) that offer valid, reliable, and generalizable results.

Many in the field have suggested that multi-site studies involving "big data" will be necessary to determine how clinically meaningful FC findings can ultimately be at the level of individuals. Dataset sizes are rapidly growing due to larger sample sizes, increasing spatial and temporal resolution, and rich multimodal data that are often acquired alongside fMRI (Xia and He, 2017). With this growth has come many of the typical computational and algorithmic challenges of big data (Lichtman et al., 2014), the need to develop efficient systems and protocols for data sharing (Poldrack et al., 2017), and specific challenges concerning how large FC datasets should be analyzed (e.g. how to extract and analyze high-dimensional FC features) to optimize inferences at the level of individuals (Bijsterbosch et al., 2020; Bzdok and Yeo, 2017). Others suggest that the "big data" approach is an incremental step unlikely to succeed in improving the clinical utility of neuroimaging on its own. Instead, it is argued that a critical next step is to use neuromodulation techniques to causally validate neural circuitries identified by neuroimaging, which can then facilitate novel treatment developments (Ward et al., 2021). Two recent neuromodulation studies for patients with SZ adopted and showed success with this strategy - they first identified networks associated with positive and negative symptoms in SZ and then used TMS (Brady et al., 2019) and real-time fMRI neurofeedback (Bauer et al., 2020) respectively to modulate the networks, which led to amelioration in symptoms.

Relatedly, harmonization of data acquisition protocols will be increasingly imperative in order to promote open science practices moving forward. Our ability to pool clinical datasets across sites will be limited if imaging protocols are not standardized. The HCP (http://protocols.humanconnectome.org/) and ABCD (https://abcdstudy.org/scientists/protocols/) protocols are examples of imaging protocols that are increasingly being adopted by individual labs and consortia in order to promote harmonization and data sharing. By leveraging the power of existing data collection and sharing initiatives, we can accelerate the pace of discovery science in clinical disorders (Uddin and Karlsgodt, 2018).

Separating signal from noise is a challenge across all subdisciplines of neuroscience (Uddin, 2020), and presents a particular problem for FC research which relies on characterization of signals with highly overlapping properties to that of commonly observed sources of noise in fMRI data. Methods for denoising fMRI data prior to FC analysis are rapidly evolving, and have been the focus of multiple published reviews (Caballero-Gaudes and Reynolds, 2017; Goto et al., 2016). Additional controversies include the extent to which head motion artifacts distort FC metrics (Power et al., 2015) and the use of pre-processing strategies such as global signal regression to mitigate motion and other artifacts (Murphy and Fox, 2017). Two other reviews in this special issue explicitly address these important topics (Chang & M. Bright papers in this issue), which are not further elaborated upon here. There are promising methodological innovations that are being developed to overcome these limitations, such as new imaging acquisition sequences (Power et al., 2018), real-time motion monitoring (Dosenbach et al., 2017), visual feedback (Greene et al., 2018), and head molds (Power et al., 2019; Weng et al., 2021). Work is ongoing to optimize these methods, which will be necessary for improving clinical utility.

Given the wide heterogeneity in most neuropsychiatric disorders, and individual differences across the population in general, there has been great interest in capturing such individual variability with FC to facilitate personalized medicine. Though FC can show high reliability (Taxali et al., 2021), several methodological factors impact specific features of FC reliability within an individual (Noble et al., 2019). One of these factors is scan duration. Repeated scanning of healthy individuals has indicated that 30–100 min of low-motion data may be desirable for reliable FC network mapping at the individual level, with the specific amount of data depending on the specific measurement (*e.g.*, parcel-to-parcel correlations, network assignments, modularity) (Gordon et al., 2017; Laumann et al., 2015). This repeated sampling 'precision functional mapping' approach has already afforded insights into functional brain network organization at the level of individual healthy subjects (Greene et al., 2020; Marek et al., 2018; Seitzman et al., 2019). Further research is necessary (and is being actively pursued) to assess feasibility and data quantities necessary for reliable individual-level FC measurements in other populations (*e.g.*, children, older adults, neuropsychiatric disorders). Determining the optimal scan duration is additionally important considering the relatively high cost of fMRI scans. Though this precision functional mapping approach faces practical issues in clinical contexts due to the need for repeated scanning sessions, it holds promise for capturing the heterogeneity that exists in clinical popula-

tions (Gratton et al., 2020). Additionally, with the constantly evolving advances in fMRI acquisition methods (*e.g.*, multiecho sequences) (Lynch et al., 2020) and advanced analyses (Sarar et al., 2021), improved reliability may be achieved with smaller quantities of data.

5. Concluding remarks

In the last two decades, FC has significantly advanced our understanding of the brain bases of clinical diseases and disorders at the network level in many ways. We have reviewed unique opportunities offered by FC, such as revealing the ubiquity of intrinsic functional architecture (Section 2.1) and probing brain function in disorders of consciousness (Section 2.6). Knowledge gained via FC builds on foundations established by earlier neuroimaging methods, such as seen in the extensions of developmental principles (Section 2.2) and distributed disruptions (Section 2.3). The rise in FC also coincides with, and supports, the recent shifts to transdiagnostic (Section 2.4) and multimodal imaging (Section 2.5) approaches. All of these factors combined to contribute to the rising popularity of FC in clinical neuroimaging, as researchers aim to eventually translate findings from clinical studies to effective care delivery.

Similar to many other successful clinical tools, FC assessments are relatively easy (albeit expensive) to administer and offer both unique and complementary information about a patient's condition compared with other tools. However, clinical applications of FC are still rare due to several challenging conceptual and methodological barriers (Section 4). Recent and ongoing studies with both large sample sizes, dense sampling of single individuals, and FC dynamics across various contexts are beginning to address the key issues that must be overcome for gaining a more nuanced understanding of FC in clinical populations. For more immediate clinical impact, neuromodulation targeting FC-identified circuitries may offer causal validation of disease mechanisms and prompt development of more precise treatments. With exciting advances in fMRI protocols, analysis techniques, and our mechanistic understanding of how FC is generated, we have reasons to believe that the knowledge generated from FC research may help clinicians to more broadly achieve more accurate and personalized diagnosis, prognosis and treatment in the not too distant future.

Declarations of Competing Interest

None.

Credit authorship contribution statement

Jiahe Zhang: Conceptualization, Writing – review & editing. **Aaron Kucyi:** Conceptualization, Writing – review & editing. **Jovicarole Raya:** Conceptualization, Writing – review & editing. **Ashley N. Nielsen:** Conceptualization, Writing – review & editing. **Jason S. Nomi:** Conceptualization, Writing – review & editing. **Jessica S. Damoiseaux:** Conceptualization, Writing – review & editing. **Deanna J. Greene:** Conceptualization, Writing – review & editing. **Silvina G. Horovitz:** Conceptualization, Writing – review & editing. **Lucina Q. Uddin:** Conceptualization, Writing – review & editing. **Susan Whitfield-Gabrieli:** Conceptualization, Writing – review & editing.

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Data/code availability statement

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