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

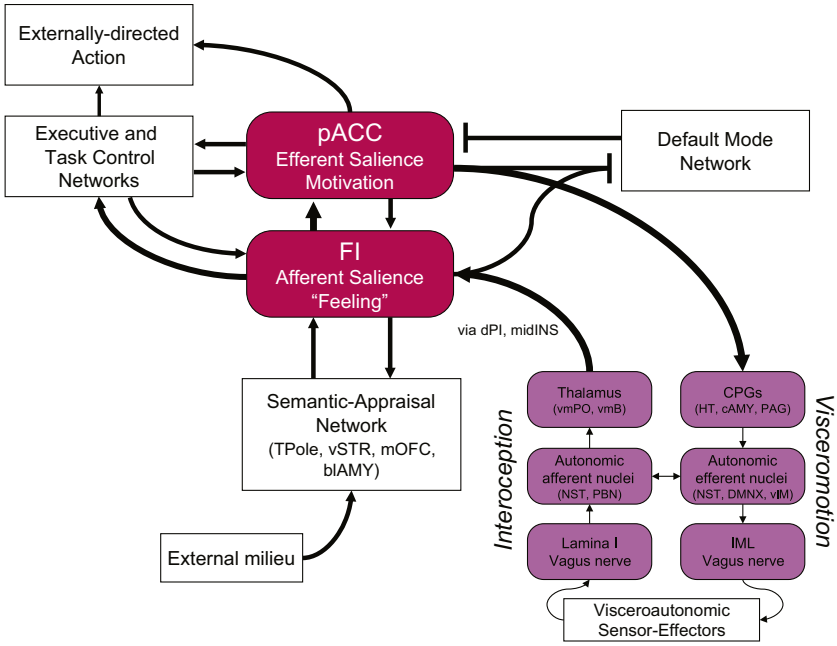

Figure 1. Working functional-anatomic model of the salience network in relation to other large-scale brain systems. Here we update a simple model (16) to suggest hypotheses for further research. This model is not intended to be comprehensive. Evidence to date suggests that bvFTD targets the salience network (colored boxes with rounded edges), beginning in central nodes for social-emotional-autonomic processing. These nodes include the frontoinsula (FI), an afferent interoceptive structure occupying the ventral portion of anterior insula, and the pregenual anterior cingulate cortex (pACC), an efferent visceromotor region. The afferent salience subnetwork processes the major ascending input streams regarding the moment-to-moment condition of the body (54). This network is closely allied with a semantic-appraisal system, which includes temporal pole (TPole), ventral striatum (vSTR), medial orbitofrontal cortex (mOFC), and basolateral amygdala (blAMY), regions that construct the meaning of social and asocial stimuli and weigh their hedonic value under prevailing conditions through two-way interactions with "feeling state" representations in FI (123). The efferent salience network, in contrast, mobilizes viscero-autonomic-emotional responses to salience; recruits executive (22) and task control (63) network resources to maintain cognitive set, weigh response options, and guide behavior; and inhibits the default mode network to keep attention focused on immediate matters at the expense of internal images from one's personal past or future. In Alzheimer's disease, default mode network degeneration is associated with liberation of the SN that correlates with "emotion-intensification" symptoms (83). In bvFTD, onset in FI predicts a socially disinhibited syndrome, especially when the right FI is first affected, whereas early pACC involvement produces a more apathetic phenotype. For visual simplicity, laterality issues have been omitted, although laterality exerts a major influence on lesion-related symptoms. Figure updated from Jabbi *et al.* (94) with permission from the publisher. cAMY, central nucleus of amygdala; CPG, central pattern generators; DMNX, dorsal motor nucleus of the vagus nerve; dPI, dorsal posterior insula; HT, hypothalamus; IML, intermediolateral cell column; INS, insula; NST, nucleus of the solitary tract; PAG, periaqueductal gray; PBN, parabrachial nucleus; vlM, ventrolateral medulla; vmB, ventromedial basal nucleus of thalamus; vmPO, ventromedial posterior nucleus of thalamus.

and control processes, functions that require the more cognitive dorsal anterior insula in cooperation with other task control network regions.

AD and bvFTD Exhibit Opposing Connectivity Changes in the DMN and SN

The myriad tasks and stimuli that activate the SN also deactivate the DMN, suggesting a reciprocal relationship between these two systems (48,49). Even in the task-free setting, DMN activity correlates inversely with activity in multiple brain regions, including several nodes of the SN (13,66,67). Although these "anticorrelations" remain controversial because they are exaggerated by global signal regression, a commonly used denoising strategy (68), the anticorrelations can be detected even in the absence of global signal regression when other denoising approaches are applied (69). Conceptually, if the functions subserved by the DMN and SN (or any other network pair) at times oppose one another, one might imagine that increased activity in one system would be associated with reduced activity in the other. Many forms of emotional salience require a focusing of attention toward homeostatic demands and behavioral responses ("here and now"), creating a need to deprioritize attention to internal ("there and then") ruminations about one's personal past or future, functions attributed to the DMN (13). Such opposing network functions might engender between-network competition for brain resources (70), shifts between "binary brain configurations" (71), or direct reciprocal suppression of one network in favor of the other, orchestrated by nodes within the two networks or by a nodal switch positioned elsewhere to reconfigure network dynamics in response to shifting conditions (72). Regardless of the mechanism, one might hypothesize that if DMN-SN anticorrelations are physiologically relevant, a lesion to either network should heighten activity and connectivity in the other network.

On the basis of the considerations detailed here and the opposing symptom-deficit-atrophy profiles seen in AD and bvFTD, we predicted divergent DMN-SN connectivity profiles in the two disorders (13) and used task-free fMRI to examine this hypothesis (73). As shown in Figure S2 in Supplement 1, AD was associated with disrupted DMN connectivity but enhanced SN connectivity. BvFTD, in contrast, showed reduced SN connectivity but enhanced posterior DMN connectivity. In addition, connectivity reductions were observed in anterior frontal and temporal DMN regions, which may contribute to

bvFTD-related deficits in self-projection, insight, and other meta-cognitive processes (74,75). Increased SN connectivity was correlated with decreased DMN connectivity in AD, whereas enhanced posterior DMN connectivity was linked to reduced SN connectivity in bvFTD. In bvFTD, patients with more severe clinical symptoms showed lower SN but elevated DMN connectivity, in keeping with an oppositional or "reciprocal" dynamic between the two systems. These task-free fMRI findings were obtained using independent component analysis, a data decomposition and denoising strategy that, despite other limitations, does not involve global signal regression. Therefore, the opposing network connectivity profiles observed in AD and bvFTD did not result from anticorrelations induced by global signal regression.

The divergent network profiles observed in AD and bvFTD (73) have been substantiated by a host of convergent findings obtained with complementary task-free fMRI and other imaging methods. In AD, reduced DMN connectivity has been widely replicated since the seminal observations of Greicius and coworkers (6). DMN disruption emerges during the presymptomatic phase (76) and has been linked to core memory and visuospatial deficits (6,77,78). A recent MEG study found prominent reductions in lateral parietal cortex functional connectivity in AD that correlated with cognitive impairment (79). Perhaps more surprising, AD-related SN enhancement has become one of the most widely replicated findings in the growing AD task-free fMRI literature (Figure 2). Evidence to date suggests that SN hub connectivity escalates in the presymptomatic and amnestic MCI stages of AD (80–82), correlates with emotion intensification symptoms (83), is accompanied by SN hyperperfusion (84), and may wane in later disease stages (82), although this issue has not been addressed longitudinally within subjects. Intriguingly, deep brain stimulation of the fornix in patients with AD produced no clinical benefit but led to parietal lobe metabolic improvement accompanied by suppressed ACC metabolism (85).

In bvFTD, SN connectivity disruption has now been observed in several studies (86–88) and correlated with apathy and disinhibition scores (87). Presymptomatic FTD gene carriers show worsening SN connectivity with advancing age accompanied by loss of white matter integrity within SN-related tracts despite preserved gray matter volume (89). Graph theoretical analysis has revealed a loss of central hublike nodes within anterior regions including the insula (90). As with AD-related SN enhancement, bvFTD-related DMN enhancement has been replicated [(86,87) but see Filippi *et al.* (88)], can be detected as DMN hyperperfusion (84), and may correlate with behavioral stereotypy (87). Graph theoretical analysis applied to task-free EEG data revealed that whereas AD deviated from an optimal "small-world" network structure toward a more random configuration, suggesting a loss of global information integration, FTD showed an opposite trend toward a more and perhaps excessively ordered structure, especially within the posterior alpha rhythm (91).

SN Enhancement in AD: Psychiatric Relevance of Aberrant Gains of Function

SN enhancement in AD is associated with strikingly preserved or even enhanced core social-emotional functions. Yet in some patients, intensified emotions bring unwelcomed agitation, restlessness, anxiety, irritability, and delusional suspiciousness, and these symptoms can become the major source of patient and caregiver distress. What forces determine the clinical impact of SN enhancement in AD? Anecdotally, caregivers for patients with below-average baseline social skills often report that the disease has made their loved one "sweeter" or "more sensitive," perhaps suggesting a shift toward optimized SN processing. Those whose "emotional cups" were always full, in contrast, may experience a spilling over into unpleasant intensification of the feeling states that drive behavior. Therefore, how SN enhancement affects any

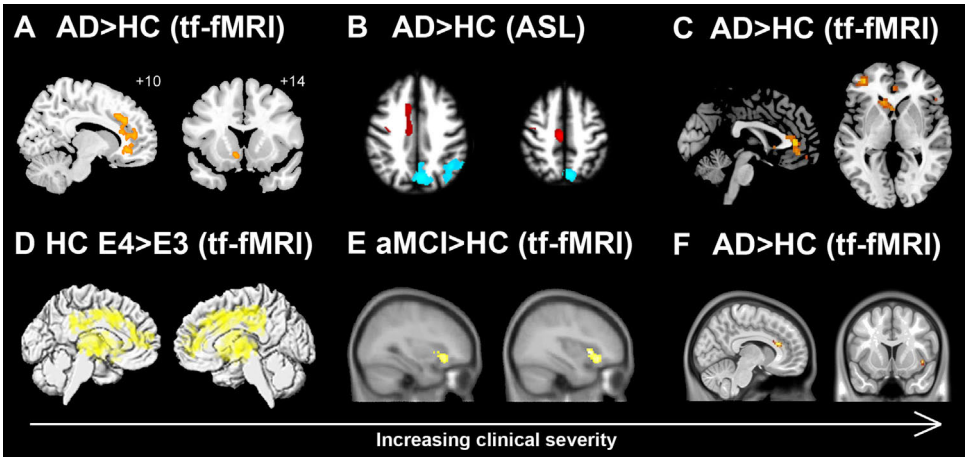

Figure 2. Converging evidence of Alzheimer's disease (AD)-related salience network (SN) enhancement. **(A)** AD showed increased SN intrinsic connectivity in anterior cingulate cortex (ACC) and ventral striatum compared with healthy control (HC) in task-free functional magnetic resonance imaging (tf-fMRI) data (73). **(B)** AD showed increased arterial spin labeled perfusion (red) in medial frontal lobe and ACC compared with controls (84), as well as reduced default mode network perfusion (cyan). **(C)** In the "ventral salience network," AD showed increased intrinsic connectivity in the pregenual ACC, left ventrolateral prefrontal cortex, and left caudate nucleus relative to HC (124). Panels D through F are ordered in terms of increasing clinical severity of AD-related cohorts. **(D)** Healthy apolipoprotein E (APOE) e4 carriers showed greater intrinsic connectivity in the salience network, including the ACC, bilateral insular cortex, striatum, and thalamus compared to noncarriers (80). **(E)** Subjects with amnestic mild cognitive impairment (aMCI) showed increased intrinsic connectivity between right frontoinsula and a so-called self-referential network (including the ventromedial prefrontal cortex, medial orbital prefrontal cortex, gyrus rectus, and pregenual anterior cingulate gyrus) compared to healthy controls (125). **(F)** In AD dementia, increased SN intrinsic connectivity (right ACC and right frontoinsula) correlated with more severe neuropsychiatric symptoms (83). Images adapted from the cited articles with permission from the authors and publishers.

given patient may depend where that patient falls on a normative SN connectivity curve before his or her illness. These unproven but testable ideas could help clarify the complex relationship between SN enhancement and its effect on individual patients.

How might SN amplification relate to other neuropsychiatric illnesses? Not surprisingly, new links are emerging rapidly in the biological psychiatry literature. Aberrant gains of SN nodal function make an appealing fit for anxiety disorders, in which gains in threat-related feeling state representations may lead to behaviors such as avoidance in simple phobias, reclusiveness in agoraphobia, compulsions in obsessive-compulsive disorder, or hypervigilance in posttraumatic stress disorder. In schizophrenia, overrepresentation of threat (SN hyperactivity) paired with faulty mental state attributions (perhaps reflecting anterior DMN impairment) could produce key features of paranoia (unwarranted fear and suspiciousness regarding other's intentions) and other "positive" symptoms (92). An important conceptual implication of this framework is that "positive" symptoms in psychiatry and neurology may reflect aberrant increases in nodal activity (or connectivity) that explain that symptom's core phenomenology. These nodal increases, in turn, may reflect specific nodal impairments within networks whose normal role is to regulate, suppress, or at least maintain a dynamic equilibrium with the symptom-related (hyperactive) network nodes.

Within the neurodevelopmental disorder spectrum, children with Williams syndrome (like patients with AD) show characteristically intense social warmth, interest, and empathy but struggle with visuospatial relations and may exhibit a variety of anxiety-related phenomena (93). On the basis of these clinical parallels, our model (Figure 1) predicts that children with Williams syndrome should show a pattern of network imbalance parallel to that seen in AD. Remarkably, a recent study focused on the insula (94) demonstrated that patients with Williams syndrome have increased gray matter volume and cerebral blood flow within the right ventral anterior insula (frontoinsula), the insular subregion most strongly linked to social-emotional-autonomic function in healthy subjects (64,95). Greater gains of right frontoinsular structure and function correlated with a more hypersocial phenotype (94). Whether these children exhibit accompanying DMN connectivity reductions remains unstudied, but a voxel-based morphometry study showed reduced gray matter volume in right angular gyrus and precuneus (major DMN hubs) alongside distributed increases in SN gray matter volume (96).

SN Disruption in bvFTD: Psychiatric Relevance of Aberrant Losses of Function

Patients with bvFTD develop a constellation of social-emotional symptoms that, once full blown, set it apart from other neuropsychiatric disorders. In its early stages, however, bvFTD is often misdiagnosed as a "midlife crisis" or psychiatric illness such as depression, bipolar disorder, or "late-life schizophrenia" (97). Many patients overeat, chain smoke, or compulsively seek out and consume alcohol. Accordingly, bvFTD and its associated atrophy and network connectivity changes provide a roadmap for exploring other disorders in which emotions become blunted, empathy is undermined, motivation is lost, and repetitive, compulsive, and stereotyped, ritualistic, or addictive behaviors emerge. Recent developments in FTD genetics have provided even more curious leads. Individuals carrying a hexanucleotide expansion in the *C9ORF72* gene often develop a smoldering psychiatric prodrome, with prominent paranoid or grandiose delusions and dysregulated affect for years or even decades before frank neurodegeneration unfolds (98,99). Structural imaging and pathologic studies suggest that SN atrophy emerges in most bvFTD patients with or without the *C9ORF72* expansion but that mutation carriers develop more severe medial thalamic and cerebellar atrophy (100,101), reinforcing a potential role for these structures in the functional anatomy of psychosis (102). On the other hand, some patients with bvFTD due to the *C9ORF72* mutation show little or no significant atrophy in any region despite florid social-emotional deficits (103). This observation suggests that 1) some patients present during a stage in which clinical deficits reflect neuronal dysfunction rather than synaptic and neuronal loss and that 2) such patients might evade diagnosis even when the treating psychiatrist or neurologist requests structural brain imaging.

Despite phenomenologic evidence that bipolar affective disorder and schizophrenia might relate to increased SN activity or connectivity (or perhaps dramatic swings in same), extensive structural MRI data make clear that patients with these disorders exhibit reduced gray matter volume within key SN hubs (Figure 3) (104,105). How should we interpret this apparent disconnect? SN volume could be progressively lost as a degenerative consequence of prolonged or phasic SN hyperactivity. Alternatively, genetic regulation of SN development may go awry, producing fewer inhibitory neurons or excessive pruning of gamma-aminobutyric acid–ergic synapses, resulting in reduced volume and SN overactivity due to lack of local inhibition. Both accounts may explain part of the picture because there seems to be a continuum of worsening SN gray matter deficits from genetically at-risk individuals to patients having had only their first psychotic episode to those with chronic schizophrenia (106,107). Considering this apparent progression, it seems likely that SN processing becomes increasingly aberrant or dysregulated even as networked regional volumes are contracting. That is, loss of volume in schizophrenia may not equate to a reduction of SN output but rather to faulty salience detection (over- or underrepresentation). Efforts to measure SN connectivity directly in bipolar affective disorder and schizophrenia have thus far yielded mixed results, even within some of the same studies. Nonetheless, the themes have been reduced within-network connectivity and failure of SN hubs to communicate with additional networks such as the default mode and executive-control networks (108–110). Therefore, the available data perpetuate a seeming mismatch between the phenomenology of "positive" psychotic symptoms (which suggest SN overactivity) and the empirical neuroimaging literature. This discrepancy might be explained in part by the fact that most studies are conducted on patients recovering from a recent psychotic episode. Reduced SN connectivity or activity could reflect a postepisode suppression state, during which "negative" dysexecutive and amotivational symptoms often persist and more naturally align with SN disruption. Emerging models have begun to formalize these and related concepts into clear and testable hypotheses (92).

Earlier in the developmental trajectory, SN miswiring or maldevelopment may contribute to some forms of autism (111), in which the behavioral parallels with bvFTD are evident. Recent network-based imaging studies have shown that the extent, distribution, and connectivity of the SN is reduced in autism (111–113), providing a mechanism for social and behavioral loss-of-function symptoms shared between autism and bvFTD. At the same time, in autism posterior elements of the DMN show increased spatial distribution (112), providing a potential substrate for the exceptional posterior visuospatial and memory functions seen in rare high-functioning individuals (114). Likewise,

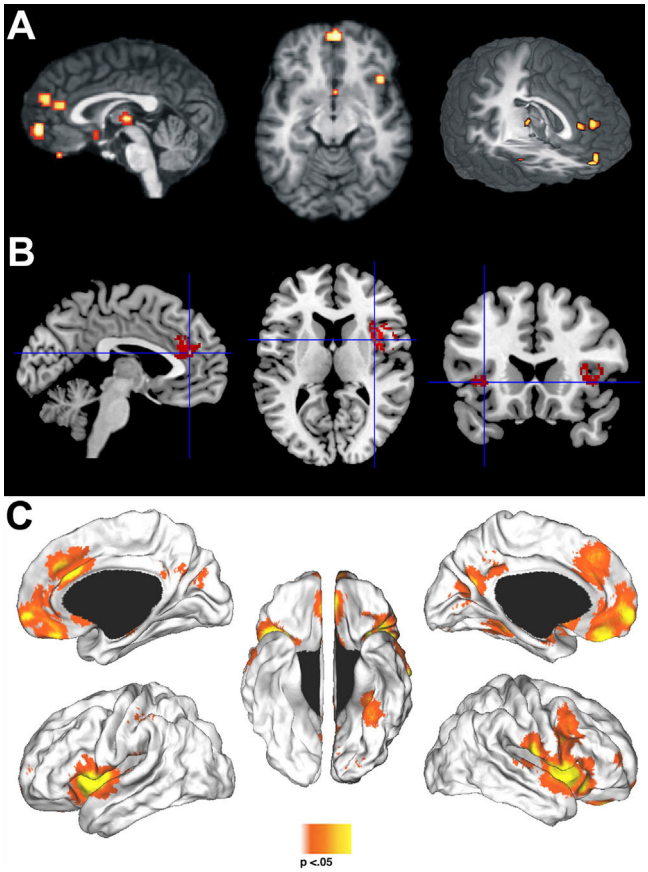

Figure 3. Relationship between the anatomy of behavioral variant frontotemporal dementia and psychiatric disease syndromes. **(A)** Quantitative meta-analysis of voxel-based morphometry and positron emission tomography studies revealed deficits in a set of regions, including pregenual anterior cingulate cortex, medial prefrontal cortex, right anterior insula, and medial thalamus, in frontotemporal dementia compared with controls (126). **(B)** Voxel-wise meta-analysis found gray matter reductions in anterior cingulate cortex and anterior insula in bipolar disorder. **(C)** An anatomic likelihood estimation analysis of voxel-based morphometry studies revealed gray matter reductions involving bilateral anterior cingulate/medial prefrontal cortex and anterior insula/operculum in patients with schizophrenia (105). Images adapted from the cited articles with permission from the authors and publishers.

occasional patients with FTD, especially those with language-predominant syndromic variants, show thriving posterior parietal functions associated with heightened visual interest, search capacity, or artistic ability (46,115,116). Further work is needed to identify meaningful connectivity-driven autism subgroups, which may facilitate genetic and biological discovery.

Future Directions

Network-based principles have begun to shed light on group-level changes across a host of neurodegenerative disease syndromes (117). To aid in the search for treatments, however, these methods will need to be developed for use in tracking single subjects over time. To date, most evidence supporting the feasibility of this goal has come from cross-sectional correlations with disease severity. By examining patients with mild, moderate, or severe AD with task-free fMRI, Zhang *et al.* found that all AD subjects showed disrupted intrinsic functional connectivity between posterior cingulate cortex and DMN regions, which worsened with increasing AD severity (78). Similarly, in bvFTD, clinical severity correlated with loss of right frontoinsular SN connectivity and enhancement of parietal DMN connectivity, suggesting that functional connectivity reductions and enhancements both carry the potential to track disease progression (73). The capacity to detect reductions and enhancements with task-free fMRI provides an advantage over structural MRI methods and may prove even more relevant to psychiatric disease. Nonetheless, to aid in drug discovery, task-free fMRI and all other connectivity-related metrics will need to become more quantitative and reliable. Although initial studies of test–retest reliability provide some hope (118,119), they also highlight how much work remains to be done to reduce noise and separate trait-related from state-related signals.

In neurodegenerative disease research, longitudinal studies are needed to follow individuals from health to disease, exploring connectivity–vulnerability interactions within single subjects. Such studies should become feasible for AD through large, ongoing, collaborative longitudinal studies (120,121). One recent longitudinal study (122) showed decreased intrinsic connectivity in the posterior DMN and increased connectivity in the anterior and ventral DMN subnetworks in AD compared with healthy controls at baseline. At follow-up, patients showed worsening connectivity across all default mode subsystems, in keeping with a network-based neurodegeneration model in which disease spreads from hot spots or "epicenters" to interconnected nodes within the target and, ultimately, off-target systems (8). Longitudinal studies of connectivity and other candidate biomarkers are needed for bvFTD, and efforts are underway to organize large-scale collaborative networks inspired by the AD model.

Open questions remain with regard to why each neurodegenerative disease adopts a network-related spatial pattern and how disease spreads across network nodes. Recent efforts have examined how well competing models predict the relationship between the healthy structural (7) or intrinsic functional (8) connectome and disease-associated regional neurodegeneration. Findings from these studies converge on the notion that neurodegenerative diseases not only target large-scale networks (4) but also spread along neural connections (7,8). In one study (8), specific regions emerged as critical network "epicenters" for each neurodegenerative syndrome, defined as regions with normal connectivity profiles that most resembled the syndrome-associated atrophy pattern. Graph theoretical analyses in healthy subjects revealed that regions with higher total connectional flow (stronger and more numerous connections) and, more consistently, shorter functional paths to the epicenters, showed greater disease-related vulnerability. These findings suggest that disease may literally "travel" between network nodes, and extensive recent cell-based and in vivo studies have supported this view by demonstrating transneuronal spread of misfolded disease proteins (9–12). Longitudinal multimodal neuroimaging studies will enable researchers to more formally test the predictions made by these various disease progression models and determine the prognostic value of these models for individual patients. Predicting a patient's trajectory based on his or her baseline connectome will enable researchers to compare predicted to actual progression and to assess the impact of candidate disease-modifying therapies.

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