Frontotemporal Dementia: What Can the Behavioral Variant Teach Us about Human Brain Organization?

The Neuroscientist
18(4) 373–385

DOI: 10.1177/1073858411410354
http://nro.sagepub.com
SAGE

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Abstract

The behavioral variant of frontotemporal dementia (bvFTD) slowly undermines emotion, social behavior, personal conduct, and decision making. These deficits occur in concert with focal neurodegeneration that can be quantified with modern structural and functional imaging and neuropathological methods. As a result, studies of bvFTD have helped to clarify brain structures, networks, and neurons that prove critical for normal social-emotional functioning. In this article, the authors review the evolving bvFTD literature and propose a simple, testable network-based working model for understanding bvFTD.

Keywords

anterior cingulate, anterior insula, frontotemporal dementia, functional connectivity, von Economo neuron

The myriad neurons of the adult human brain exhibit differential vulnerability to each neurodegenerative disease. As a result, each disease features an incipient preclinical stage during which the patient's lesion remains focal, affecting just one or few brain regions and only the most susceptible cells and circuits within the target regions. Over time, the diseases progress throughout functionally cohesive large-scale networks (Seeley and others 2009). Applied to Alzheimer disease (AD), these principles have informed our understanding of the medial temporal lobe episodic memory system and related large-scale distributed networks (Buckner and others 2005; Greicius and others 2004; Hyman and others 1984; Mitchell and others 2002). Applied to Parkinson and Huntington diseases, early selective vulnerability has helped reveal the organization of the major frontal-subcortical motor "loops" (Penney and Young 1983).

Frontotemporal dementia (FTD) is an umbrella term that refers to at least three clinical syndromes: a behavioral variant (bvFTD), characterized by early social-emotional dysfunction, and two primary progressive aphasia (PPA) subtypes (Gorno-Tempini and others 2011), the semantic and nonfluent/agrammatic variants. Studies of semantic variant PPA have begun to characterize an anterior temporal lobe semantic memory system critical for representing word, object, person-specific, and emotional meaning (Hodges and Patterson 2007). Likewise, patients with nonfluent/agrammatic PPA have helped researchers explore the neuroanatomy of speech and grammar (Wilson and others 2010). With regard to bvFTD, most of what we may learn from this mysterious and complex disorder continues to lie ahead. Because broader reviews of bvFTD clinical, pathological, and genetic features have been published (Mackenzie and others 2010; Piguet and others 2010; Seeley 2008, 2010), this article focuses on recent advances that help to build an integrative, testable, working bvFTD functional-anatomical model. What, then, can bvFTD teach us about human brain organization?

bvFTD Can Identify Regions Whose Structural Integrity Proves Critical for Specific Human Social-Emotional Functions

Classical lesion-deficit correlation studies have examined the behavioral impact of focal lesions, such as those arising from stroke, trauma, or surgical resection. Interpreting these studies, when they are performed during the chronic phase, can be difficult due to plastic

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neural reorganization that occurs during the months to years before (in the case of surgery for epilepsy or tumor) or after the lesion is created. Over the past decade, quantitative structural imaging methods such as voxel-based morphometry (VBM) and cortical thickness mapping have enabled researchers to correlate early stage neurodegenerative injury with patient symptoms and deficits. Like other lesion models, the neurodegenerative lesion-deficit approach offers complementary information to functional imaging studies. In particular, neurodegenerative lesions can identify and lateralize brain regions that prove critical for a given function, whereas functional MRI (fMRI) studies illuminate bihemispheric homologous structures that, although recruited for task completion, may or may not be necessary for the task. A prevalent criticism of neurodegenerative lesions is that they extend beyond regions where imaging changes can be demonstrated. This concern, although valid, also applies to other lesion types (especially trauma), in which sub-radiographic injury may be less constrained to a specific neural network. In contrast to stroke or trauma, neurodegenerative lesions may be less likely to induce massive plasticity and reorganization of lost functions within spared cortex. Moreover, because neurodegenerative lesions build incrementally within a targeted brain structure, they facilitate layer- or even cell-specific lesion-deficit correlations (Mitchell and others 2002).

Patients with bvFTD are most often brought in by family members due to changes in social and personal conduct. Subtle at first, these changes may manifest as reduced initiative at work or indifference to minor social conflicts. Over time, the syndrome progresses to erode all social, professional, and familial relations due to the patient's unconcern for others, violation of social rules (despite retained knowledge of those rules), and profound apathy toward previous goals and priorities. It is as if both the gas pedal (motivation) and the brakes (behavioral inhibition) are broken, resulting in errors of omission and commission.

bvFTD-related focal degeneration emerges first and most prominently in the pregenual anterior cingulate cortex (pACC) and frontoinsular cortex, as well as the dorsomedial prefrontal cortex, frontal pole, striatum, and thalamus (Boccardi and others 2005; Broe and others 2003; Schroeter and others 2008; Seeley, Crawford, and others 2008). Over time, the disease spreads into adjacent orbital and dorsolateral frontal regions and ultimately into the parietal lobe (Fig. 1). In most patients, right hemisphere structures are more affected than left, or the pattern is symmetrical. This targeted injury provides a unique opportunity to investigate structures critical for social-emotional functions (Eslinger and others 2011; Moll and others 2011; Omar and others 2011; Rosen and others 2006; Sollberger and others 2009; Sturm and others 2008; Sturm and others 2006; Sturm and others 2011), especially when

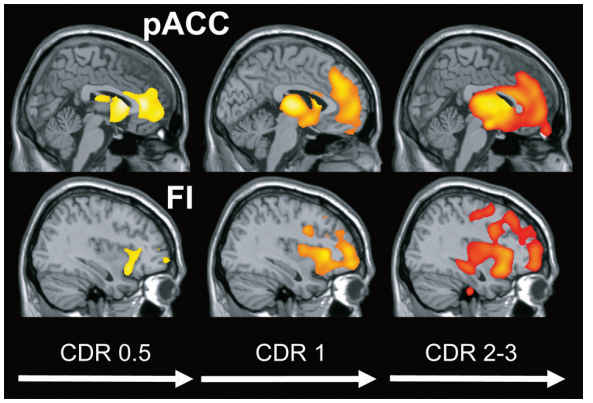


Figure 1. Anatomical progression of the behavioral variant of frontotemporal dementia (bvFTD). Patients with bvFTD were categorized as having very mild, mild, or moderate to severe functional severity, as assessed using the Clinical Dementia Rating (CDR) scale. Each group (n = 15) was compared to a group of 45 age-matched controls using voxel-based morphometry. Slices are from the right hemisphere. FI, frontoinsula; pACC, pregenual anterior cingulate cortex. Data adapted from Seeley, Crawford, and others (2008).

lesion-deficit correlations are pursued across bvFTD and related disorders that cover the rest of the brain, including posterior temporal and parietal structures (affected in AD) and left hemisphere regions (affected in PPA subtypes). Table 1 highlights selected recent studies that have helped to clarify core bvFTD social-emotional deficits and their anatomical underpinnings. Importantly, correlations between a specific behavior and a region's volume, glucose metabolism, or perfusion (Table 1) do not indicate that the identified region performs the studied function in isolation; rather, such correlations suggest that the region is a critical node within a network of participating regions. One overarching conclusion supported by Table 1 is the critical role of the right hemisphere, especially the right frontoinsula (FI), pACC, temporal pole, and orbitofrontal cortex, in social-emotional function. Recent diffusion tensor imaging studies have begun to interrogate the microstructural integrity of major white matter tracts in bvFTD (Borroni and others 2007; Matsuo and others 2008; Zhang and others 2009). This approach, once applied to bvFTD clinical deficits, may help pinpoint anatomical connections that enable specific behavioral capacities.

bvFTD Can Illuminate "Salience Network" Organization, Function, and Interactions with Other Networks

As the bvFTD-related spatial pattern became clear, new fMRI techniques emerged for large-scale network

Table 1. Regional Correlates of Core bvFTD Social-Emotional Deficits

Deficit	Imaging	Patients Included	Regional Correlates	Reference
Emotional empathy (empathic concern)	MRI	bvFTD, svPPA, nfvPPA, CBS, PSP, AD	Right ATL, FI, sACC, pACC, striatum	Rankin and others (2006)
	MRI	bvFTD, svPPA, nfvPPA	dmPFC, pACC	Eslinger and others (2011)
Cognitive empathy (perspective taking)	MRI	bvFTD, svPPA, nfvPPA, CBS, PSP, AD	Right ATL, fusiform gyrus, dmPFC, sACC, striatum	Rankin and others (2006)
	MRI	bvFTD, svPPA, nfvPPA	FP, dmPFC, dlPFC, ATL, lateral parietal	Eslinger and others (2011)
Interpersonal warmth	MRI	bvFTD, svPPA, nfvPPA, CBS, AD	Right FI, mOFC > ATL	Sollberger and others (2009)
Emotion recognition: faces (negative emotion)	MRI	bvFTD, svPPA, nfvPPA, PSP, MCI, AD, HC	Right ITG, lat OFC	Rosen and others (2006)
	MRI	bvFTD, svPPA	Bilateral AI, lat OFC	Omar and others (2011)
Emotion recognition: music	MRI	bvFTD, svPPA	Bilateral pACC, sACC, AI, OFC, dmPFC, ATL, amygdala, striatum	Omar and others (2011)
Emotional moral judgment	SPECT	bvFTD, AD, HC	Right frontotemporal[a]	Mendez and Shapira (2009)
Prosocial sentiments (guilt, pity, embarrassment)	PET	bvFTD	Right FP, septum	Moll and others (2011)
Other critical sentiments (anger, disgust)	PET	bvFTD	dmPFC, right amygdala	Moll and others (2011)
Embarrassment	NA	bvFTD, svPPA, nfvPPA, HC	Not studied	Sturm and others (2006)
Autonomic response to embarrassment	MRI	bvFTD, svPPA, nfvPPA, HC	pACC	Sturm and others (2008), Sturm and others (2011)
Mutual gaze during dyadic interaction	NA	bvFTD, svPPA, AD, HC	Not studied	Sturm and others (2010)

AD = Alzheimer disease; AI = anterior insula; ATL = anterior temporal lobe; bvFTD, behavioral variant of frontotemporal dementia; CBS = corticobasal syndrome; dlPFC = dorsolateral prefrontal cortex; dmPFC = dorsomedial prefrontal cortex; FI = frontoinsula; FP = frontal pole; HC = healthy controls; ITG = inferior temporal gyrus; lat OFC = lateral orbitofrontal cortex; MCI = mild cognitive impairment; mOFC = medial orbitofrontal cortex; MRI = magnetic resonance imaging; NA = not applicable; nfvPPA = nonfluent/agrammatic variant primary progressive aphasia; pACC = pregenual anterior cingulate cortex; PET = positron emission tomography; PSP = progressive supranuclear palsy; sACC = subgenual anterior cingulate cortex; SPECT = single photon emission computed tomography; svPPA, semantic variant primary progressive aphasia.
[a]Sub-lobar resolution not provided by chosen analytical strategy.

mapping in the healthy human brain. In ongoing work, "resting-state" or "intrinsic connectivity" fMRI studies have begun to delineate the human brain's functional architecture (Fox and Raichle 2007). This method identifies regions with correlated blood oxygen level–dependent (BOLD) signals in task-free settings, and a group of 8 to 10 widely replicated networks has been identified (Beckmann and others 2005; Damoiseaux and others 2006; Dosenbach and others 2007; Seeley and others 2009). Motivated in part by the early atrophy pattern seen in bvFTD, Seeley, Menon, and colleagues (2007) studied healthy young adults to outline regions functionally correlated with the right FI. The resulting map was striking (Fig. 2). Bilateral ACC, left FI, and subcortical, limbic, and brainstem sites with known connections from primate and rodent axonal tracer studies (Mesulam and Mufson 1982; Ongur and Price 2000; Saper 2002) all shared functional connectivity to the right FI, and the network findings recapitulated the bvFTD atrophy pattern. This network was referred to as the "salience network" in light of previous observations that ACC and FI coactivate in response to emotionally significant ambient stimuli and events, from pain, thirst, and hunger to social rejection, embarrassment, collaboration, and adoration (Craig 2002; Critchley 2005). Combining primate anatomical work with a broad survey of the human functional imaging and lesion literatures, Craig (2009a, 2009b) has proposed that the right FI, as a convergence zone within this larger network, may represent a "global emotional moment" built from integration of interoceptive inputs with personal goals, hedonic conditions, and contextual information.

Alzheimer disease, in contrast to bvFTD, targets a large-scale network often referred to as the "default mode network" (DMN) due to its consistent deactivation during cognitively demanding tasks (Buckner and others 2005; Greicius and others 2003; Raichle and others 2001). This system, which includes posterior cingulate-precuneus,

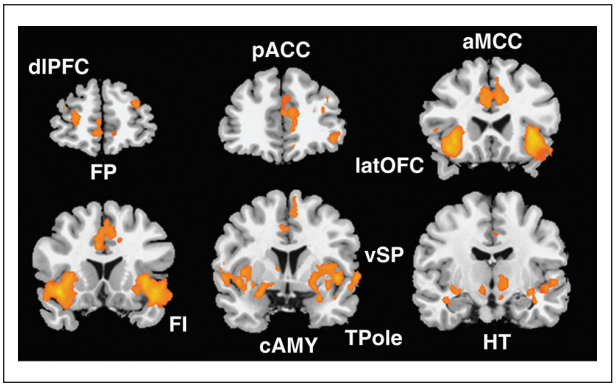


Figure 2. The salience network. Healthy young subjects were studied using intrinsic connectivity fMRI under task-free conditions. Regions whose spontaneous activity fluctuations correlated with those of the right frontoinsula (FI) were plotted and used as a template to select a best fit among components generated for each subject using independent component analysis (ICA). The resulting group-level ICA map is shown here. The right side of the image corresponds to the right side of the brain. aMCC = anterior midcingulate cortex; cAMY = central nucleus of the amygdala; dlPFC = dorsolateral prefrontal cortex; FP = frontal pole; HT = hypothalamus; latOFC = lateral orbitofrontal cortex; pACC = pregenual anterior cingulate cortex; TPole = temporal pole; vSP = ventral striatopallidum. Data adapted from Seeley, Menon, and others (2007).

medial temporal, lateral temporoparietal, and dorsomedial prefrontal regions, may encompass two to three distinct subnetworks with related but dissociable functions (Andrews-Hanna and others 2010). One way to think about the DMN's overall function is that it constructs internal images of external events, whether those images are memories of one's personal past, visions of one's future, or simulations of another's perspective (Buckner and others 2008). This role stands in contrast to that of the salience network, which responds to the immediate emotional weight of current (internal or external) conditions (Seeley, Allman, and others 2007). Interestingly, task-based paradigms designed to elicit present > future self-oriented processing highlight salience network hubs (pACC and FI) alongside select DMN subregions, such as the dorsomedial prefrontal cortex (Andrews-Hanna and others 2010).

Noting the inverse correlation between the salience network and DMN functional time series in the healthy brain (Fox and others 2005; Greicius and Menon 2004), Seeley, Allman, and others (2007) proposed a simple model in which each network exerts an inhibitory influence on the other, allowing these systems to toggle back and forth in response to prevailing goals and conditions. Despite some controversy surrounding the origin and significance of the DMN's "anticorrelated" relationships to the salience network and other networks (for a discussion, see Deco and Corbetta 2011), recent computational modeling experiments have predicted spontaneous assembly of large-scale networks into competitive and inversely correlated time series (Deco and others 2009). From a functional-anatomical standpoint, the "reciprocal networks" model predicts that a) lesions of one network will produce functional enhancements in the other, b) stimulation of one network will suppress activity in the other, and c) patient groups that doubly dissociate salience network and DMN injury should feature divergent strength and deficit profiles.

Several recent clinical studies provide support for predictions made by the reciprocal networks model. First, with intrinsic connectivity fMRI, Zhou and colleagues (2010) found divergent salience network and DMN changes in bvFTD and AD (Fig. 3). That is, the salience network was disrupted in bvFTD but enhanced in AD, whereas the DMN was disrupted in AD but showed bvFTD-related enhancements within parietal DMN regions. In bvFTD, weaker salience network connectivity in right FI and ACC predicted greater parietal DMN connectivity enhancement. Patients with more advanced bvFTD showed greater salience network impairment in right FI and intensified biparietal DMN connectivity. Providing a remarkable set of convergent findings, Hu and coworkers (2010) quantified cerebral blood flow with arterial spin-labeled perfusion MRI and found divergent perfusion patterns in FTD (across bvFTD and PPA variants) and AD compared to controls. FTD showed hypoperfusion in salience network regions (right FI, lateral prefrontal cortex) and hyperperfusion in the DMN (posterior cingulate/precuneus), whereas AD showed the opposite pattern. Data from the two studies combine to suggest that progressive damage to either network intensifies activity and connectivity in the other network, perhaps due to disrupted inhibitory interactions. Furthermore, it appears that enhancements within the reciprocal network may occur early, and future studies will address whether these changes might even occur in patients with preclinical disease.

Does DMN stimulation suppress salience network activity? This question seemed unlikely to be addressed in humans until Laxton and others (2010) reported the findings from a phase 1 clinical trial using deep brain stimulation of the fornix in patients with mild to moderate AD. Acute stimulation drove activity in the DMN, as assessed using electrophysiological methods. After 12 months of chronic stimulation, patients showed sustained DMN metabolic improvement, as predicted by the authors, but also robust ACC metabolic impairment, as predicted by the reciprocal networks model. The intervention was safe, but no definite clinical benefits were realized; nonetheless, patients in this trial provide a unique window into network dynamics. Future opportunities to explore the reciprocal interactions between the human salience network and DMN may come from patients with intradural electrode grids, as used to plan surgery for

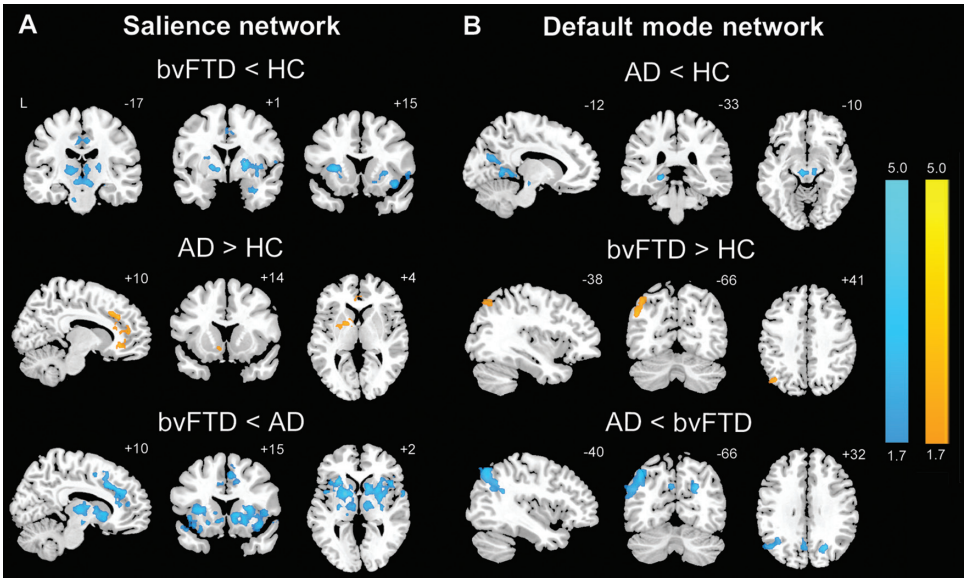


Figure 3. Divergent intrinsic connectivity changes in the behavioral variant of frontotemporal dementia (bvFTD) and Alzheimer disease (AD). Here, intrinsic connectivity within the salience network (A) and default mode network (B) was assessed, comparing patients with bvFTD and AD (n = 12 per group) to healthy age-matched controls and each other. The findings support the notion that salience network damage enhances default mode network connectivity and vice versa. HC = healthy controls. Figure adapted from Zhou and others (2010).

refractory epilepsy, or from transcranial magnetic stimulation in healthy subjects. These approaches benefit from reversibility, enabling cause-effect relationships to be explored, although as surface-oriented approaches they may struggle to detect signals arising from deep-seated structures such as the ACC and FI.

The opposing network changes in bvFTD and AD predict divergent patterns of clinical strength and weakness, and studying both disorders provides richer information than examining either alone. Patients with AD often show preservation or enhancement of the emotional warmth, sensitivity, and connectedness lost in bvFTD (Mendez and Shapira 2009; Rankin and others 2006; Sollberger and others 2009; Sturm and others 2010), whereas patients with bvFTD typically retain visuospatial and other parietal lobe functions lost early in AD (Mendez and others 1996). In some patients with FTD, especially those with PPA variants, posterior parietal functions seem to thrive, associated with heightened visual interest, search capacity, or artistic ability (Miller and others 1998; Seeley, Matthews, and others 2008; Viskontas and others 2011). Neurodevelopmental disorders provide a parallel illustration. Patients with autism (like those with bvFTD) lack emotional warmth and connection with others but may excel when it comes to posterior visuospatial or memory functions (Treffert 2009). Children with Williams syndrome (like patients with AD) show intense social warmth and interest but struggle with visuospatial relations (Meyer-Lindenberg and others 2006). The push and pull between the salience network and DMN could help to explain a host of other mysterious phenomena, from suppressed memories of traumatic events (salience network overdrive suppresses DMN-associated episodic memory encoding, retrieval, or both) to the ability we all have to ignore internal homeostatic needs (full bladder, rising serum osmolarity) when absorbed in a film or novel that transports us elsewhere in space and time (DMN activity suppresses salience network sensitivity to interoceptive stimuli). These unproven ideas seem testable. The DMN is also anticorrelated with task-related networks (Fox and others 2005) other than the salience network, which, in turn, may show anticorrelations with networks other than the DMN. These complex network-network interactions provide ample opportunities to explore the physiological basis of normal and abnormal brain function.

bvFTD Can Help Dissect Cell-, Layer-, and Circuit-Specific Contributions to Human Social-Emotional Functions

In AD, early entorhinal cortex neurofibrillary pathology targets the layer 2 stellate pyramidal neurons that project to the dentate gyrus via the perforant pathway (Braak and Braak 1995; Gomez-Isla and others 1996). This lesion disconnects the broader cortex from the hippocampus,

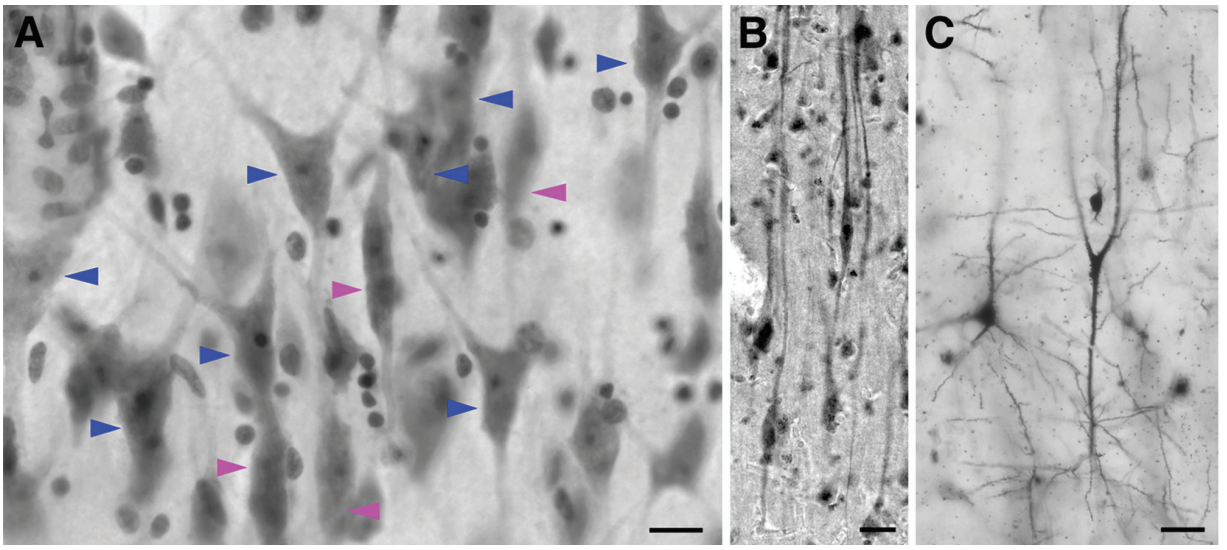


Figure 4. von Economo neurons and fork cells in the healthy human brain. von Economo neurons (VENs) are large, bipolar projection neurons found in layer 5 of the anterior cingulate and frontoinsular cortices. A related neuronal morphotype, the fork cell, features two large, divergent apical dendrites. (A) VENs (pink arrowheads) and fork cells (blue arrowheads) cluster in the frontoinsula (cresyl violet stain). (B) VENs are oriented perpendicularly to the pia, often arranged in columns (antibody to MAP2). (C) Golgi impregnation reveals the simple, elongated, Y-shaped fork cell dendritic architecture. Apical is toward the top of all images; scale bars represent 20 μM.

preventing the hippocampus from indexing experience-related cortical activity patterns for later recollection. By analogy, we might expect some unique pACC-FI neuronal population to prove vulnerable in bvFTD and impede the salience network's capacity to feel or respond to the "global emotional moment" (Craig 2009a, 2009b). In recent years, Seeley and coworkers have begun to explore an unusual layer 5b neuron found only in ACC and FI and more abundantly in the right hemisphere (Allman and others 2010). These large, bipolar projection neurons, now called von Economo neurons (VENs), are distinguished by their size, shape, and location, as eloquently described by von Economo in his celebrated atlas with George Koskinas (von Economo and Kosikinas 1925) and in a subsequent monograph (von Economo 1926) that was recently translated from German to English (Seeley and others forthcoming). Comparative studies suggest that a focal concentration of VENs in ACC and FI distinguishes large-brained, highly social mammals, including humans, apes, cetaceans, and elephants (Allman and others 2010; Hakeem and others 2009; Hof and Van der Gucht 2007; Nimchinsky and others 1999; Rose 1928), from other mammalian species. In addition, FI features a second distinctive layer 5 neuron, the fork cell, which is scarcely seen in ACC (Ngowyang 1932). Fork cells, like VENs and unlike all other layer 5 pyramidal neurons, feature a single, large basal dendrite that courses toward the white matter. In contrast to VENs, fork cells possess two large apical dendrites that diverge from each other and the vertical axis as they extend into superficial layers (Fig. 4). Comparative analyses of fork cell number and location are still needed; Ngowyang (1932, 1936) identified these cells in the chimpanzee and orangutan but not in the cat.

In bvFTD, pACC and FI VENs show striking selective vulnerability when compared to the neighboring layer 5 neurons (Kim and others forthcoming; Seeley, Allman, and others 2007; Seeley and others 2006). This lesion was not seen in AD, suggesting that it does not reflect a non-specific response to neurodegeneration. Fork cells, examined only in FI, show a similar pattern (Kim and others forthcoming). These studies surveyed a range of bvFTD severities, assessed using a validated FTD postmortem staging scheme (Broe and others 2003). Even patients with little or no gross atrophy, as seen when death occurs prematurely due to comorbid motor neuron disease, showed selective VEN and fork cells losses (Figure 5), and depletion of these cells correlated with atrophy severity. Parallel to the findings from intrinsic connectivity mapping in vivo, right (but not left) FI VEN loss correlated with clinical severity (Fig. 6B). Furthermore, right (but not left) FI VEN and fork cell loss predicted greater disinhibition and overall behavioral symptom severity.

Future studies will help to address many lingering questions about VEN and fork cell injury in bvFTD. Of greatest relevance to the present review, more sophisticated lesion-deficit correlation analyses could tease apart which social-emotional deficits (Table 1) result from

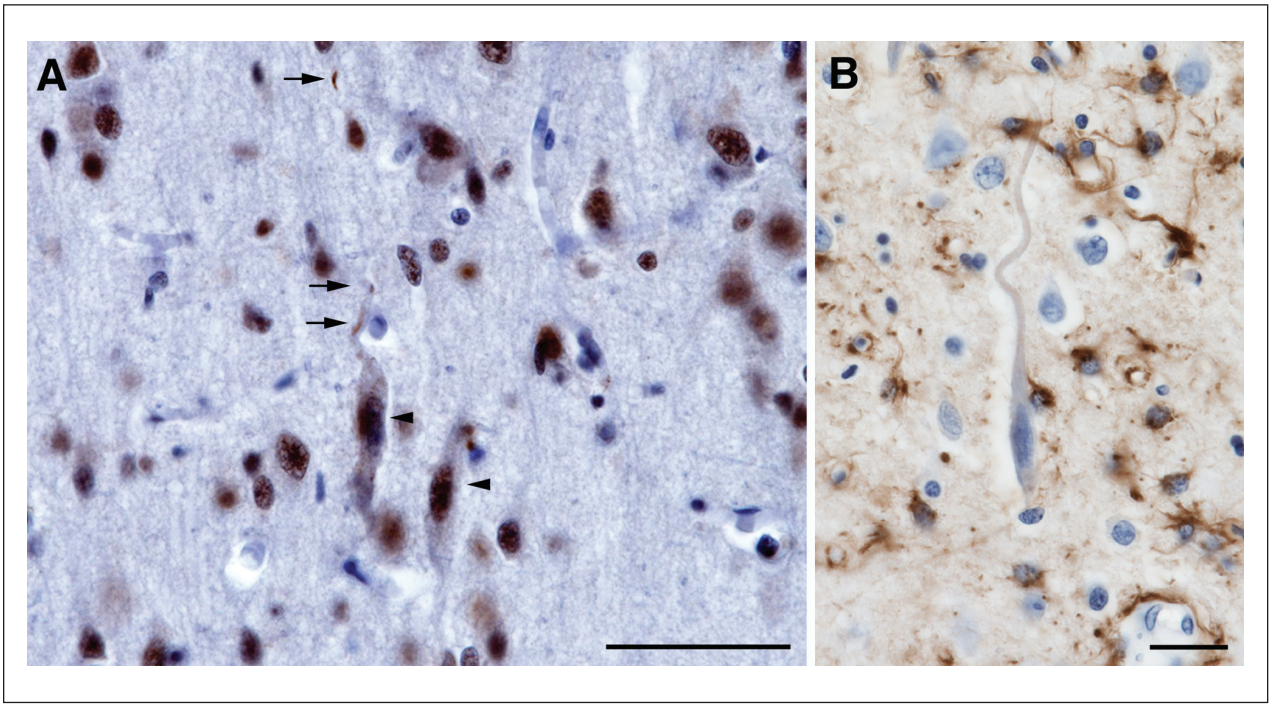


Figure 5. von Economo neurons (VENs) in the behavioral variant of frontotemporal dementia (bvFTD). The bvFTD syndrome most often results from frontotemporal lobar degeneration with neuronal cytoplasmic inclusions containing either tau (FTLD-tau) or transactive response DNA binding protein of 43 kDa (TDP-43, FTLD-TDP). (A) A 59-year-old man died of motor neuron disease during the earliest stages of bvFTD due to FTLD-TDP. TDP-43 immunohistochemistry (hematoxylin counterstain) identified few neuronal cytoplasmic inclusions in pregenual anterior cingulate (pACC) and fewer in other brain regions. Here, a pair of VENs (arrowheads) is shown. The affected, dysmorphic VEN (left) shows loss of nuclear TDP-43 (brown) and small, linear TDP-43 deposits along the apical dendrite at variable distances from the soma (arrows). Surrounding pyramidal neurons lack inclusions and show normal nuclear TDP-43 signal. (B) A rare surviving VEN in pACC is surrounded by reactive astrocytes in this patient with advanced Pick disease, a subtype of FTLD-tau. Antibody to glial fibrillary acidic protein (GFAP), hematoxylin counterstain. Scale bars represent 100 μM (A) and 50 μM (B).

region- and hemisphere-specific VEN and fork cell losses. Despite important limitations, postmortem studies remain among the few opportunities to determine how different neuronal subtypes, even within the same region or layer, relate to functions measured in humans during life.

The nearest living relatives within each VEN-endowed mammalian lineage have now been examined, and these species do not possess a focal concentration of VENs in ACC or FI (Allman and others 2010; Hakeem and others 2009). Therefore, VENs would seem to have emerged much more recently than when the nearest common ancestor of apes, elephants, and cetaceans existed. Alternatively, the nearest living ancestors within each lineage (or their predecessors) may have once possessed VENs, only to lose this neuronal morphotype later in their evolutionary trajectory. Regardless, considering their consistent localization within ACC and FI, VENs most likely evolved from an ancestral ACC-FI layer 5 pyramidal neuron, perhaps in response to some shared selective pressure faced by the VEN-endowed lineages. Candidate pressures include increasing absolute brain size (but not relative brain size; see Allman and others 2010), social network size and complexity, or a need to dissociate salience network activity from the workings of other networks, such as the DMN, which may also have expanded in these long-lived, late-maturing species that rely on mental time travel to reexperience feeding and seasonal migration routes or instructive past encounters with conspecifics. A mechanism for rapid toggling between present (salience network) and past/future (DMN) dealings might have only been required among species that evolved more elaborate processing modes on both time scales (Seeley, Allman, and others 2007).

Lingering Questions and Working Functional-Anatomical Model

As suggested throughout the preceding sections, many bare patches remain to be filled within the bvFTD functional-anatomical landscape. Within which salience network node or nodes does intrinsic connectivity fail first? Through what anatomical sequence does the network break down? Where do the VENs and fork cells send their axons, and what inputs do they receive? What molecular

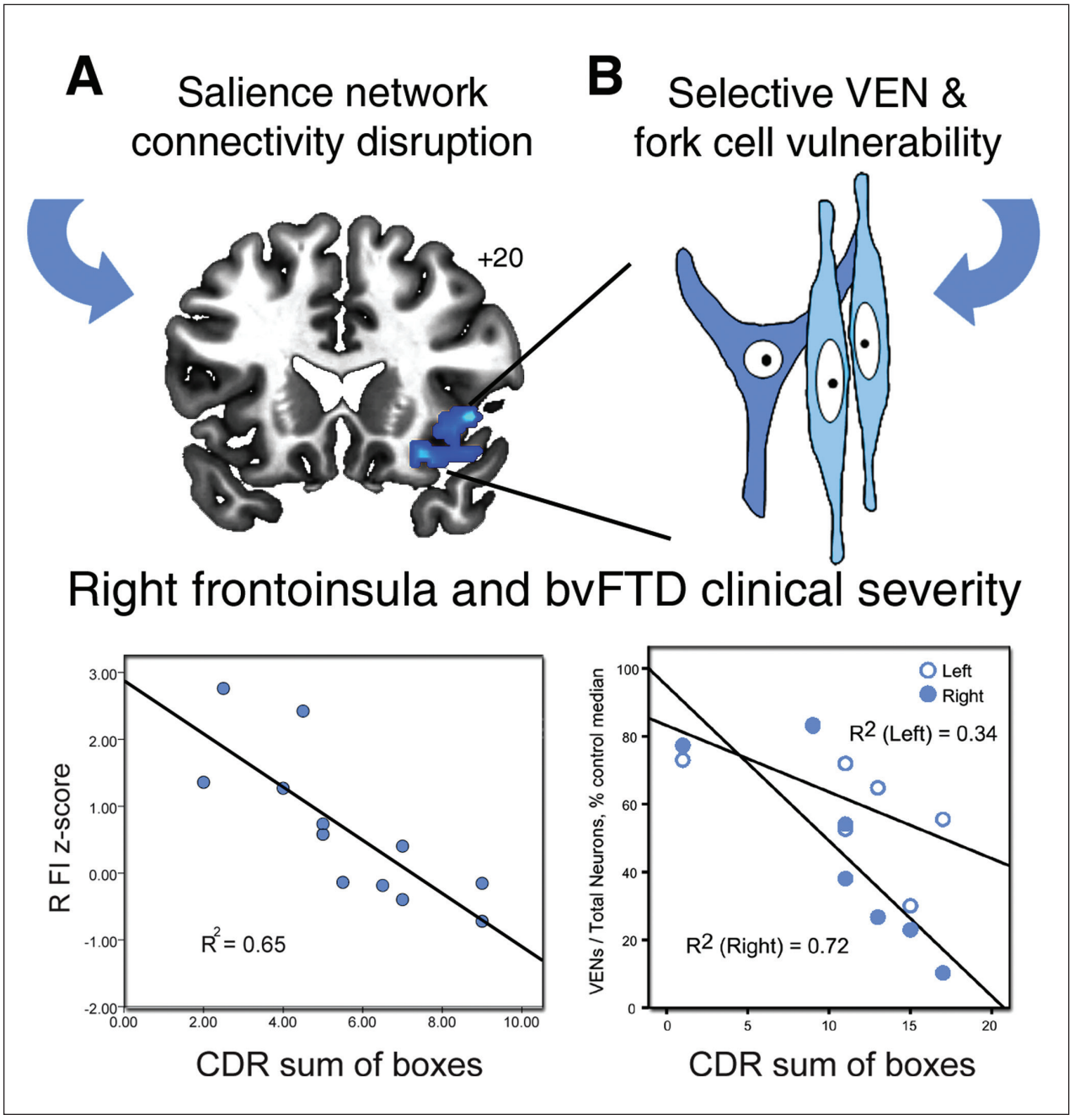
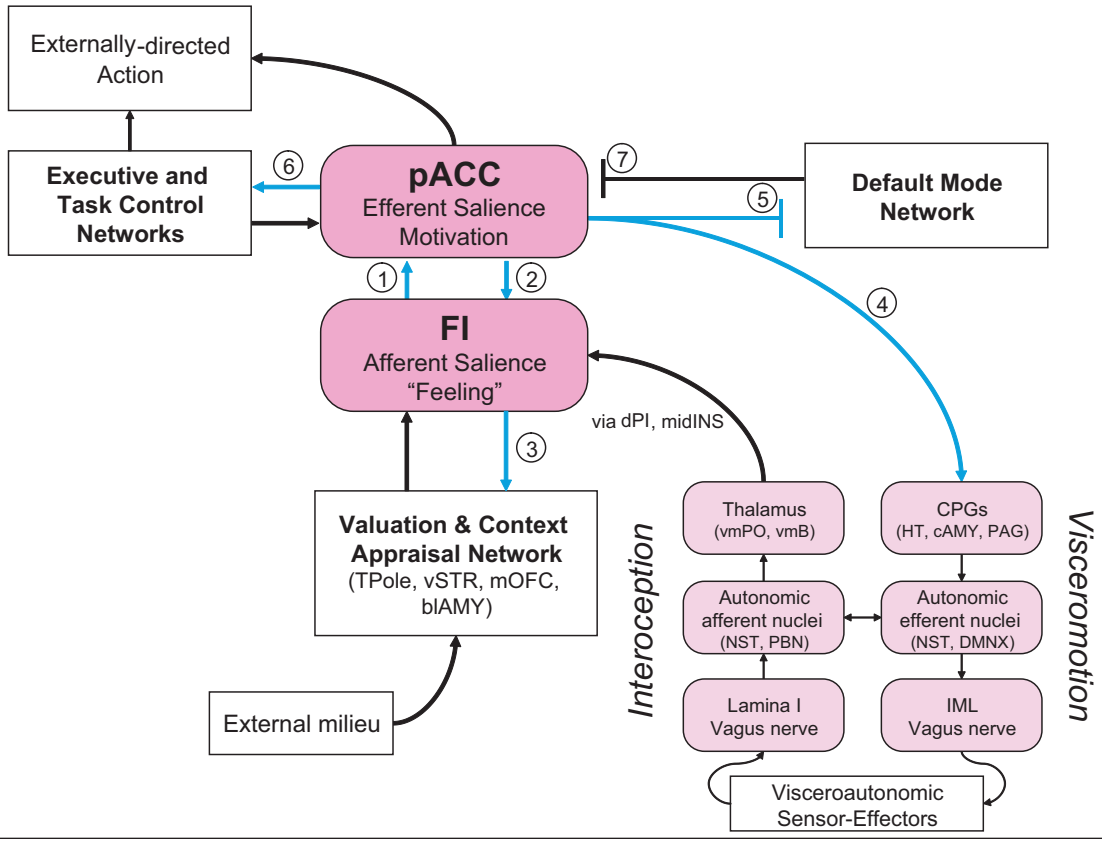


Figure 6. Right frontoinsula (FI) dysconnectivity and von Economo neuron (VEN) loss correlate with the behavioral variant of frontotemporal dementia (bvFTD) functional severity. Two recent studies sought the neuroanatomical correlates of bvFTD disease severity, as measured using the Clinical Dementia Rating (CDR) scale, sum of boxes score. (A) Intrinsic connectivity mapping in vivo revealed that disease severity correlated with right FI connectivity to the rest of the salience network. (B) Postmortem quantitative neuropathological analysis of bilateral FI, performed on a nonoverlapping group of patients, revealed a convergent finding, with right-sided VEN loss correlating best with bvFTD clinical severity.

or electrophysiological features distinguish VENs and fork cells from each other and from other layer 5 neurons? Can ancestral VEN/fork cell precursors be studied in laboratory mammals to shed light on the role VENs and fork cells play in humans? Despite significant barriers, we contend that many of these questions can be addressed and that the knowledge gained will help clarify bvFTD pathogenesis, elucidate human social brain organization and evolution, and set the stage for restoring salience network function in patients with bvFTD and other prevalent neuropsychiatric disorders, such as autism and schizophrenia, that show abnormalities within this system (Fornito and others 2009; Santos and others 2011). A working bvFTD model with many testable components is provided in Box 1.

Box 1. Simplified Working Model for Functional-Anatomical Deficits Seen in the Behavioral Variant of Frontotemporal Dementia (bvFTD)

Simplified working model for functional-anatomical deficits of the behavioral variant of frontotemporal dementia (bvFTD). Here we provide a simple model to suggest hypotheses for further bvFTD exploration. This model is neither all-encompassing nor definitive. Evidence to date suggests that bvFTD targets the salience network (colored boxes with rounded edges), beginning in central nodes for social-emotional-autonomic processing, including afferent interoceptive (frontoinsula, FI) and efferent visceromotor (pregenual anterior cingulate cortex, pACC) structures. The afferent salience network processes the major ascending input streams regarding the moment-to-moment condition of the body. This network is closely allied with a ventral valuation/context appraisal system, which includes the 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. When bvFTD begins in FI, socially disinhibited behaviors predominate, especially when the right FI is first affected. The efferent salience network, in contrast, serves to mobilize viscero-autonomic responses to salience, recruit executive and task control resources to guide behavior, and inhibit the default mode network (DMN) to keep attention focused on immediate matters at the expense of internal images from one's personal past or future. Early pACC involvement produces a more apathetic bvFTD phenotype. A subtotal account of candidate von Economo neuron (VEN) projections is shown with blue connector arrows. As large, clustered, layer 5 projection neurons, VENs may enhance long-range cortico-cortical or cortico-subcortical interactions within or between networks. To date, only a projection from pACC VENs into the cingulum bundle (to unknown targets) has been identified (Nimchinsky and others 1999). Arrows indicate excitatory projections, whereas connections 5 and 7 indicate inhibitory interactions. For visual simplicity, laterality issues have been omitted, although laterality may have a major influence on lesion-related symptoms. Predicted intra-hemispheric lesion consequences within the model are detailed below, with numbers corresponding to numbered connections in the figure:



(continued)

Box 1. (continued)

1. FI to pACC: Inability to use feeling states to drive behavior, manifested as inertia (when approach signals are lost) or disinhibition (when avoidance signals are degraded). The correlation of right greater than left FI VEN counts with disinhibition (Kim and others forthcoming) may support the view that avoidance signals are right-lateralized.
2. pACC to FI: May provide a visceromotor "efference copy" to alert the afferent division of the salience network about impending interoceptive changes (akin to comparator mechanisms within the skeletal somatomotor system). Lesion consequence could be failure to anticipate and experience subjective feeling states quickly enough to guide real-life behavior within dynamic social contexts. This efference copy mechanism is related to the notion of "as if" loops within Damasio's (1999) somatic marker hypothesis.
3. FI to valuation/context appraisal network: Detachment of person/object meaning from emotional impact, resulting in reduced emotion recognition and empathy when the right hemisphere is affected.
4. pACC to visceromotor central pattern generators (CPGs): Failure to drive viscero-autonomic responses to salience, resulting in reduced autonomic reactivity to motivating social or asocial stimuli. This deficit could accentuate either apathy or disinhibition, depending on the context.
5. pACC to DMN: Disrupting this inhibitory interaction should enhance DMN activity, possibly resulting in impaired attention to the emotional moment at hand. A previous study (Zhou and others 2010) found DMN connectivity increases in bvFTD that correlated with reduced salience network connectivity in pACC and right FI. Normal inhibition of the DMN could occur via a pACC to posterior cingulate cortex projection (cingulum bundle) or through an as yet unidentified subcortical "switching" node.
6. pACC to executive and task control networks: Reduced recruitment of executive resources for task set maintenance, manifesting as distractibility, impersistence, and problem-solving difficulties.
7. DMN to salience network (not a predicted bvFTD lesion): Disrupting this inhibitory interaction should enhance salience network activity, resulting in increased autonomic responding to salience and intensified feeling states, manifesting as emotional warmth but also anxiety. Increased salience network connectivity in Alzheimer disease has been correlated with reduced DMN connectivity (Zhou and others 2010).

This model also suggests downstream bvFTD targets based on the first-affected region(s): Early FI disease predicts spread to pACC and ventral valuation/context appraisal structures, whereas early pACC involvement predicts spread to FI, subcortical autonomic output nodes, and the executive and task control networks. Anatomical and functional elements of this model were adapted in part from Saper (2002), Craig (2002, 2009b), Heimer and Van Hoesen (2006), Dosenbach and others (2007), and Seeley et al. (Seeley, Allman, and others 2007; Seeley, Menon, and others 2007). cAMY = central nucleus of the amygdala; DMNX = dorsal motor nucleus of the vagus nerve; dPI = dorsal posterior insula; HT = hypothalamus; IML = intermediolateral cell column; midINS = middle insula; NST = nucleus of the solitary tract; PAG = periaqueductal gray; PBN = parabrachial nucleus; vmB = ventromedial nucleus of the thalamus, basal part; vmPO = ventromedial nucleus of the thalamus, posterior part.

Acknowledgments

We thank Stephanie Gaus, Manu Sidhu, Bruce Miller, Michael Greicius, Stephen DeArmond, Robert Levenson, Katherine Rankin, Virginia Sturm, John Allman, A. D. (Bud) Craig, and Patrick Hof for their contributions to the research reviewed here and for helpful discussions related to this work. Finally, we thank our patients and their families for their invaluable contributions to neurodegenerative disease research.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interests with respect to the authorship and/or publication of this article.

Financial Disclosure/Funding

The author(s) disclosed receipt of the following financial support for the research and/or authorship of this article: Research reviewed here was supported by the National Institutes on Aging (grant numbers AG027086, AG03006, AG033017, and AG023501), the James S. McDonnell Foundation, the John Douglas French Alzheimer Foundation, the Larry L. Hillblom Foundation, and the Consortium for Frontotemporal Dementia Research.

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