Network Dysfunction in Alzheimer's Disease and Frontotemporal Dementia: Implications for Psychiatry

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Structural and functional connectivity methods are changing how researchers conceptualize and explore neuropsychiatric disease. Here, we summarize emerging evidence of large-scale network dysfunction in Alzheimer's disease and behavioral variant frontotemporal dementia, focusing on the divergent impact these disorders have on the default mode network and the salience network. We update a working model for understanding the functions of these networks within a broader anatomical context and highlight the relevance of this model for understanding psychiatric illness. Finally, we look ahead to persistent challenges in the application of network-based imaging methods to patients with Alzheimer's disease, behavioral variant frontotemporal dementia, and other neuropsychiatric conditions. Recent advances and persistent needs are discussed, with an eye toward anticipating the hurdles that must be overcome for a network-based framework to clarify the biology of psychiatric illness and aid in the drug discovery process.

Key Words: Alzheimer's disease, biomarker, connectome, frontotemporal dementia, network, psychiatric disorders

Neurodegenerative diseases are united by gradual and anatomically selective spread of pathologic disease protein inclusions within neurons and glia, accompanied by synaptic and neuronal loss. The prototypical patterns of regional spread give rise to clinically distinctive, relentlessly progressive, fatal syndromes for which no disease-modifying therapies are available. Data accumulated over decades of neuropathologic research have suggested that each syndrome reflects a neural system disorder (1–3). More recently developed neuroimaging approaches, however, have produced a tide of direct support for the network-based neurodegeneration hypothesis in living humans (4–8). Complementary in vitro and animal model studies have begun to clarify mechanisms of network-based dysfunction and spread, which may be most parsimoniously explained by prion-like dissemination of misfolded disease protein conformers within and between neurons and across synapses (9–12).

In this article, we summarize the divergent clinical, anatomical, and network connectivity changes seen in Alzheimer's disease (AD) and behavioral variant frontotemporal dementia (bvFTD) (13), the two most common causes of neurodegenerative dementia among patients younger than 65 years of age (14,15). Our goal is to highlight how network connectivity may increase or decrease—each with clinical consequences—in the context of disease. We update a simple and testable network-based working model (16) for understanding the behavioral symptoms seen in bvFTD and AD. Because the most prevalent psychiatric conditions, such as schizophrenia, anxiety disorders, depression, and autism, lack diagnostic structural brain imaging abnormalities, we anticipate that data-driven network-based imaging approaches will reveal new patterns, subgroups, and principles that will have a major long-term impact on clarifying disease pathophysiology. Several goals must be achieved for network analysis to realize this potential and aid in the search for new treatments, and we review these issues in a closing section.

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Network-based Neuroimaging: Methodologic Background

Structural and functional connectivity analyses provide noninvasive methods for mapping large-scale networks in the living healthy human brain [see recent reviews (17–19)] and for detecting early network-level alterations in disease (20). With task-free functional magnetic resonance imaging (fMRI), researchers can now identify functional intrinsic connectivity networks derived from temporally synchronous, spatially distributed, spontaneous low-frequency (<.1 Hz) blood oxygen level–dependent signal fluctuations (21,22). Synchronization across neuronal assemblies can likewise be computed from task-free electroencephalography (EEG) or magnetoencephalography (MEG) data (23). Structural connectivity, derived using diffusion tensor imaging, delineates white matter pathways connecting brain regions at ever-increasing resolution (24). In addition to the subject-level network maps derived from fMRI, EEG/MEG, and diffusion tensor imaging, researchers can use gray matter density, cortical thickness, or glucose metabolism to examine brain regional covariance across subjects (4,25,26). Finally, by modeling networks as graphs (brain regions as nodes and node-to-node connections as edges), graph theoretical analyses offer a flexible and quantitative approach for characterizing how structural and functional brain network architectures influence disease and change with disease progression [see helpful reviews by Bullmore and Sporns (27), He and Evans (28), and Wig *et al.* (29)]. When referring to a comprehensive map of the brain's connections, the term connectome is often used (30), whether the connections are based on structural or functional connectivity methods. Despite these marvelous new methodologic tools, all human brain connectivity metrics can only be considered indirect proxies—each with its own strengths and limitations—for the neuron-to-neuron axonal connectivity that anchors true neural network communication and represents the likely target of neuropsychiatric illness.

AD and Frontotemporal Dementia Background

Typical amnestic AD begins with episodic memory loss linked to early medial temporal lobe neurofibrillary pathology (31). Frontotemporal dementia (FTD), in contrast, describes a group

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of clinical syndromes in which behavioral or language symptoms predominate (32,33). BvFTD, the most common FTD syndrome, presents with social conduct and emotion processing deficits associated with early anterior cingulate and frontoinsular cortex degeneration (34–36). The amnestic AD clinical syndrome strongly predicts underlying AD neuropathological change, with beta-amyloid-rich neuritic plaques and hyperphosphorylated tau-containing neurofibrillary tangles and neuropil threads. FTD syndromes, in contrast, result from a group of distinct underlying molecular pathologic entities referred to collectively as frontotemporal lobar degeneration (FTLD). FTLD is divided into three major molecular classes based on the protein composition of neuronal and glial inclusions, which may contain tau, transactive response DNA binding protein of 43 kDA (TDP-43), or, least commonly, fused in sarcoma protein (37). Although most patients with FTLD exhibit sporadic disease, several highly penetrant, autosomal dominant mutations have been identified, with mutations in the genes encoding microtubule-associated protein tau, progranulin, and C9ORF72 accounting for the majority of known genetic causes (38).

Phenotypic heterogeneity remains a major issue in neurodegenerative disease, just as in most psychiatric diseases. AD pathology, for example, may present with nonmemory first symptoms such as language, visuospatial, praxis, or even executive impairment. Patients with FTLD, likewise, can vary even within each clinical syndrome, molecular category, or genetic mutation. Considerable work is needed to develop network-based imaging methods equipped to handle the broad range of clinicoanatomical presentations associated with each illness. To constrain scope, however, this article focuses on findings derived from patients with clinically typical amnestic AD (referred to henceforth as simply "AD") and bvFTD.

The Curious Contrast Between AD and bvFTD

AD and bvFTD Feature Opposing Symptom-Deficit Profiles

AD begins with insidious forgetfulness for recent events before progressing to involve posterior cortical cognitive functions such as word retrieval, visuospatial function, arithmetic, and praxis. During the prodromal phase, often referred to as amnestic mild cognitive impairment (aMCI), many patients (or their loved ones) report a heightened emotional experience, sometimes manifesting as increased sensitivity to the needs or criticism of others. Intensified emotions may take the form of anxiety, irritability, and other affective symptoms, but social grace, decorum, and emotional connectedness with family members often persist into the latest stages. Many patients with aMCI or mild AD withdraw from social interactions due to shame and embarrassment or fears of exposing their cognitive deficits but rarely due to lack of social warmth or interest. Questionnaire- and laboratory-based studies suggest that patients with AD show retained or enhanced interpersonal warmth and empathy, mutual gaze, and emotional morality (39–42). Emotional contagion (sharing emotional states with others) appears to increase linearly across the healthy to aMCI to AD dementia spectrum (43).

In diametric contrast to AD, patients with bvFTD become progressively cold, detached, tactless, and difficult to embarrass or disgust, while lacking emotional empathy or engagement in mutual gaze (39–42,44). These symptoms and deficits often result in job loss, marital strife, estrangement from friends and neighbors, and financial injury. At the same time, drawing, navigation, and other parietal lobe functions are retained or intensified in bvFTD until late-stage disease (45,46).

AD and bvFTD Target Distinct Large-scale Networks

As the phenomenology of AD and bvFTD suggests, these disorders show contrasting patterns of regional neurodegeneration. AD is associated with atrophy and hypometabolism in posterior hippocampal, cingulate, temporal, and parietal regions, which collectively resemble the default mode network (DMN) as mapped in healthy subjects with task-free fMRI (47). Although the DMN was identified as an ensemble that deactivates in response to diverse cognitive tasks (48,49), it is recruited during episodic memory retrieval, mental state attribution, and visual imagery (50,51), and it was quickly recognized that DMN topology recapitulates the neuroanatomy of AD (5,47) (see also Figure S1 in Supplement 1).

BvFTD, in contrast to AD, begins in anterior insula, anterior cingulate cortex (ACC), medial/orbital prefrontal cortex, striatum, thalamus, and amygdala, regions critical for social and emotional processing (34,36). Building on the link between AD and the DMN, bvFTD-targeted regions were hypothesized to represent a large-scale network that could be delineated in healthy subjects by studying the intrinsic connectivity of the right ventral anterior insula (i.e., frontoinsula). This seed region-of-interest was shown to anchor an ensemble of brain regions, termed the "salience network" (SN), that included the bilateral ventral and dorsal anterior insulae, ACC, ventral striatum, thalamus, central nucleus of the amygdala, hypothalamus, and brainstem (22), regions that feature robust anatomical interconnections based on primate axonal tracer studies (52,53). The role of this network in salience processing was emphasized because its key hubs, the ACC and frontoinsula, activate in response to diverse emotionally significant internal and external stimuli or conditions (54,55). Early intrinsic connectivity analyses focusing on this system revealed that SN connectivity strength correlated with interindividual differences in social-emotional function, even when these characteristics were measured outside the scanner (22,56). For example, higher prescan anxiety was observed in healthy subjects with higher intrinsic ACC connectivity to the SN (22). Healthy individuals exhibiting more autistic spectrum traits, in contrast, showed lower connectivity between anterior insula and ACC (56).

On the basis of a wide array of anatomical connectivity, lesion-deficit correlation, and task-based functional imaging evidence and building on concepts put forth by previous work (52–55,57–62), we proposed (Figure 1) that the frontoinsula represents the major afferent SN hub, representing subjective "feeling states" by integrating inputs from the interoceptive stream with those arriving from other networks (54), whereas the ACC serves as an efferent SN hub for mobilizing visceroautonomic, emotional, cognitive, and behavioral responses to the salience detected in the frontoinsula.

The continued rapid growth of the task-free fMRI literature has allowed researchers to clarify the functions, key hubs, and anatomic boundaries of distinct but related intrinsic connectivity networks. This iterative process has helped to disambiguate the SN from a closely related network often referred to as the "cingulo-opercular" or "task control" network first identified by Dosenbach and colleagues (63), who analyzed the transitional fixation intervals between task sets in task-based fMRI studies. Whereas the SN is anchored by the frontoinsula, a ventral anterior insula hub for social-emotional processing (64), and contains links to the homeostatic regulatory systems (22), the task control network contains a key hub in the dorsal anterior insula (65), a region linked to cognitive rather than social-emotional processing (64). In our view (Figure 1), the SN connects directly with the task control network to communicate the need for task set maintenance