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Review

Clinical Concepts Emerging from fMRI Functional Connectomics

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Recent advances in connectomics have led to a synthesis of perspectives regarding the brain's functional organization that reconciles classical concepts of localized specialization with an appreciation for properties that emerge from interactions across distributed functional networks. This provides a more comprehensive framework for understanding neural mechanisms of normal cognition and disease. Although fMRI has not become a routine clinical tool, research has already had important influences on clinical concepts guiding diagnosis and patient management. Here we review illustrative examples. Studies demonstrating the network plasticity possible in adults and the global consequences of even focal brain injuries or disease both have had substantial impact on modern concepts of disease evolution and expression. Applications of functional connectomics in studies of clinical populations are challenging traditional disease classifications and helping to clarify biological relationships between clinical syndromes (and thus also ways of extending indications for, or "re-purposing," current treatments). Large datasets from prospective, longitudinal studies promise to enable the discovery and validation of functional connectomic biomarkers with the potential to identify people at high risk of disease before clinical onset, at a time when treatments may be most effective. Studies of pain and consciousness have catalyzed reconsiderations of approaches to clinical management, but also have stimulated debate about the clinical meaningfulness of differences in internal perceptual or cognitive states inferred from functional connectomics or other physiological correlates. By way of a closing summary, we offer a personal view of immediate challenges and potential opportunities for clinically relevant applications of fMRI-based functional connectomics.

Introduction

Historically, there has been a conceptual division in clinical neuroscience between localist and distributed processing perspectives on brain function. The former are derived from classical lesion studies, which, in the tradition of Charcot, view the brain as a set of discrete processing modules. The latter are derived from theories of equipotentiality, which, in accordance with views popularized by the Harvard physiologist Karl Lashley, view the brain in terms of distributed functions. Localist models represent a natural extension of traditional interpretations of neuropsychological studies after focal lesions. They remain useful for clinical diagnosis, e.g., for recognizing and localizing strokes or brain tumors with major acute deficits of motor or primary sensory systems. However, in recent years, distributed processing models have proven more powerful for explaining complex cognitive functions, their individual variation, and the behavioral expression particularly of more generalized pathologies in neurological and psychiatric diseases (e.g., cognitive impairments with diffuse small vessel disease [Dey et al., 2016; Schaefer et al., 2014b]) and generalized inflammatory diseases such as HIV (Ann et al., 2016), or for discrimination between the overlapping symptom presentations of bipolar disease and depression (Jie et al., 2015).

Much has been written about how structural connectomics has contributed to the discrimination or understanding of neurological and psychiatric diseases. Recent work has explored how brain structural connectomic principles help to explain key aspects of disease expression or brain resilience (Fornito et al., 2015). To complement this, our focus in this review will be on the clinical relevance of fMRI functional connectomics. We will briefly outline evidence for two fundamental concepts central to clinical applications: how individual variation can be characterized, and how this variation is related to cognition and behavior. We then will discuss applications having a current or developing impact on medical practice. Finally, we will reflect on challenges to realizing this impact more comprehensively and rapidly. To cover such a wide range of topics, our approach necessarily has been selective.

One of us reviewed clinical applications of fMRI early in this millennium (Matthews et al., 2006), but applications of functional connectomics have progressed rapidly since. Important foundations for extension of these toward problems in clinical medicine include the observations that distributed spatiotemporal network organization is reproducible across subjects (Damoiseaux et al., 2006) and that network components are relevant to behavior (Smith et al., 2009). There has been a convergence of complementary insights from studies that have used other techniques, such as MRI arterial spin labeling, [^{18}F]-Fluorodeoxyglucose PET, or electrophysiological methods (e.g., electroencephalography [EEG] or magnetoencephalography [MEG]) (Brookes et al., 2011). However, fMRI may be unique insofar as it is widely accessible, directly links functional with structural brain measures, and is practical to implement in many clinical contexts.

Relationships between regional human brain anatomy and different behaviors classically were based on clinical-pathological associations made in studies of patients suffering from brain diseases or brain injuries that impaired behaviors or psychological functions. The hypothesis that structural connectomics can explain relationships between brain lesions and associated behavioral impairments is not new (Fornito et al., 2015). For example, the ideas of ''réseau de cellules anastomosées,'' positing that brain regions sub-serving the same function are connected (Koehler, 1996), and of connectional diaschisis (Carrera and Tononi, 2014) have been influential for decades. Diagnostic approaches to language impairments based on connectional models that use clinical signs to localize lesions either to functionally specialized regions (nodes) or to their disconnection have been among the core canons of behavioral neurology throughout its modern era (Lichtheim, 1885). Specific variants of the concept also have been important in the context of generalized epilepsies or the disconnexion syndrome (Catani and ffytche, 2005). Recent work extends these concepts in structured or quantitative frameworks that can be applied across levels of spatiotemporal organization (Bullmore and Sporns, 2009; Park and Friston, 2013).

Functional connectomics provides a related, but distinct, level of description. A sign of its maturation has been the transition from theoretical constructs that describe characteristics of brain functional organization *qualitatively* to *quantitative* measures and predictive models that are becoming practical for guiding clinical diagnosis in disease or treatment monitoring. While we and others have noted that fMRI has not been integrated into routine clinical practice with anything like the speed that was seen with the introduction of structural MRI three decades ago (Matthews et al., 2006), we believe that advances in functional connectomics have made important contributions. Here we selectively review major conceptual insights from fMRI-based functional connectomics that are contributing to a fuller understanding of individual variation in brain-behavior relationships relevant to clinical problems. We then describe examples of applications of these ideas more directly in an illustrative range of clinical applications, including patient assessment, pre-symptomatic disease diagnosis, and the development of new treatments. Finally, we offer a personal view of short- to medium-term challenges and opportunities for greater clinical impact from this growing understanding of fMRI-based functional connectomics in health and disease.

Properties of the Functional Connectome

Structural and Functional Connectivity of the Brain

Functional interactions throughout the brain are fundamentally constrained by structural connectivity, so it is unsurprising that there are significant correspondences between structural and functional connectomes (Baria et al., 2013). Nonetheless, macro-scale human functional connectomes derived from human fMRI data offer additional descriptive power. These descriptions can differ substantially from those of structural connectomes. Some of these differences can be attributed trivially to the distinct properties of these two descriptions. Strong fMRI functional connectivity can be found between brain areas that lack direct structural connections (Honey et al., 2009), e.g., as illustrated by the preserved inter-hemispheric motor cortical functional connectivity in rhesus monkeys even after sectioning direct callosal connections (O'Reilly et al., 2013). An additional factor may be that structural connectomic models developed from diffusion tensor MRI have spatial resolutions that are orders of magnitude lower than needed to resolve inter-neuronal connectivity: micro-scale circuitry determines local information processing that also contributes substantially to large-scale network dynamics (Gerits et al., 2012).

Correspondences between structure and function are expressed because of the general constraints that structure imposes on the range of functional states that can be assumed, although functional connectional interactions are much more dynamic than those of the structural connectome (even allowing for high synaptic turnover and remodeling) (Chen et al., 2014). The architecture of the functional connectome converges over time on an average (steady-state) set of interactions, but is intrinsically dynamic (Baker et al., 2014). A comprehensive illustration was given by comparison of resting-state functional connectivity derived from BOLD-fMRI in macaques (*Macaca fascicularis*) to structural connectivity derived from macaque axonal tract tracing studies. Correspondences between these descriptions increased with the duration over which the resting-state correlations were sampled (Shen et al., 2015).

Functional Connectomic Dynamics: Measures or State and Trait?

Task-based fMRI studies are designed to determine differences between brain states that are expressed during specific processing conditions. When sampled with greater temporal resolution, the functional connectome also provides measures of transient or dynamic states that relate to specific internal states of mind (Spiers and Maguire, 2007). By contrast, functional connectivity assessed over longer periods of rest provides measures that may relate more to trait. The now large body of literature defining steady-state, resting-state functional networks thus offers a basis for understanding traits that distinguish individuals or diseases (De Luca et al., 2006; Smith et al., 2009).

Considerable attention has been placed on mapping brain functional-anatomical networks to understand how individual differences in their persistent (traits) or transient (states) interactions relate to behavioral variability and disease. Steady-state measures of inter-network coupling are associated with normal and pathological variability in cognition, for example (Geerligs et al., 2015). The potential range of these dynamic spatiotemporal interactions differentiates networks and their functional roles for enabling behavior (de Pasquale et al., 2012). For example, the fronto-parietal brain network shows particularly highly variable functional connectional architectures across brain states associated with different tasks (Cole et al., 2013b), consistent with a flexible resource that combines processing across various brain regions to support the broad range of behavioral demands needed in everyday life (Duncan, 2001).

Despite the low-pass filter of neurovascular coupling, resting-state fMRI reflects rapid, coordinated spontaneous activity underpinning connectivity within and between functional networks (Baker et al., 2014). This activity varies dynamically around a stable or slowly changing mean state, highlighting a fundamental principle of brain functional architecture: in order to maintain

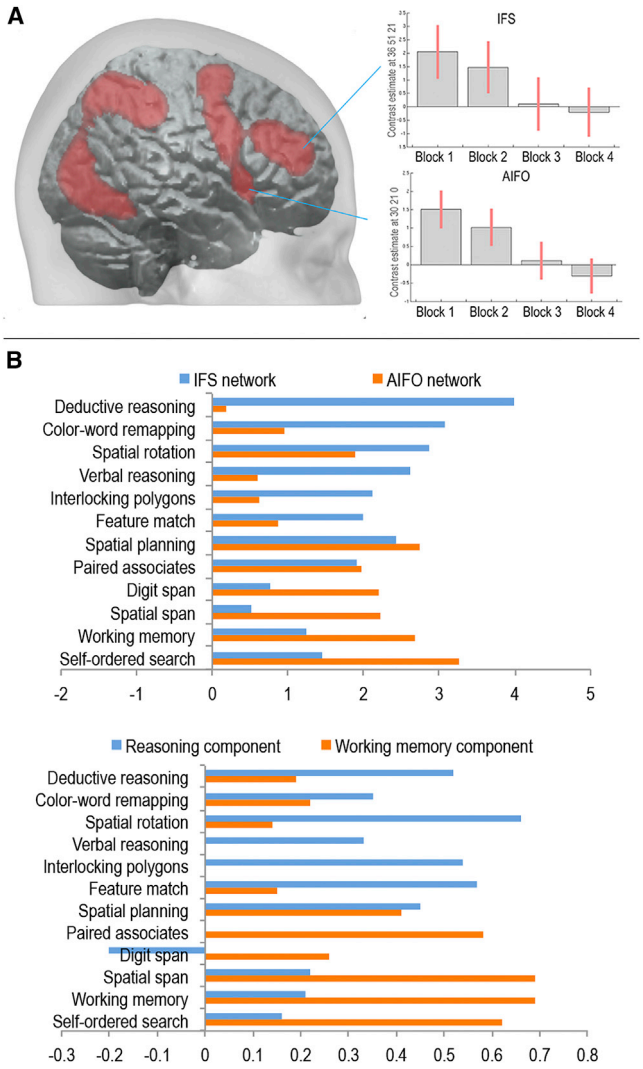

Figure 1. Dissociable Roles of Fronto-Parietal Cortex Component Networks

(A) A set of brain regions are commonly activated when a very broad range of cognitive task demands are manipulated (left panel). These are often referred to as multiple demand (MD) cortex (Duncan and Owen, 2000; Fedorenko et al., 2013). They include an area of the lateral frontal cortex centered on the inferior frontal sulcus (IFS), anterior insula extending into the frontal operculum (AIFO), anterior cingulate and pre-supplementary motor area, and inferior parietal cortex. MD cortex is strongly active during the performance of novel or complex demands such as the stop signal task (right panel) (Erika-Florence et al., 2014), but becomes less active when the same task has been practiced. (B) Although MD cortex has a broad response to cognitive tasks, it houses component networks that respond most strongly to different demands (upper figure) (Hampshire et al., 2012). Tasks that tend to activate one or other MD component network also tend to load onto the same behavioral psychometric factors (lower figure).

the potential to adapt rapidly to changing demands, a network must operate at the "edge of chaos" to enable flexible shifts between the transient processing states (Beggs, 2008). Patterns of activity that distinguish different mental states reflect very small differences relative to total brain energy expenditure (Raichle and Mintun, 2006; Shulman et al., 2014). The brain's functional connectomic dynamics thus can be modeled as a set of alternative network activation states, each of which is close to destabilization (Deco et al., 2013; Hellyer et al., 2014). At the same time, dynamic variations within or between functionally connective elements is constrained (metastable). Extensions of such models enable quantitative, in silico hypotheses to be generated regarding the potential influence of diverse factors on network behaviors, e.g., the molecular events and synaptic activity that underlie conductance changes sub-serving neural information processing (Markram et al., 2015).

Expression of brain functional connectomics in terms of dynamic spatiotemporal models provides a quantitative framework that can reconcile localist and distributed views of the brain. From this perspective, the brain is viewed as having a functional architecture built from nodes that show variable functional connectivity with other nodes. In the healthy brain, these nodes function as elements within highly interactive networks responsible for cognitive information processing. Some nodes are specialized for local processing (e.g., in primary sensory or motor cortex or, for expressive language, in the posterior superior temporal gyrus [BA 22] and the pars operculis/pars triangularis of the inferior frontal gyrus [BA 44 or 45]). Others (e.g., lateral prefrontal cortical nodes with high topological centrality) perform more general functions to modulate global network activities for control of cognitive states (Koechlin et al., 2003). For example, Hellyer et al. showed that richly connected network hubs in the fronto-parietal control/dorsal attention or the posterior cingulate-precuneas/anterior cingulate/default mode networks (Hellyer et al., 2014) modulate the metastability of networks more globally. These features create a nested architecture associated with variable correlations within and between networks. Results of these analyses can be expressed in terms of average correlation strengths (defining hypotheses for determinants of traits) or as fluctuations and directed connectivities that change over time with shifting task demands (defining hypotheses for determinants of states). These expressions allow dysfunction or injury to systems with disease to be quantified as multivariate measures of the interactions between key nodes and networks.

Explaining Individual Variation with Disease through the Functional Connectome

A brief review of observations made of fronto-parietal networks provides good illustrations of how functional connectomic traits and states relate to individual cognitive variation. These illustrations also have broad clinical relevance; sub-regions within the frontal-parietal cortex co-activate during diverse cognitive tasks (Duncan and Owen, 2000) (Figure 1). In patients studied after focal lesions (e.g., from strokes), core cognitive abilities are reduced in direct proportion to the extent of damage to the frontal (lateral and dorsomedial) and mid-parietal cortex (Woolgar et al., 2010). While the individual networks within fronto-parietal cortex often activate together, functional dissociations with different task demands demonstrate that they have distinct roles in cognitive processing (Hampshire and Owen, 2006; Smith et al., 2009). These functional dissociations correlate with the behavioral latent variables that explain population variability in cognitive ability. The constituent networks of the fronto-parietal cortex provide a framework for quantitative, functional connectomic models predicting the different cognitive impairments

associated with such differences in the distribution of pathological changes, e.g., as illustrated by studies of Parkinson's disease (Nombela et al., 2014).

Analogous approaches relying on functional connectomic mapping and analyses of individual nodes or network activity have contributed to explaining individual differences in other aspects of cognition (see McNab and Klingberg, 2008; Mukai et al., 2007; Tom et al., 2007; Wig et al., 2008). This can be more complex than simply assessing relative correlations across a canonical set of networks, as functional networks may show variable topologies in different people. Models based on one-to-one mappings between patterns of fMRI brain activation and behavior are overly-simplistic. Individuals can apply different cognitive strategies and, thereby, assume different functional connectivity states when performing the same task; the functional architecture of individual cognitive processing networks is not necessarily fixed across the whole population. For example, Seghier et al. described distinguishable correlated activations alternatively of left inferior frontal and anterior occipito-temporal regions or right inferior parietal and left posterior occipito-temporal cortex while different subjects read familiar words, suggesting physiologically distinct cognitive strategies for reading (Seghier et al., 2008). In another example, Kraemer et al. asked study participants to perform a task involving both word-based and picture-based feature matching. They found modality-specific correlated cortical activities that distinguished individuals who used either predominantly visual or verbal cognitive strategies (Kraemer et al., 2009). Accounting for the potential heterogeneity in such mappings is a key challenge for confident clinical application of fMRI functional connectomics.

A growing trend in the study of individual differences is toward evaluating networks using data-driven models that can account for generalizable aspects of this heterogeneity. In a pioneering example of this, Smith and colleagues explored correlations between resting-state network connectivities and a wide range of demographic, psychometric, and clinical measures for a large-scale population of volunteers in the Human Connectome Project (HCP) (Smith et al., 2015; Van Essen et al., 2013). They used group independent components analysis (ICA) to define a consensus brain parcellation from resting-state fMRI data and then applied canonical correlation analysis (CCA) across the individual subject measures to identify common modes of variation between the two sets of data. A single statistically significant CCA mode was identified. This was reported to be related most strongly ($r = 0.87$) to default mode network connectivity. Individual subject phenotypic measures also were correlated with this mode ($r = \sim 0.2–0.4$). These appeared to cluster into distinct "positive" (e.g., those with good health, higher IQ, and a safer lifestyle) or "negative" (e.g., those who were less healthy, had lower IQ, or higher risk lifestyle) axes, suggesting that it reflects a common latent factor. This result is striking, although the CCA mode explained only a very small percentage of the overall variability in the individual subject measures (<2%). The low explanatory power suggests either that the phenotypic measures selected do not represent modes of brain functional variation well or that important aspects of brain function that were not considered here (e.g., dynamics of functional network interactions [Cole et al., 2013b; Scott et al., 2015]) play dominant roles.

Another early large population study reported by Rosenberg and colleagues (Rosenberg et al., 2016) had similar general objectives, but focused specifically on brain functional associations explaining attentional control, rather than a data-driven phenotypic construct. Mean (steady-state) coupling strengths were calculated between anatomically parcellated sub-regions of the brain. These mean couplings implicitly provide information regarding connectional coupling both within and between networks. Using these measures, they generated a multivariate model that predicted a more substantial component of variance ($r = \sim 0.8$, explaining $\sim 60\%$) in performance of a sustained attention task. They validated their model by predicting task performance based on the resting-state fMRI data. They then demonstrated how the model could be used to make predictions about clinical presentations by predicting symptom severity in an attentional deficit hyperactivity patient cohort.

Together, the Smith and Rosenberg studies confirm that cognitive and brain functional connectivity traits significantly co-vary in healthy and clinical populations. They suggest that such analyses may enable more general discovery of functional connectomic states associated with specific behavioral symptoms or signs related to the expression of disease. They also suggest that many individual subject characteristics used for describing lifestyle or behavior may themselves not have strong direct associations with common features of brain functional connectivity. It is possible the level of description provided by functional connectomic analyses may relate more closely to emergent cognitive traits (such as attentional control) or latent features (as implied by the CCA analysis).

However, improving the predictive power of correlations between functional connectomics and other subject characteristics for individual subjects also will require methods that allow for topological variation in networks between individuals (Wang et al., 2015). A recent report from Jbabdi's group described a way of defining individual differences in task-associated network mappings using resting-state fMRI data (Tavor et al., 2016). Briefly, a functional parcellation was performed at the group level using resting-state data from 98 subjects in the HCP dataset in order to define "seeds" for functional connectivity mapping. A "dual" regression analysis was performed in which the summary cortical map for the group first was used as a regressor to define time series in individual datasets, and then, in a second step, these were used to define individual spatial maps. These maps were then used (in addition to a handful of structural features) to predict individualized task activations. A "leave one out" approach prevented circularity in this analysis. Results showed that their method could define qualitative differences (shape, position, size, and topography) of networks between individual subjects. These differences were validated in several instances for functional networks identified by task-based fMRI. Clear examples of topological variability between individuals were demonstrated (Figure 2). There are many ways in which this (or related) approaches could be extended to allow exploration of population modes of variation in associations between functional connectivity and cognitive, behavioral, or lifestyle measures, extending the kinds of associations proposed in the Smith et al. or Rosenberg et al. reports.

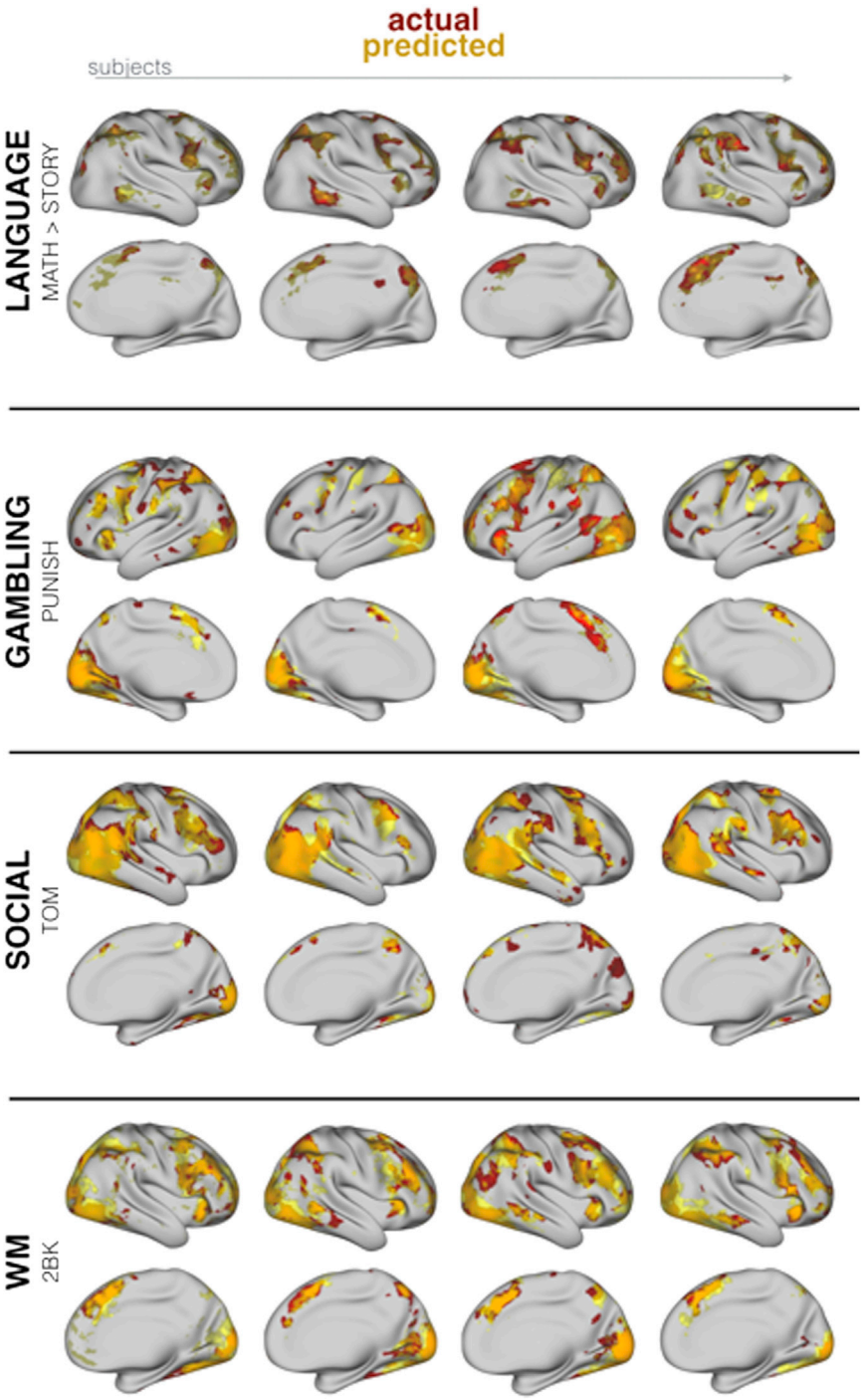

Figure 2. Topological Heterogeneity in Functional Networks between Healthy Volunteers

Jbabdi et al. developed a model that predicted functional connectomic topological variability between subjects for networks associated with a range of task-related cognitive states (Tavor et al., 2016). In each row, thresholded, task-related activations are shown for a representative hemisphere (red) with superimposed model predictions for the network based solely on the resting-state fMRI (yellow). Individual topological heterogeneity is apparent for both the task-associated and the predicted network activations. The model captures this variation well, demonstrating that the network architecture is a trait embedded within the resting-state brain activity. Punish, punishment condition; TOM, theory of mind task; WM, working memory; 2BK, two-back task. Image provided courtesy of Dr. S. Jbabdi, Centre for Functional Magnetic Resonance Imaging of the Brain, University of Oxford.

More richly descriptive approaches such as that proposed by Jbabdi and his colleagues also may be needed to encompass more extreme variations in brain function triggered by disease or injury. This could allow quantitative definition of concepts such as functional "degeneracy" (in which brain networks have multiple pathways for realizing the same output) to refine predictions of outcome after acute brain injury (Noppeney et al., 2004; Tononi et al., 1999). A similar approach could make the clinical concept of "resilience" to neuropathological change—which is important on an individual level for predicting future disease onset (in the case of observations before symptoms) or rates of disease progression (when disease already is manifest)—physiologically meaningful (Reijneveld et al., 2007). A persuasive illustration of how symptoms and signs of disease worsen as adaptive changes in brain activity responsible for functional resilience fail with the progression of pathology is provided by a recent longitudinal study of functional connectivity in people with multiple sclerosis (Fleischer et al., 2016).

Implications of Network Metastability for Understanding Human Variation in Health and Disease

Models relating functional connectomics to clinically relevant variations in cognitive state or behavior can be extended in other ways. Theoretically, variations in network metastability and synchrony provide optimal conditions for different aspects of information processing (Friston, 2000). Dynamic network models thus may provide better discriminants of individual variation. Time-varying correlations among nodes have been reported to explain a greater amount of associated behavior than do stationary measures (Madhyastha et al., 2015).

An example of this class of phenomena pertains to how time-dependent changes in synchrony across networks support relational integration, the process by which task rules are combined into higher-order constructs during reasoning. In a recent study, integration task demands elicited increases in functional

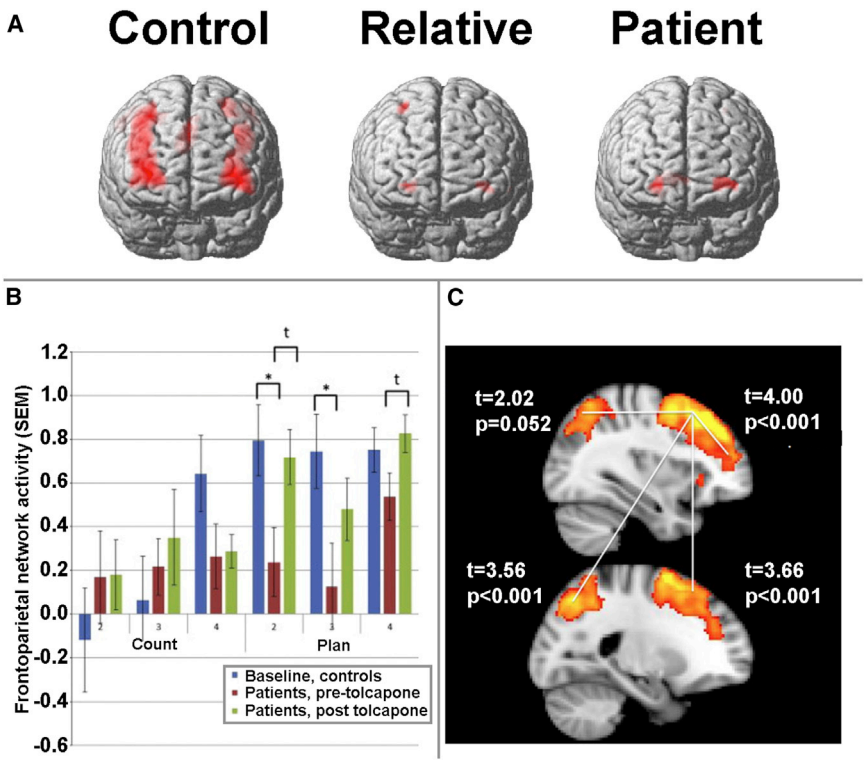

Figure 3. Convergence of Pathological Activities and Connectivities within Fronto-Parietal Networks

(A) During contingency reversal learning, a network of brain regions including the lateral orbitofrontal cortex, extending through the lateral fronto-polar cortex, and including the posterior middle frontal gyrus and parietal cortex bilaterally is hypoactivated in individuals with obsessive compulsive disorder (Chamberlain et al., 2008). This same network also is hypoactivated in first-degree relatives of the patients when compared to matched controls, forming an endophenotype.

(B) Pathological gamblers show hypoactivation within a similar set of frontal and parietal brain regions during spatial planning (Grant et al., 2013). This hypoactivation is normalized by dopaminergic medication, although the normalization effects on behavior are modulated by COMT genotype.

(C) During performance of the same planning task, retired professional American football players show hyperactivation and hypoconnectivity within a similar network of frontal and parietal brain regions (Hampshire et al., 2013).

connectivity within and between lateral frontal cortical networks (Parkin et al., 2015). Similarly, individual differences in motor response inhibition relate more closely to dynamic interactions between the nodes of multiple fronto-parietal networks than to the magnitudes of event-related activations at particular nodes (Erika-Florence et al., 2014). A directly clinical application showed how dynamic functional interactions between salience and default mode networks explain important aspects of syndromes following closed head injury (Hellyer et al., 2015; Jilka et al., 2014).

If differences in such global network interactions play dominant roles in population variation in cognitive ability or with pathology underlying specific types of cognitive impairments, then nodes that drive these broader network activities should be major determinants of this variation. Considerable evidence already has shown that injury to the more highly connected network hubs is most closely associated with impairments after brain injury (Crossley et al., 2014). Furthermore, abnormal functional activity and connectivity of a similar lateral fronto-polar cortex region that is associated with relational reasoning is also associated with executive impairments in a variety of clinical populations, including obsessive compulsive disorder patients (Chamberlain et al., 2008) and individuals who have repeatedly suffered sports-related traumatic brain injuries (Hampshire et al., 2013) (Figure 3). A logical extension of this concept is that these network "hub" nodes provide optimal targets for magnetic and electronic therapeutic neurostimulation intended to improve cognition through normalization of global network dynamics or to enhance recovery of lost functions by facilitating re-learning.

Inferring Molecular Determinants from Network Level Descriptions

Functional imaging provides endophenotypes reflecting traits that can be measured quantitatively and reliably. The conceptual proximity of these endophenotypes to neurobiological mechanisms enhances their potential to aid in the discovery of new molecular determinants of diseases. Although efforts to date have predominantly been more for hypothesis generation than validation, there is encouraging evidence that specific genetic variation in population behavioral traits or disease is reflected in differences in functional connectivity states or traits (Filippini et al., 2011; Hariri, 2009; Thompson et al., 2013, 2014).

The basis for optimism about this approach is that brain structure is highly heritable, consistent with neurodevelopmental predictions (Chen et al., 2012). Properties of resting-state networks show some heritability, although there is a substantial environmentally determined component (Fu et al., 2015; Glahn et al., 2010). Differences in network functional architecture also appear modestly heritable (Sinclair et al., 2015), consequences of which may relate to the heritability of intelligence (Deary et al., 2009). Heritable differences may even be associated with population variability in the transient activation states of functional networks associated with cognitive tasks (Koten et al., 2009). An fMRI twin study of digit working memory tasks illustrates this latter point. It was observed that individuals who activated frontal-parietal networks during the task responded faster than those who activated language-related brain networks. These population differences in processing states were shared between twin pairs. More generally, preliminary research indicates that task-related network activation and connectivity are highly heritable (Blokland et al., 2011). However, the heritability of macroscopic features of brain structural and functional connectivities may differ, e.g., heritable factors influencing

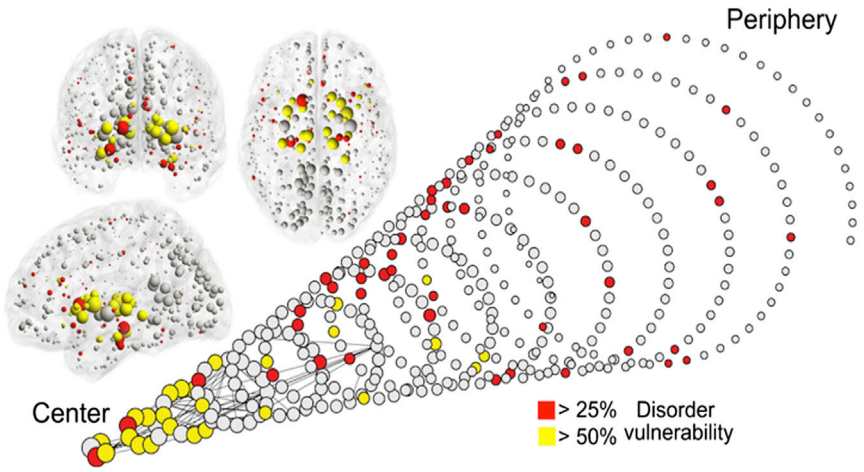

Figure 4. Brain Functional Network Hubs Are Common Lesion Sites in Brain Disorders

Well-connected (metabolically highly active) network hubs are more likely to be primary regions affected in brain disorders (Crossley et al., 2014). A literature meta-analysis localized MRI lesions associated with 26 clinical brain disorders, which were mapped onto nodes in the normal human brain structural connectome. On the left, nodes of the normative connectome are represented in a standard anatomical space. On the right, they are shown in a spiral, with nodes having similar numbers of connections in the network arranged in the same circle, along a spiral arranged so that its tip includes those nodes with greatest numbers of connections. The sizes of the nodes reflect their numbers of connections. The colors reflect their relative likelihood of parts of lesions identified in the literature meta-analysis (red if >25% and ≤50% of their volume includes a lesion, yellow for >50%) and colored according to the proportion of voxels, which are generically lesioned, i.e., the percentage of lesion voxels each node comprises. The strongest 0.1% of edges between nodes also are shown to highlight the high connectivity between nodes near the apex. Image provided courtesy of Dr. N.A. Crossley and Prof. E. Bullmore, Department of Psychiatry, University of Cambridge; this figure originally appeared in Crossley et al., 2014 and is reused by permission of Oxford University Press.

default-mode functional connectivity and gray-matter density are distinct (Glahn et al., 2010).

In a few instances, specific genetic factors that determine the activity of functional connectional networks have been defined. Initial attempts to do this focused on candidate genes, e.g., for testing how variations in dopamine transporter and catechol-O-methyltransferase genotypes influence variations in dopamine transmission and how this impacts on the fMRI activity of brain regions that are involved in the anticipation and reception of reward (Dreher et al., 2009) or in planning and attentional control (Williams-Gray et al., 2007, 2008). However, with the power afforded by larger datasets, first steps have been taken toward larger-scale discovery, with unbiased searches based on genome-wide analyses, e.g., for functional activation associated with ambiguous face presentation (Dickie et al., 2014). As data from larger study populations become available, more studies of disease or pathological traits undoubtedly will be undertaken.

With the mounting evidence that functional connectivities are meaningfully sensitive to environment and experience, as well as to genetic determinants, functional connectomics provides a tool for exploring interactions between nature and nurture, e.g., for understanding how BDNF polymorphisms interact with exercise to influence hippocampal connectivities or how life stress modulates effects of serotonin transporter genotype on amygdala and hippocampal resting activations (Canli et al., 2006). The availability of very large datasets, including clinical phenotypic functional connectomic and genetic data from diverse populations, could make it possible to move beyond the identification of associations to determination of causal influences using methods such as Mendelian randomization (Debette et al., 2014).

Emerging Clinical Applications Arising from Functional Connectomics

Despite this potential, the sole (relatively) widely accepted, more routine use of fMRI in clinical medicine is as an adjunctive diagnostic for localization of eloquent cortex to support neurosurgical planning to lower risks of functional deficits after temporal lobe or tumor resections (Matthews et al., 2006; Peck et al., 2009; Pittau et al., 2014). While, strictly speaking, these methods have relied more on the localization of regional activation than on connectomics, efforts to improve their predictive potential have brought extensions that include explicit characterization of functional networks (e.g., see Jbabdi et al., 2013).

More generally, functional connectomics has had substantial impact in neurology and psychiatry by advancing understanding of disease course, potential mechanisms responsible for the efficacies of interventions, and population heterogeneity. It also is contributing to emerging clinical concepts, particularly for early disease risk assessment and for personalized medicine. Selected illustrations of this will be discussed below.

From Focal Mapping to Global Consequences of Localized Brain Pathologies

Less obvious than applications for functional mapping have been the influential clinical insights that have arisen from the use of fMRI functional connectomics for network-based modeling of the distributed consequences of localized neuropathology. This has been most widely explored in patients after stroke (Grefkes and Fink, 2014). These efforts have illustrated that localized brain injuries have effects that are distributed widely across otherwise intact brain regions. The integrity of wider brain regions and the nature of these distributed effects can have important implications for cognition and behavior after the local injury (Fornito et al., 2015). This understanding forms the core of a modern reconciliation of localist and distributed views of brain functional organization.

Graph metrics provide a useful way of describing these phenomena (Sporns, 2015). A broad range of studies have emphasized how the functional impact of damage (e.g., from stroke [Váša et al., 2015] or traumatic brain injury [Fagerholm et al., 2015]) depends on local connectional topology: "centrality" (the influence that any node has on other network components) is a major predictor of the behavioral impact of damage to a brain region. Symptomatic lesions brain disorders are more

likely to be localized to such hub nodes (Crossley et al., 2014) (Figure 4).

Similarly, the potential contributions of intact brain regions to functional recovery after local injury or disease can be understood in terms of their functional connectivities. Highly connected, less functionally specialized hub nodes in the prefrontal cortex and parietal cortices are most likely to show compensatory activity in response to remote dysfunction (in a task-dependent manner). Appreciation of roles for such hubs in learning (Floyer-Lea and Matthews, 2005; Toni and Passingham, 1999) provides a basis for network models of brain "resilience" or "functional reserve," e.g., with functional recovery after stroke (Crofts et al., 2011). Direct demonstrations of functional compensatory roles for such remotely recruited regions were described with behavioral monitoring of effects of transcranial magnetic stimulation (TMS) inhibition on the secondarily recruited regions after stroke (Johansen-Berg et al., 2002; O'Shea et al., 2007).

"Functional reserve" hypotheses imply that with loss of connectivity from disease or injury in some network pathways, there are compensatory increases in the connectivity of others. Disease expression depends not just on the direct impact of disease or injury, but also on the integrity and potential of preserved brain regions to support adaptive compensation. Graph theoretical network models also can explain how disease emerges as a result of multiple "hits," none of which independently would be symptomatic (Reijmer et al., 2015). This has provided an influential heuristic for understanding disease risk or expression more generally with diffuse pathologies, such as with other forms of multi-focal small vessel ischemic disease (Schaefer et al., 2014b), multiple sclerosis (Faivre et al., 2016), or traumatic brain injury (Sharp et al., 2014). Individual differences in functional connectional architectures have been associated with individual differences in susceptibility or expression of disease (Kehagia et al., 2010; Nettiksimmons et al., 2014).

Functional Connectomics and the Development of New Treatments for Brain Disease

These concepts underpin emerging opportunities for more rapid progress in the use of fMRI functional connectomics to guide the discovery, development, and personalized applications of bioelectronic interventions (Sale et al., 2015). For example, maladaptive increases in the activity of M1 cortex ipsilateral to a hemiparetic hand after focal injury are found with loss of transcallosal inhibitory input from the injured cortex. This not only can be associated with the emergence of "mirror" movements in the contralateral hand when the hemiparetic hand is moved, but may more generally lead to a reciprocal increase in inhibition of the injured cortex (Grefkes and Fink, 2014). Characterization of this dual mechanism is leading to new concepts for treatment that involve both enhancing function of the injured tissue and suppressing activity in healthy regions of brain that may inihibit any residual function of the damaged brain. For example, repetitive TMS can inhibit healthy motor cortex contralateral to a stroke to reduce inter-hemispheric inhibition (Kirton et al., 2010). While still speculative, the strategy may be more effective if it is combined with interventions intended to promote adaptive plasticity in the injured brain, e.g., by delivering excitability-enhancing intermittent theta burst TMS to the lesioned hemisphere contralateral to "prime" the motor cortex before rehabilitation training periods (Volz et al., 2016).

Predictive models to guide development of these interventions have been a welcome recent development. An early effort demonstrated that the spatial distribution and magnitude of resting-state connectivities predict the pattern and magnitude of the distributed cortical-evoked potentials elicited after single-pulse electrical stimulation of the brain with intracranial electrodes (Keller et al., 2011). Subsequently, Pascual-Leone and colleagues (Fox et al., 2014) provided a compelling description of a general approach to relating the anatomy of targeting of deep brain stimulation (DBS) to that of non-invasive methods such as TMS and tDCS. They showed that functional connectional maps derived from fMRI could be used to relate targets for non-invasive stimulation with those of DBS in common networks. The sites at which delivery of an inhibitory non-invasive stimulation (cathodal transcranial direct current stimulation or low-frequency TMS) proved beneficial tended to correlate positively with the DBS site, whereas those at which an excitatory stimulation was beneficial correlated negatively. With validation, this strategy could provide a rational, general route for personalized targeting of non-invasive interventions.

An example of how these concepts could be extended for discovery of new bioelectronics treatment targets is provided by the functional connectivity characterization of levodopa-induced dyskinesias (Cerasa et al., 2015). Patients with or without levodopa-induced dyskinesias were contrasted. Connectivity of the right inferior frontal cortex with the left motor cortex was decreased, while that to the right putamen was increased, in the dyskinetic patients. This abnormal pattern of connectivity was evident only during the "on" phase of levodopa treatment and the degrees of the alterations were correlated with motor disability. The analysis suggested that repetitive TMS applied to the right inferior frontal cortical region could reduce dyskinesia even with a supramaximal dose of levodopa.

With growing confidence in their interpretation, functional connectivity measures also are being applied cautiously as pharmacodynamic biomarkers in clinical trials. In some instances, they enable early decision-making more rapidly and confidently even with small numbers of subjects. For example, early-phase stroke trials have been notoriously difficult to design because of heterogeneity among patients and the insensitivity of clinical measures to change. A multimodal model incorporating behavioral and fMRI measures predicted treatment-induced changes in gait velocity in a clinical trial setting, suggesting a potential use of fMRI measures as more precise biomarkers predictive of treatment response (Burke et al., 2014). Modeling also may be able to predict risks of adverse events with treatments, e.g., for the development of dyskinesias in people treated for Parkinson's disease (Herz et al., 2016). A notably elegant recent functional network meta-analytic model of the effects of a range of analgesics on brain functional connectomics used machine learning to demonstrate how generalizable inferences could be made to infer clinical effects of a novel therapeutic from pharmacodynamics assessed using multi-study functional connectomics data (Duff et al., 2015).

Integration of fMRI measures with other modalities may add explanatory power. For example, fMRI and simultaneous

electroencephalogram (EEG) recordings were used to discover functional correlates of cognitive impairment after smoking cessation in a Phase IV clinical trial evaluating the cognitive effects of nicotine replacement in habitual smokers (Beaver et al., 2011). Positron emission tomography (PET) molecular imaging can also be combined with fMRI, relating target occupancy directly to functional connectomic measures of pharmacodynamic responses. In another example from our own work, the pharmacology of two μ-opioid antagonists was contrasted, and antagonist-dependent modulation of food reward brain salience measures were demonstrated with use of [^{11}C]carfentanil PET (for determining target occupancy by the experimental molecules) in conjunction with an fMRI paradigm based on presentation of selected images of food. This efficient design simultaneously allowed dose dependence of target occupancy and its influence on activation of a food salience network to be demonstrated.

Similar approaches provide insights concerning the mechanisms of action of widely used drugs influencing modulatory neurotransmitter signaling. Widely projecting modulatory neurotransmitter systems influence information transfer within or between brain networks. For example, age-related impairment in dopaminergic modulation with reduction of striatal D1 receptor density is correlated positively with lower dorsolateral PFC connectivity to the right parietal cortex and negatively with that between the medial PFC and right parietal cortex during a memory task (Rieckmann et al., 2011). Opposing neuromodulatory effects of dopamine agonist and antagonist effects were found on functional interactions between specific subcortical regions and corresponding neocortical "resting-state" networks known to be involved in distinct aspects of cognition and reward processing. Relative to placebo, levodopa and haloperidol challenges, respectively, increased or decreased the functional connectivity between the midbrain and the default mode network, a right caudate and a right-lateralized fronto-parietal network, and the ventral striatum and a fronto-insular network (Cole et al., 2013a). A single dose of a serotonin reuptake inhibitor dramatically alters functional connectivity throughout the whole brain in healthy subjects (Schaefer et al., 2014a).

Cholinergic modulation currently is one of the major pharmaco-therapeutic options for mild to moderate Alzheimer's disease. Increases in functional network connectivity of the left fusiform face area (FFA) and both the hippocampus and inferior frontal cortex, as well as enhanced functional network connectivity between the FFA and hippocampus, were associated with donepezil treatment that improved response times in tests of face or scene memory (Pa et al., 2013). The pervasiveness of effects was shown in an earlier study demonstrating enhancement of the intrinsic FC across the whole medial cholinergic pathway network in the parahippocampal, temporal, parietal, and prefrontal cortices (Li et al., 2012). Underlying nicotinic receptor-mediated mechanisms were evaluated using a nicotine challenge, which was shown to increase network local efficiency, a parameter that estimates the network's tolerance to local errors in communication (Wylie et al., 2012).

Identifying Brain Functional Pathology before the Clinical Expression of Disease

Functional connectomics defines endophenotypes that could contribute to the early diagnosis or characterization of disease before its clinical expression. Although Huntington's disease (HD) can be diagnosed genetically in people at risk before the onset of symptoms, current methods for predicting the (highly variable) age of disease onset are imprecise. More accurate prediction of disease onset is important to patients. It also is critical to the design and implementation of pre-symptomatic intervention trials. This preclinical population displays a progressive pathology with an evolving pattern of weakening fronto-striatal connections, reflecting the primary pathology and strengthening frontal-posterior connections believed to represent compensatory responses as disease burden increases (Harrington et al., 2015). Combining these may better predict the onset of symptoms. The measures also may help understand and predict differences in symptoms expressed by different people. Deficits in performance measures of executive dysfunction can be related to whole-brain connectivity disturbances from nodes known to mediate executive control (right inferior parietal, right thalamus, and left anterior cingulate). Evidence for compensatory brain activity with degenerative brain structural changes came with observation of correlated increases in functional coupling between the right dorsolateral prefrontal cortex and over a left hemisphere network in the resting state (Klöppel et al., 2015). Multivariate combinations of functional and structural connectomic measures may provide a useful endophenotype for biological staging of HD and other pre-symptomatic neurodegenerative diseases.

People with autosomal dominant Alzheimer's disease (ADAD) show reductions in resting-state "default mode" connectivity some years before expected symptom onset. Similar relationships between changes in network connectivity and cognitive dementia ratings have been found for late-onset Alzheimer's disease (LOAD) (Thomas et al., 2014). With the increasing availability of data from large populations (e.g., the Alzheimer's Disease Neuroimaging Initiative [Weiner et al., 2015], the Consortium for Reliability and Reproducibility [Zuo et al., 2014], the HCP [Barch et al., 2013], IMAGEN [Schumann et al., 2010], UK Biobank [Sudlow et al., 2015]) who display a range of traits or symptoms and include people before manifestation of disease, rapid growth in this area can be expected. A recent prediction model based on longitudinal changes in functional network architectures highlights the predictive power that already can be achieved using imaging measures alone (Chen and Herskovits, 2015).

Reductions in network connectivity with healthy aging help to explain why aging is such a powerful risk factor for Alzheimer's disease. Decreases in functional connectivity are found between the hippocampus and posteromedial cortex, including the precuneus, with clinically healthy aging (Wang et al., 2010). This reduction is accelerated with development of Alzheimer's disease (Dennis and Thompson, 2014). Inter-network coupling also is reduced with aging and correlated with behavioral impairments of memory (Spreng and Schacter, 2012) in ways qualitatively similar to but quantitatively less profound than in Alzheimer's disease (Brier et al., 2012). Resting-state functional connectomic changes have been suggested as a risk marker, as well as for monitoring the progression of ADAD (Chhatwal et al., 2013). Together, these examples illustrate the more general point that functional connectivity measures can provide

continuous descriptors of pathophysiology that link susceptibility to preclinical pathology and early expression of disease.

Toward Development of a Biologically Based Nosology for Brain Disease

The impact of connectomics and other biologically based measures on the way in which psychiatric disease is conceptualized and managed could be substantial. It has been recognized for some time that pathologically distinct disorders may not be distinguished well by the clusters of symptoms used currently to define neuropsychiatric diseases. Current diagnostic frameworks risk obscuring biological relationships between disorders, and this nosological obfuscation is slowing therapeutic advances (Krystal and State, 2014). The rapid growth in evidence for specific biological determinants of different clinical outcomes has supported efforts to move toward development of a more biologically based nosology of disease (Rubinov and Bullmore, 2013). The need for new nosological concepts also is suggested by recognition of common behavioral features for diseases that are currently classified as distinct but that share common associations with altered functional connectivity. Groups of diseases sharing common symptoms all may be associations with pathologies of the same brain functional systems. For example, diseases associated with deficits of executive function are associated with lesions of the lateral prefrontal-cingulate-parietal network, some presenting with pathological arousal and vigilance have been associated with altered patterns of connectivity in corticolimbic circuits, and those with impaired motivational or hedonic responses commonly show abnormal fronto-striatal connectivities. As discussed above, there already are proofs of principal for how biologically based reclassifications might contribute to better disease understanding. For example, the identification of the common networks involving limbic networks in depression and anxiety disorders or dopaminergic networks for reward responses in addictions and impulse control disorders have provided a foundation for understanding their co-morbidities, as well as paths toward the development of new treatments (Krystal and State, 2014). Reconsidering neuropsychiatric diseases in terms of psychopathological domains that can be described in terms of associated functional connectomic networks promises an attractive heuristic. This also is contributing to a new consensus regarding their biological foundations that should enable more accurate diagnosis, assessment of risk, and prediction of responses to treatment. The U.S. National Institute of Mental Health has provided strong impetus for this through its Research Domain Criteria Initiative (RDoC), which sets out a vision for the study of mental disorders that involves integration of levels of information drawn all of the way from molecular to patient-reported data (NIMH, 2016).

Such a reformulation could fundamentally change the way mental disorders are viewed by shifting from a categorical conception to one in which measures (e.g., functional connectivities) of their defining mental traits are expressed in terms of continuous, multidimensional variables. This would likely emphasize that component biological determinants of mental disorders merely reflect extremes in the population distributions of brain functional states. This should have profound implications regarding indications for treatment. Just as is being considered for later-onset neurodegenerative diseases, it could lead to personalizing early interventions for people at higher risk of some diseases in order to delay or prevent their onset, for example.

A paradigmatic example of the first steps toward this approach is provided by schizophrenia. A range of analyses defines how functional networks mediating higher cognitive processes are disrupted in people at risk of schizophrenia (Dauvermann et al., 2014). For example, young people at very high risk of developing schizophrenia have increased connectivity in the salience network linking anterior fronto-insular and anterior cingulate cortex relative to healthy volunteers at low risk. The magnitude of these differences is correlated with behavioral abnormalities prodromal to schizophrenia (Pelletier-Baldelli et al., 2015). Insight into how these effects could be mediated comes from a network model suggesting that the salience network may play a central role in switching between global brain connectivity states (Palaniyappan et al., 2012).

There is increasing potential to extend computational modeling as an explanatory bridge between altered cognitive function and its associated neurobiological mechanisms (Dauvermann et al., 2014). This enables framing of quantitative causal hypotheses in terms of the molecular mechanisms. One class of methods involves dynamic causal modeling, which includes biophysical data priors that describe component neuronal dynamic processes. These can be applied in deterministic or Bayesian frameworks that can test the model and set precise hypotheses based on simulations with relevant network perturbations. Network modeling also allows mechanistic understanding to be linked across molecular, synaptic, and systems levels and to be refined as new data is acquired for each; scale-free network models integrated across levels of organization can relate molecular and cellular changes to functional connectivities, symptoms, and social context. Looijestijn and colleagues have summarized their work on this topic recently and proposed an illustrative synthesis that relates neural circuit attractor networks to positive symptom generation in schizophrenia. With their model, they explain actions of current anti-psychotics and suggest new treatments through stabilization of desirable attractor network states in neural circuits (Looijestijn et al., 2015). The utility of the model lies in the potential to motivate experiments that test key features and, ideally, provide a quantitative framework for their interpretation. The concept is being generalized (e.g., The Virtual Brain [Sanz-Leon et al., 2015], the Blue Brain Project [Markram et al., 2015]) in other laboratories with incorporation of an increasingly wide range of molecular data in brain functional connectomic models. With causal models linking network activity to factors such as the balance of excitatory and inhibitory neuronal circuit activity and neurotransmitter-mediated changes in neuronal membrane ionic conductivities), fMRI functional connectomic changes can be characterized more confidently in terms of the underlying physiological phenomena. Creating multi-level networks that additionally relate functional connectomics to models of symptoms (and signs) creates an informative endophenotype "bridge" between molecular determinants and disease expression. This provides a conceptual path to understanding the clinical meaningfulness of potential pharmacological perturbations or biomarker measures related to disease risk.

Contextual and Conceptual Limitations for Clinical Applications of Functional Connectomics

Applications of functional connectomics to clinical problems also have made clear the limitations and the context dependence of inferences from functional connectomics. These problems are well illustrated by results from studies of pain and consciousness. These studies have stimulated important debates about their best clinical management, but also have highlighted fundamental challenges to the interpretation of their functional connectomic or other physiological correlates.

A Physiological Basis for Assessing Pain

The subjective experience of pain cannot directly be measured independent of reports from the person experiencing it. However, assessment of pain is widely important in clinical practice, including in situations when patients cannot reliably provide report themselves. Functional connectomic characterizations of network activity associated with acute or chronic pain have contributed to changes in clinical awareness of pain—especially chronic pain—in people who cannot report it well. While fMRI remains relatively expensive and may not itself be practical for routine monitoring of pain and responses to treatment in the clinic, brain activity in people with dementia (Cole et al., 2006) (or infants [Slater et al., 2010]) is no less responsive to noxious stimuli than that in healthy adults, despite often lower behavioral responses to the stimuli from patients (or infants) than is seen with healthy adults. Indeed, Alzheimer's disease patients show greater amplitude and duration of pain-related fMRI activity in sensory, affective, and cognitive processing networks than do volunteers without dementia, consistent with more sustained attention to the noxious stimulus (Cole et al., 2006). People with Alzheimer's disease typically have been administered fewer analgesics. This and related research has provoked greater concerns for analgesia (and alertness to secondary markers of discomfort) even among such patients who are unable to reliably report pain.

fMRI connectivity provides "signatures" of transient functional network states associated with the quality, intensity, and emotional salience of pain (Coghill, 2010; Wager et al., 2013). For example, quantitative measures of pain relating connectivity changes within the default mode network provide a way of objectifying this (even in people with chronic pain) as abnormally increased functional coupling of the medial prefrontal cortex to the insula (Baliki et al., 2014). This work has contributed influentially to understanding the pathophysiology of alerting mechanisms related to chronic pain. Consequently, fMRI connectomic measures have been proposed as biomarkers of treatment response (Borsook et al., 2013; Duff et al., 2015). However, the recent demonstration of similar brain patterns of activation in healthy subjects and in people with genetic mutations conferring insensitivity to pain suggests that the associated functional connectional networks do not themselves represent pain specifically, but instead reflect consequences of highly salient somatosensory inputs such as pain (Salomons et al., 2016). Interpretations therefore must be context specific.

Insights into Conscious Awareness

A second application further illustrating limitations of functional connectomic associations with subjective or internal states is provided by consciousness. Disorders of consciousness traditionally have been difficult to classify except in terms of associated diseases or observed behaviors. Functional connectomics provides a new approach to their characterization based on their physiological correlates.

At the basis of much recent work has been evidence that many types of complex perceptions show consistent enough patterns of brain activation between people to enable internal mental states to be reliably inferred from patterns of brain activity, allowing "decoding" of thoughts, at least to a limited extent (Haxby et al., 2014). The application of this logic in the context of disorders of consciousness has expanded clinical appreciation for environmental awareness in some apparently unresponsive patients. Laureys, Owen, and colleagues identified brain regions activated in healthy volunteers after verbal instructions to perform specific types of tasks during mental imagery (e.g., spatial navigation or playing tennis). Patients previously diagnosed as being in persistent vegetative or minimally conscious states were assessed in the same way. A first case report showed that meaningful patterns of regional activation could be observed in association with appropriate verbal instructions to engage in mental imagery in one such patient (Owen et al., 2006). The authors interpreted this as evidence for conscious awareness and suggested that the patient (and potentially others) had been misdiagnosed as vegetative; they argued that this patient should more accurately be considered as being "locked in" and consciously aware.

In a subsequent report, potential experimental biases with this simple study design were addressed. A larger cohort of patients was asked to respond to simple questions (the correct answers to which the experimenter was blinded) using alternative forms of mental imagery to respond either yes or no. The authors generalized their conclusion by demonstrating that ~10% of the patients could respond accurately. This was interpreted as evidence for (at least transient) awareness (Monti et al., 2010).

These results highlight potential limitations of usual diagnostic practices. However, the application of fMRI to such ethically significant clinical decisions also provokes reflection on the methodological limitations of the approach. False negatives seem likely; not even all healthy controls show "typical" patterns of regional activation during mental imagery. In part this may be explained by the intrinsically low signal-to-noise ratio, but as discussed above, it also likely reflects population heterogeneity in mental imagery strategies or traits. Even if technical false negatives were better controlled, the information from this single testing approach could be misleading with patients who may have some degree of awareness, but are unable to engage receptive language or other specific networks needed to perform the task.

Interpretation of fMRI also can lead to false positives if distinctions between evidence for conscious awareness and the more limited evidence for activity in individual component processes (as networks) that correlate individually with conscious awareness are not made appropriately. As patients with blindsight have shown, brain activations (and behaviors) can occur in response to stimuli, with or without conscious awareness (Persaud et al., 2011). Imagery responses to simple commands and questions may result from learnt perception-action couplings rather than consciousness per se (Greenberg, 2007;

Nachev and Husain, 2007). Contents of working memory also can affect behavior without awareness (Soto and Silvanto, 2014).

More fundamentally, although a well-preserved minimal global brain energetic state seems to be a necessary condition for consciousness, isolated network activations probed using fMRI do not reflect the global activity and energy state of the brain (Shulman et al., 2009; Dehaene et al., 1998). High global energy utilization enables the high global information transfer that sustains a regulated metastability. In this context, consciousness is distinguished from its contents by the potential for the coordinated dynamic activity that enables shifts in brain and mental states.

Nonetheless, the functional connectomic studies have had an important impact on the field. They are leading to new developments for patient assessment. For example, Rosanova et al. extended the results and developed a more practical tool for routine clinical applications using a lower-cost bedside electroencephalography in conjunction with TMS (Rosanova et al., 2012). With more complete clinical follow-up, they provided evidence for the potential clinical value of functional testing by showing that patients who retained distributed network responses associated with preserved effective connectivity were more likely to show subsequent recovery. In a conceptual extension of this, another group has shown that an index of consciousness can be derived from measures of complexity in electrocortical responses to TMS perturbation that is able to distinguish states of consciousness in healthy subjects and in patients with minimal levels of consciousness after partial recovery from coma (Casali et al., 2013).

Such complex, multivariate functional connectomic biomarkers (and, potentially, their fMRI equivalents) that reflect more global network dynamics may limit both false negative and false positive results. Much needs to be learned, but together these reports illustrate some of the conceptual and practical challenges for translation of concepts derived from research fMRI for medical applications. Clinical utility then depends on their robustness, the feasibility of consistent implementation at different centers, and the availability of long-term follow-up data concerning the relationships between measures and clinical outcomes. A challenge for the future must be to move beyond passive stimulation paradigms to capture more direct evidence for both meaningful and context-relevant internal transformations of perception reflecting conscious awareness. Adjudication of the criteria for the paradigm and responses needs to be made in ways analogous to those suggested by Turing for recognition of intelligent behavior in a machine (Turing, 1950).

Conclusions

This review has highlighted some of the ways in which the last two decades of applications of fMRI functional connectomics have contributed to modern concepts of brain disease and its treatment. While the range of routine clinical applications has not progressed since one of us last reviewed the area in 2006, substantial clinical impact has been realized from fMRI functional connectomics through applications in research contexts. We are optimistic that some of this work will lead to new diagnostic methods and the development of new treatments. Areas that seem particularly promising include applications that support decision-making in the development of new drug candidates or that guide the targeting of bioelectronic interventions for novel indications. Over the longer term, we anticipate that functional connectomics also could contribute to early disease risk assessment and to stratification of neuropsychiatric patients for their improved management.

Meeting the Challenges Posed by Functional Connectomics in Medicine

Nonetheless, in addition to the need to address the conceptual limitations of the approach as described above, there are technical challenges for the field if sustainable progress is to be made. Many of these have been summarized in a neuroimaging consensus statement regarding best practices that was published recently (Nichols et al., 2015). Foremost is the need for reliably high-quality data. Signal to noise is low in fMRI. Physiological noise, motion, and instrumental confounds all contribute artifacts that must be accounted for appropriately or removed (Váša et al., 2015; Beckmann and Smith, 2004; Nikolaou et al., 2015). This can be particularly challenging when such factors differ between datasets being compared, e.g., motion artifacts had proportionally greater influence on the youngest subjects in a study of functional connectomic changes with aging (Power et al., 2014). Greater spatial resolution should enhance the potential to discriminate closely spaced network mappings, but with the tradeoff of longer gradient readout time (and potentially greater image distortions) unless more advanced echo planar imaging (or other) sequences are used.

A more fundamental limitation of the fMRI functional connectomics is that it provides only an indirect measure of neuronal electrophysiological activity. The signal reflects neurovascular responses and tissue metabolism (Hillman, 2014), which may vary with the contrast independently of the neuronal activity. These effects may dominate in some situations, e.g., Filippini and his colleagues described apparently increased default mode network activity in people carrying the APOE4 allele relative to non-carriers (Filippini et al., 2009), but later reported that much or all of this reflected vascular contributions (Suri et al., 2015). Neurovascular coupling may vary quantitatively across brain regions (Devonshire et al., 2012; Lauritzen et al., 2012), although this has been difficult to characterize precisely. While the BOLD response may largely reflect the extracellular field potential (Logothetis, 2002), the relationships are complex and influenced strongly by differences in the balance of excitatory and inhibitory inputs (Lauritzen et al., 2012). BOLD-based fMRI measures of functional connectivity alone thus provide a relatively qualitative index. In addition, response times are slow relative to electrophysiological changes, although a much wider temporal spectrum of signal correlations are accessible than is commonly recognized (Niazy et al., 2011).

A number of investigator practices have compounded these problems. The magnitude of effects is often not well reported and is typically low. Many studies also have not been sufficiently large for confidence in their conclusions (Button et al., 2013). Complicating this has been the perhaps too frequent reporting of results arrived at only after considerable uncontrolled exploration of the same dataset, so that the reported measures of confidence are unreliable. Highly multivariate analyses also may be difficult to interpret biologically with the information

available, so that, even if well conducted, statistically significant results may not have obvious meaningfulness in a neurobiological or clinical context.

Fortunately, the field is maturing and each of these problems can be addressed in some way. Improvements in MRI acquisition methods and instrument stability have dramatically enhanced the quality of fMRI data since first reports. We anticipate additional technical advances in imaging. Integration of other physiological MRI approaches with fMRI can report on specific elements of the neurovascular response, such as blood flow assessed using arterial spin labeling (Bulte et al., 2012), to enhance measurement precision and interpretability. There has been a strong focus on developing robust methods for integration of EEG with fMRI (see, e.g., Larsen and O'Doherty, 2014) to provide greater sensitivity to rapid, transient phenomena (Lee et al., 2013). Supported particularly by new, integrated MRI-PET scanners, there is greater potential to directly relate fMRI functional connectomics to PET markers of local energy metabolism or neurotransmitter signaling. Such "chemo-connectomics" would allow, e.g., anatomical distributions of drug targets and their engagement by a candidate drug to be related directly to changes in brain functional connectomics (Aiello et al., 2016; Carbonell et al., 2014) in individual subjects. Given the need to resolve detail in nested network structures (as in the prefrontal cortex), such work would be enhanced by the improvements in fMRI resolution and sensitivity promised by ultra-high-field MRI (Moerel et al., 2014).

Scientific culture and practice also are maturing in encouraging ways. The community has recognized the need for more robust, replicable results. Considerations for study design and analyses have been summarized recently by an expert group (Poldrack et al., 2016). There is a positive and increasing trend toward data sharing. The importance of making this the standard of practice cannot be overstated. Reports based on data from large-scale initiatives already are beginning to effect this change by "raising the bar" for all studies (Matthews and Sudlow, 2015). Open access quality control software could further contribute by providing benchmark metrics for datasets. Standardized, automated tools are needed to allow researchers to meet minimum data standards and recognize factors that might compromise the reliability of their connectomic data early.

Major improvements in data analytics will continue to drive much of the field forward, although deriving novel and clinically meaningful information from increasingly large datasets will demand analytical strategies that preserve both sensitivity and interpretability. Direct correlational strategies will be of increasingly limited value as numbers of variables rise or for simultaneous evaluations of multiple networks. Machine learning can be highly optimized, but specific interpretations or validations of factors driving classifications are complicated by their intrinsically "black box" nature. Attractive complementary methods employ generative forward models based on prior information (Moran et al., 2011). The former logically inform hypotheses that guide progression for development of the latter. In any case, depending on the specific application, different tradeoffs will need to be made between the extent of feature space search, biological interpretability, sensitivity, and computational efficiency. Applications intended to characterize promising biomarkers should be extended toward their qualification, particularly with efforts to validate the relationship between a measure and a clinically relevant concept of interest (Castellanos et al., 2013). An important element for all of these efforts remains to be able to relate population-level descriptions to observations in individual subjects. For this, further development of individually precise, generalizable functional anatomical descriptors will be needed.

There are challenges, but it is hard to overstate our optimism for this growing field of inquiry. Current science promises much—and new directions undoubtedly will deliver much more—even over the near to medium term. We believe that advances in fMRI spatial and temporal resolution and more powerful approaches to information mining from multivariate datasets (particularly with incorporation of molecular imaging data for chemo-connectomics) hold great promise. All of these developments should fuel discovery and foster novel approaches to disease risk prediction, personalization of patient management, and the design of new interventions to improve clinical outcomes.

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