Clinical Applications of Complex Network Analysis

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Complex Network Models

The contemporary formalism of complex network theory stems from the historical mathematical discipline of graph theory. Complex network theory provides representation rules that can be used to describe any complex system specifically in terms of its subcomponents and their relationships to one another. As such, complex network theory can be widely applied and provides an extremely powerful tool for comparing disparate systems within the same representational scheme. A complex network model is simply one representation of any given system constructed in terms of the complex network formalism. Important parameter choices for these models therefore include the definition of nodes and edges, whereas model results can be analyzed using graph theoretical metrics such as clustering or modularity. Although these choices and metrics have been discussed in detail elsewhere (Bullmore and Sporns, 2009; Rubinov and Sporns, 2009), here we will review complex network applications to clinical neuroscience and suggest relevant open research questions.

Network Organization in Health and Disease

Complex network theory provides a compelling framework in which to study the human brain, whose intricacies span a broad range of spatial and temporal scales. In particular, network formalism is particularly suited to a system such as the brain, which can be broken down into functional or anatomical subsystems, and in which hard-wired or functional relationships between these subsystems are foundational to the system's behavior as a whole. Indeed, the brain's discrete organization into modules has been studied extensively, both anatomically (Brodmann, 1909) and functionally (Hubel and Wiesel, 2005). Complex network theory is particularly appealing when applied to the study of clinical neuroscience, where disease states and other clinical states have been characterized by a range of hypoconnectivity, hyperconnectivity, and dysconnectivity profiles. For example, in schizophrenia, a profound disconnection between frontal and temporal cortices has been suggested to characterize the brain (Friston and Frith, 1995); in contrast, people with autism may display a complex pattern of hyperconnectivity within frontal cortices but hypoconnectivity between the frontal cortex and the rest of the brain (Courchesne and Pierce, 2005).

Biological plausibility

In order for any proposed modeling endeavor to be useful, it must produce results that are inherently plausible, i.e., realistic within the bounds of current knowledge. Simple tests have therefore sought to determine whether constructed network organization displays characteristics consistent with known brain architecture. Initial studies have been performed across a wide range of imaging modalities: functional magnetic resonance imaging (fMRI) (Achard et al., 2006); EEG (Micheloyannis et al., 2006a); magnetoencephalography (MEG) (Bassett et al., 2006); MRI (He et al., 2007); and diffusion spectrum imaging (DSI) (Hagmann et al., 2008). Their results have shown that human brain networks are characterized by the nonrandom property of local connection clustering, while the entire system maintains global integration (Sporns et al., 2004). Complementary studies have also highlighted the wiring efficiency of anatomical brain networks, consistent with the existing constraints on energy consumption during both brain development and daily metabolic function (He et al., 2007; Bassett et al., 2008, 2010). Wiring efficiency is further reflected in the organization of both low-frequency and high-frequency functional networks (Achard et al., 2007; Bassett et al., 2009).

Biological relevance

Even though healthy brain networks display a significant nonrandom and apparent energy-efficient structure, it is still necessary to prove that the modeling endeavor is biologically relevant. In particular, a model of the brain should be sensitive to factors that might alter underlying connectivity structure or cognitive function. For example, we might expect disease states to display significantly different network architectures or for behavioral or cognitive variables to correlate with measured network metrics. In a stream of successes, complex brain networks have been shown to be sensitive to numerous factors:

- Behavioral variability (Bassett et al., 2009);
- Cognitive ability (van den Heuvel et al., 2009; Li et al., 2009);
- Shared genetic factors (Smit et al., 2008);
- Genetic information (Schmitt et al., 2008);
- Experimental task (Bassett et al., 2006; De Vico Fallani et al., 2008b);
- Age (Meunier et al., 2009; Micheloyannis et al., 2009);
- Gender (Gong et al., 2009);
- Drug exposure (the dopamine receptor antagonist sulpiride) (Achard et al., 2007); and
- Disease.

Clinical findings

Given their biological plausibility and relevance, complex network models of the human brain could

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theoretically provide a sensitive framework in which to compare healthy and clinically abnormal brain states. Indeed, complex network analyses have recently been used to probe several disease states, including schizophrenia and Alzheimer's disease (AD), as well as other clinical states, such as stroke and spinal cord injury. In each case, complex network models of brain structure and function have corroborated previous findings from alternative analysis paradigms and provided novel insights into both global and local cortical (dys)organization.

Complex Network Models of Schizophrenia

Schizophrenia is a neuropsychiatric disease characterized by a complex pattern of structural and functional abnormalities that are evident across a gamut of neuroimaging modalities. In a large-scale study (N = 203 people with schizophrenia, N = 259 controls) of a complex network model of brain structure in schizophrenia, we found broad structural connectivity to be altered in the three classical subnetworks of unimodal cortex (primary areas), multimodal cortex (heteromodal association areas), and transmodal cortex (extended limbic system). Specifically, whereas the connection length in the schizophrenia population was increased over all subnetworks, suggesting an inherent inefficiency of wiring, the multimodal subnetwork, composed of prefrontal and temporal cortices, among others, was characterized by a particularly inverted hierarchical structure (Bassett et al., 2008).

It is intuitively plausible that such structural disconnection signatures could constrain cortical function. Indeed, studies of both fMRI and EEG/MEG data suggest that functional network architecture in schizophrenia is altered in kind. Both Lynall et al. (2010) and Liu et al. (2008) found that the strength of functional connectivity measured during resting-state fMRI experiments was significantly decreased in people with schizophrenia. Collectively, they further reported that network measures derived from these data correlated significantly with both verbal fluency and duration of illness. These findings open up the possibility of using network architectural signatures as biomarkers for the disease and its severity.

In contrast to these studies, EEG and MEG experiments in both resting and n-back tasks have demonstrated increased functional connectivity in schizophrenia in comparison with controls (Bassett et al., 2009; Rubinov et al., 2009). At rest, proband networks display an increase in intercluster connections and an associated lack of central hubs, consistent with a subtle randomization of network architecture predicted by medication dose (Rubinov et al., 2009). And, although medication dose was not predictive of network alterations during a working memory task condition (Micheloyannis et al., 2006b), randomization of that network architecture was maintained (Micheloyannis et al., 2006b; Bassett et al., 2009). Such randomization could theoretically lead to an increase in point-to-point efficiency, albeit at an increased connection cost. Network cost-efficiency of high frequency (β-band, 12-20 Hz) function captured the trade-off between network efficiency and communication cost: It not only significantly decreased in the patient group, but was significantly predictive of individual performance accuracy on the working memory task in both patients and controls (Bassett et al., 2009) (Fig. 1).

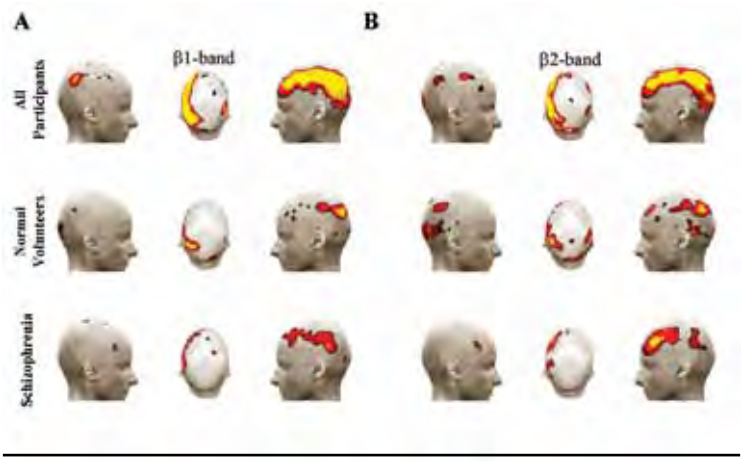

Figure 1. Associations between cognitive performance and cost-efficiency of upper and lower β band networks. Head surface maps show regions where nodal cost-efficiency in the β1-band (***A***) and β2-band (***B***) networks predicted accuracy of task performance across all subjects (top), in healthy controls alone (middle), and in schizophrenics alone (bottom). Red indicates that an association between task accuracy and nodal cost-efficiency was significant ($p < 0.05$ uncorrected); orange indicates that the association passed false-positive correction (all $p < 0.0036$); and bright yellow indicates that the association passed false discovery rate (FDR) correction (minimum $p < 0.00018$). Data are as reported in Bassett et al., 2009.

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Complex Network Models of Alzheimer's Disease

In addition to estimating alterations in underlying structure, network studies in AD have focused predominantly on resting state rather than task-related functional connectivity (He et al., 2009a). Using covariation in cortical thickness as an indirect measurement of anatomical connectivity, He et al. (2008) reported an increase in local connectivity and a corresponding decrease in global connectivity in a sample of 92 elderly AD subjects they compared with 97 elderly controls. Regional differences between the control and patient groups were located in temporal and parietal areas (decreased centrality) and occipital regions (increased centrality).

The regional specificity of AD-related changes in network structure was further underscored by the work of Buckner et al. (2009). They showed that amyloid-β deposition, as measured using positron emission tomography (PET) radiotracer Pittsburgh Compound-B (PiB) imaging, was concentrated in functional hub areas defined in healthy human resting state fMRI (Fig. 2). This finding suggests that cortical hubs may be particularly vulnerable in AD because of their relatively high activity, associated metabolism, and consistent recruitment across task states.

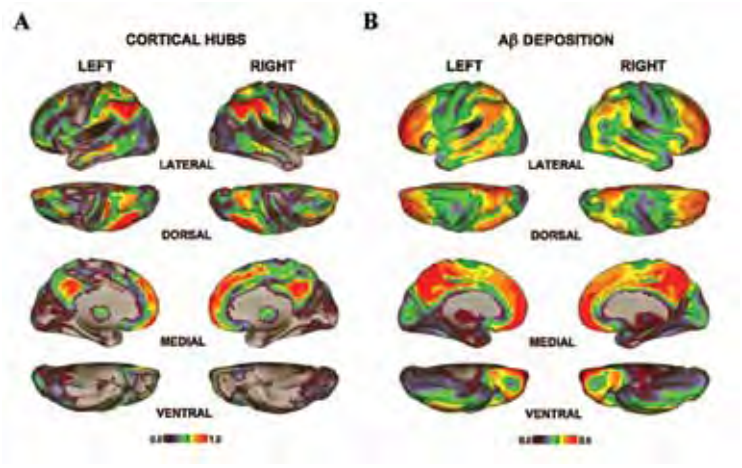

Figure 2. Network hubs have increased amyloid-β (Aβ) deposition in AD. *A,* Location of cortical hubs, that is, nodes with a high number of connections or degree centrality in healthy resting-state fMRI networks. *B*, Location of greatest Aβ deposition in people with AD, as measured in a PET study. Data are reproduced with permission from Buckner et al., 2009.

The direct characterization of functional brain networks in AD has been undertaken using fMRI, EEG, and MEG imaging modalities. In a resting-state fMRI experiment, Supekar et al. (2008) found that the clustering coefficient was significantly decreased in AD—specifically in bilateral hippocampus—and could be used to distinguish AD participants from controls with a specificity of 78% and a sensitivity of 72%. This finding implies that clustering coefficient might be useful as an imaging biomarker for the disease. In a resting-state MEG study, Stam and colleagues also reported a decreased clustering of functional connectivity in AD (Stam et al., 2009), consistent with Supekar's low-frequency fMRI measurements. Mini Mental State Examination (MMSE) scores, which provide a measurement of disease severity, positively correlated with clustering across individuals. However, this pattern of results was not retained in a resting-state EEG study in which no difference in clustering was found, and the MMSE scores were instead found to negatively correlate with path length (Stam et al., 2007).

Complex Network Models of Other Diseases and Clinical States

In addition to schizophrenia and AD, complex network analyses have been carried out in several other disease and clinical states. These include epilepsy (van Dellen et al., 2009; Horstmann et al., 2010; Raj et al., 2010), multiple sclerosis (He et al., 2009b), acute depression (Leistedt et al., 2009), absence seizures (Ponten et al., 2009), medial temporal lobe seizures (Ponten et al., 2007), attention deficit hyperactivity disorder (Wang et al., 2009), stroke (De Vico Fallani et al., 2009; Wang et al., 2010), spinal cord injury (De Vico Fallani et al., 2008a), frontotemporal lobar degeneration (de Haan et al., 2009), and early blindness (Shu et al., 2009).

In light of these results, several opportunities exist to pursue complementary modeling efforts. Numerical simulations, in particular, could be undertaken to positive advantage where the relationship between putative generative mechanisms of disease or clinical state and resultant network topology is either categorically unknown or incompletely understood. Honey

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and Sporns (2008) and Netoff et al. (2004) provide recent examples of studies conducted in lesions and epilepsy, respectively. Future studies of this kind are likely to be highly instructive because they will enable researchers to directly compare the theoretical network consequences of abnormal growth or neurodegenerative mechanisms with empirically determined network architectures in clinical states.

Open Frontiers

Reproducibility and specificity

Although applications of complex network theory to the study of human brain structure and function have proven useful in a broad range of clinical states, several lines of inquiry remain open for further exploration. While the majority of disease states studied display altered topological properties of brain networks, it is as yet unclear to what degree the patterns of alterations are both reproducible and disease-specific. In this context, it is interesting to note that several functional analyses of schizophrenia have reported a decreased path length or increased global efficiency, suggesting a randomization of network architecture (Bassett et al., 2009; Rubinov et al., 2009;), whereas AD networks display a relatively increased path length (Stam et al., 2007, 2009), suggesting a regularization of network architecture. Thus, additional studies are needed to highlight specific network measures, or groups of networks measures, that can successfully distinguish between disease states. In addition to their lack of disease specificity, very few studies have addressed the issue of reproducibility in the context of disease, although a few have reported relatively good reproducibility over either scanning sessions or imaging acquisition parameters in healthy controls (Deuker et al., 2009; Vaessen et al., 2010).

Structure-function

Another set of comparisons to be made are those spanning diverse imaging modalities. Such studies raise important theoretical questions, such as, "To what extent should we expect agreement between clinically specific network alterations in structure–versus-function? Or across disparate functional modalities such as fMRI and EEG? Or between arguably more similar imaging modalities such as EEG and MEG?" Preliminary evidence from work in AD suggests that the picture may be complicated: While morphometric structural network analyses showed increased clustering in AD (He et al., 2008), functional resting-state analyses in both fMRI and MEG showed decreased clustering (Supekar et al., 2008; Stam et al., 2009). In healthy populations, by contrast, diffusion-based rather than morphometric-based structural networks display a significant topological overlap with resting-state fMRI connectivity profiles (Honey et al., 2009). Furthermore, combining anatomical and functional connectivity profiles has been shown to provide a more comprehensive description of disease-specific architectural changes in schizophrenia (Camchong et al., 2009; Skudlarski et al., 2010).

Function-function

Structure aside, simpler comparisons between functional imaging modalities are likely to be sensitive to modality-specific noise or artifact and differential signatures of neuro-oscillatory function. For example, resting-state functional connectivity, as measured by fMRI, is decreased in schizophrenia (Liu et al., 2008; Lynall et al., 2010), while connectivity measured by EEG/MEG is reportedly increased (Rubinov et al., 2009). In order to clarify the interaction between disease and measured function in such cases, it is becoming increasingly important to apply a more precise understanding of the inherent relationships between neurophysiological time series, classical measures of functional connectivity (e.g., principal components analysis), and the resultant network structures (Lynall et al., 2010).

Methods

In addition to providing insight into neurophysiological disease markers, the relationship between functional connectivity and network structure directly impacts the methodological challenge of comparing graphs between subject populations or comparing individual graph metrics with behavior, cognitive variables, or symptom scores. Parsing the effects of functional connectivity differences, network fragmentation profile differences, and inherent network architectural differences constitutes an important methodological challenge to the current analysis stream. In the flow of analysis, the use of weighted network measures and alternative thresholding strategies are likely to add value.

Conclusion

Complex network models of human brain structure and function have produced biologically relevant and plausible results. Subsequent applications of this framework to clinically relevant topics have been highly successful, particularly in the study of schizophrenia and AD. Important future directions for research to take include assessing disease specificity and network reproducibility; in addition, researchers will need to characterize similarities and

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differences in network structure as measured over multiple imaging modalities.

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