Selective functional, regional, and neuronal vulnerability in frontotemporal dementia

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Purpose of review

The molecular neuroscience revolution has begun to rekindle interest in fundamental neuroanatomy. Blending these disciplines may prove critical to our understanding of neurodegenerative diseases, which target specific anatomical systems. Recent research on frontotemporal dementia highlights the potential value of these approaches.

Recent findings

The behavioral variant of frontotemporal dementia leads to progressive social–emotional processing deficits accompanied by anterior cingulate and frontal insular degeneration. These sites form a discrete human neural network and feature a class of layer 5b projection neurons, von Economo neurons, found only in large-brained, socially complex mammals. von Economo neurons have been shown to represent an early target in the behavioral variant of frontotemporal dementia but not in Alzheimer's disease.

Summary

Integrative approaches to selective vulnerability may help clarify neurodegenerative disease pathogenesis.

Keywords

anterior cingulate, frontotemporal dementia, insula, von Economo neuron

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Introduction

Selective vulnerability defines neurodegenerative disease. In frontotemporal dementia (FTD) biology, recent discoveries have propelled the field closer to understanding molecular pathogenesis. No clear links have been forged, however, between misprocessed proteins and their associated neuronal, regional, and functional targets. This review highlights an emerging FTD selective vulnerability framework and describes promising approaches for building a more integrated FTD pathogenesis model.

The problem of selective vulnerability: disease model limitations for Alzheimer's disease and frontotemporal dementia

The degenerative dementias represent a heterogeneous class of progressive, treatment-refractory diseases, each defined by selectively vulnerable functions, regions, and neurons that fail in response to complex molecular pathophysiological events. No disease model, however, has forged an explanatory link between molecular pathogenesis and selective vulnerability. This deficiency, though often overlooked by neurodegeneration researchers, may impede progress toward dementia treatments, which will need to begin while the diseases remain incipient and focal.

For Alzheimer's disease (AD), a comprehensive disease model seems nearly within reach. This optimism rests upon a substantial 'knowledge scaffolding', constructed over 30 years of intensive research. Rigorous investigations that today might be criticized as 'descriptive' have shown that AD begins with episodic memory impairment, a specific cognitive deficit that correlates with early synaptic loss [1] and neurofibrillary tangle (NFT) formation in entorhinal cortex layer II pyramidal projection neurons [2]. These neurons die, and NFT formation proceeds along a local circuit of interconnected medial temporal subregions before spreading throughout a large-scale posterior cingulo-temporal-parietal network [3–5]. These fundamental, widely replicated observations have provided an AD pathological staging scheme; facilitated development of AD clinical and neuroimaging biomarkers; enabled recognition of atypical language, visual, and motor presentations of AD; and provided a reference standard for validating AD animal models and testing interventions. Many aspects of AD pathogenesis, therefore, provide a useful foothold for those exploring less well characterized dementias.

FTD rivals AD in prevalence among dementia patients under 65 years of age [6], but the FTD knowledge scaffolding remains far less sturdy and complete. In

Table 1 Current understanding of Alzheimer's disease and frontotemporal dementia selective vulnerability and molecular-genetic features

Syndrome	Early deficit	Early network/region	Early vulnerable neuron	Pathogenic proteins	Genes[a]
AD	Episodic memory	MTL–posterior cingulated–lateral temporoparietal	ERC layer II pyramidal neurons	Aβ42, Tau	*APP*; *PS1; PS2*
bvFTD	Social–emotional function	R > L ACC–frontal insula, frontal pole, amygdala, striatum	VENs?	Tau = TDP-43	*MAPT*; *PGRN*
SD	Semantic knowledge or emotional meaning	L or R temporal pole, amygdala, sACC, frontal insula	Unknown	TDP-43 > Tau	*MAPT*; *PGRN*
PNFA	Motor speech and language fluency	L inferior frontal cortex, precentral insula, striatum	Unknown	Tau > TDP-43	*MAPT*; *PGRN*
FTD–MND	Social–emotional function or motor power	ACC–frontal insula network or bulbar > spinal motor nuclei	VENs? or lower > upper motor neurons	TDP-43	??

ACC, anterior cingulate cortex; AD, Alzheimer's disease; APP, amyloid precursor protein; bvFTD, behavioral variant of frontotemporal dementia; ERC, entorhinal cortex; FTD, frontotemporal dementia; L, left; MND, motor neuron disease; MTL, medial temporal lobe; PGRN, progranulin; PNFA, progressive nonfluent aphasia; R, right; sACC, subgenual ACC; SD, semantic dementia; VEN, von Economo neurons.
[a] Only the most common genetic associations are listed.

particular, mystery surrounds how and where – exactly – FTD begins. Recent anatomical findings suggest, however, that FTD should no longer be viewed as a diffuse 'frontotemporal' disorder. This review will highlight progress toward understanding FTD selective vulnerability and will identify several key questions for future investigation.

Frontotemporal dementia syndromic, pathological, and genetic taxonomy

Table 1 highlights the functions, regions/networks, neurons, molecules, and genes now implicated in AD and FTD. Typical AD presents as an amnestic dementia that relates to medial temporal and posterior cortical involvement. FTD, in contrast, encompasses a small group of anterior syndromes that include a behavioral variant (bvFTD) and two language variants, a fluent aphasia known as semantic dementia that erodes word, object, and emotional meaning, and a progressive nonfluent aphasia (PNFA), which leads to effortful, dysfluent, agrammatic speech [7]. Any of these syndromes, but most often bvFTD, may be accompanied by clinical motor neuron disease (FTD–MND). In addition, clinical corticobasal syndrome (CBS) and progressive supranuclear palsy (PSP) are sometimes grouped with FTD, though their anatomic patterns often lack predominant frontotemporal involvement.

FTD results from underlying frontotemporal lobar degeneration (FTLD), a pathological category united by synapse loss, microvacuolation, reactive astroglial proliferation, and ultimately neuron loss, especially in superficial laminae of anterior brain regions [8]. FTLD subtyping reflects the protein composition of neuronal and glial inclusions, which can be grouped as tau-positive (FTLD-T) or tau-negative. FTLD-T includes Pick's disease, FTDP-17, corticobasal degeneration, PSP, and nonspecific tauopathies. Tau-negative FTLD most often features ubiquitin and TDP-43-immunoreactive intraneuronal inclusions (FTLD-U) [9] but can also show ubiquitinated inclusions containing neuronal intermediate filaments [10] or no known additional inclusion protein. These diverse histopathologies form one category based on their overlapping regional predilections (Table 1), yet no FTLD model explains this anatomical convergence.

Recent genetic discoveries have invigorated the search for FTD treatments and may help to elucidate selective vulnerability mechanisms. Inherited FTLD-T results from mutations in the *MAPT* gene for tau, a widely expressed neuronal protein that binds to and stabilizes microtubules and supports axonal transport [11]. Inherited FTLD-U, in contrast, most often relates to null or missense mutations in the gene for progranulin (*PGRN*), a growth factor associated with cell proliferation, motility, and repair [12,13]. Together, these findings suggest that FTD should target neurons sensitive to cytoskeletal dysfunction, trophic insufficiency, neuroinflammation, or a combination of these factors. Uncommon mutations in genes for the valosin-containing protein (*VCP*) and the charged multivesicular body protein 2B (*CHMP2B*) also produce FTD. With subtle variations, these diverse genetic lesions can all produce the same clinical syndromes, suggesting mechanistic convergence toward a specific neural system or systems. The gene underlying familial FTD–MND, once identified, will add yet another vital clue toward solving the FTD selective vulnerability mystery.

The bvFTD syndrome (with or without MND) accounts for half of all FTD [14] and results equally from FTLD-T and FTLD-U [15]. Comorbid MND often truncates the disease course, providing a unique opportunity to explore early bvFTD pathology [16]. Although the functional and regional vulnerability patterns in bvFTD, semantic dementia, and PNFA overlap (prompting the clinical group label, FTD), mixing these syndromes can be misleading, especially from a quantitative neuroanatomical perspective. For these reasons, our

work, and the remainder of this review, focuses primarily on bvFTD.

Behavioral variant frontotemporal dementia targets the social brain: functional, evolutionary, and developmental considerations

No longer seen as a vague disorder of behavior or personality, the bvFTD syndrome has now been examined within a modern social neuroscientific framework. Early on, patients lose complex social functions, including self-conscious emotions, theory of mind, empathy, metacognitive judgment, and moral sensibility [17••,18,19••, 20•,21]. Some patients even shift long-held core aspects of their personal identity, especially when the right frontal lobe is preferentially affected [22]. These findings suggest specific impairments in the ability to represent the self and others and to use these internal signals to motivate and guide behavior (reviewed in [23]). Comparative neuropsychologists have long suggested that these sophisticated 'social brain' capacities may be phylogenetically restricted – among primates – to great apes and humans [24]. Brain size correlates better with social group size and complexity than with other ecological variables [25], and human toddlers outperform adult chimpanzees on language-independent social cognitive tasks, even while their spatial skills remain equivalent [26]. Intriguingly, socially complex mammals from other lineages, such as elephants and cetaceans, have also evolved large brains and self-representational capacities not seen in lesser apes or monkeys [27,28].

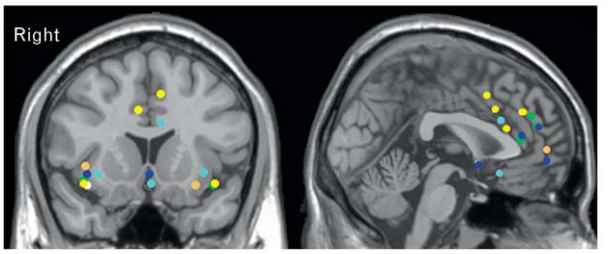
During human development, as in phylogeny, complex self and other-representational capacities emerge late. Infants achieve mirror self-recognition at 15–24 months of age, providing a necessary substrate for self-conscious emotions and other social competencies [29] lost in early bvFTD. Patients with AD, in contrast, score at or near control levels on many of the same social paradigms that have defined the early bvFTD syndrome [18,21]. This comparative-developmental framework has motivated our bvFTD investigations, which explore rapidly evolving human social brain networks, regions, and neurons.

Behavioral variant frontotemporal dementia targets the social brain: selective anterior cingulate cortex–frontal insula network injury

Pathological and neuroimaging studies have begun to reveal the striking focality of early bvFTD. Brun and Gustafson [4] first observed that FTD affects the pregenual anterior cingulate cortex (ACC), extending back to mid-cingulate cortex, whereas AD involves posterior cingulate regions and spares ACC. Later, on the basis of a small series of early-stage patients, Broe *et al.* [30] proposed that orbital frontal insula and medial frontal cortex (including ACC) represent the sites of earliest atrophy, degenerating in stage 1 of their four-stage gross anatomical FTD staging system. Around the same time, bvFTD neuroimaging studies revealed severe deficits in ACC–frontal insula volume [31,32•], perfusion [33], and serotonin receptor density [34]. These and other studies, combined in a recent meta-analysis [35••], revealed rostral and subgenual ACC, frontal insula (especially on the right), and the frontal pole as the most consistent cortical foci of bvFTD-related degeneration (Fig. 1). Furthermore, ACC and frontal insula deficits best differentiate bvFTD from AD [33,36•] and focally worsen over 1 year in patients with mild disease [37]. Finally, ACC, frontal insula, and the frontal pole stand out within a circumscribed 'network' of regions atrophied in very mild bvFTD [Clinical Dementia Rating Scale (CDR) = 0.5], with or without MND [38•].

What is known about the anatomy, connectivity, and function of ACC and frontal insula? How do these data relate to bvFTD functional–anatomic deficits? Despite their spatial discontinuity, ACC and frontal insula share cytoarchitectonic features that reflect their close kinship. Both regions are agranular paralimbic cortices, with a prominent sublaminated layer 5, that form transition

Figure 1 Converging evidence implicates the anterior cingulate cortex and frontal insula in behavioral variant frontotemporal dementia



ACC and frontal insula local maxima are shown from six neuroimaging studies, whose major findings are summarized below. For illustration purposes, dots are projected onto single coronal and sagittal slices of the Montreal Neurological Institute (MNI) template brain; therefore, actual maxima may have fallen on neighboring sections of the same plane. ACC, anterior cingulate cortex; AD, Alzheimer's disease; bvFTD, behavioral variant of frontotemporal dementia; CDR, Clinical Dementia Rating Scale; FTLD, frontotemporal lobar degeneration; TBM, tensor-based morphometry; VBM, voxel-based morphometry. ●, bvFTD neuroimaging meta-analysis, Schroeter *et al.* [35••]; ○, bvFTD longitudinal gray matter loss (TBM), Brambati *et al.* [37]; ○, pathological FTLD < AD, gray matter (VBM), Rabinovici *et al.* [36•]; ●, bvFTD CDR 0.5 < controls, gray matter (VBM), Seeley *et al.* [38•]; ○, RFI functional connectivity (fMRI), Seeley *et al.* [45•]; ○, bvFTD overeaters > nonovereaters (VBM), Woolley *et al.* [47•].

zones between primitive allocortex and dysgranular neocortex [39]. In monkeys, connectional and cytoarchitectonic methods have been combined to reveal two dissociable orbitomedial prefrontal cortex networks [40]. One, a 'medial network' includes the ACC complex (areas 24/25/32), frontal insula (areas Iai, 12o), and frontal pole (areas 10m, 10o, and, in humans, 10p). Early affected bvFTD regions belong to this medial network. In contrast, an 'orbital network' includes areas 11, 13, and most of 12, regions atrophied at more severe bvFTD stages [38•]. In monkeys, only the medial network sends robust projections to ventral striatum, hypothalamus, and periaqueductal gray [40], subcortical sites that degenerate in bvFTD [32•,38•]. Based on this organizational scheme, Price and colleagues have updated previous notions that the medial network orchestrates visceral-autonomic responses used to guide behavior [41–43]. Substantial imaging and lesion evidence also links ACC and frontal insula to visceral-autonomic processing in humans (reviewed in [44]), and we have used fMRI to map a healthy human functional intrinsic connectivity network, anchored by right frontal insula, that mirrors primate connectivity and early bvFTD atrophy (Fig. 1) [38•,45•]. In human functional imaging experiments, the ACC and frontal insula coactivate in response to diverse homeostatically salient stimuli and experiences, from pain and thirst to envy and adoration (reviewed in [46]). In bvFTD, right frontal insula atrophy correlates with core clinical symptoms, including loss of empathy and aberrant food intake (Fig. 1) [20•,47•,48], which may reflect failures to integrate visceral guidance cues with behavior.

Microevolution within the anterior cingulate cortex–frontal insula network: von Economo neurons

Previous accounts of FTLD neuronal loss have emphasized superficial laminae (layers 2–3), which exhibit marked synapse loss and reactive gliosis even in early-stage FTD. Most of these studies, however, surveyed the broad bvFTD landscape, before in-vivo neuroimaging data became available to suggest specific early regional targets. Building on ideas outlined in the previous two sections, we have begun to investigate a unique neuronal population buried in the core of the bvFTD regional injury pattern. These cells, now referred to as von Economo neurons (VENs), were first observed by Betz and then Cajal, who referred to an ACC 'layer of spindle cells' [49,50]. von Economo became fascinated by these neurons, scouring the brain for them while compiling his celebrated human cytoarchitectural atlas [51]. Finding this 'peculiar cell type' (p. 706) only in ACC and frontal insula, he presaged that these ancient 'olfactory brain' (p. 712) regions might provide phylogenetically novel maps of the autonomic nervous system, as human 'powers of olfaction have wasted away' [42]. Braak [52] later noted a focal VEN abundance in pregenual ACC, as well as conspicuous lipofuscin pigment content in VENs. Nimchinsky *et al.* [53] first showed that VENs are projection neurons, backfilling VEN somata with Di-I injections into the postmortem human cingulum bundle and reported a lack of VEN calcium-binding protein expression. Recent attempts to find VENs outside ACC and frontal insula have uncovered only rare, scattered VEN-like neurons in layer 5 of area 9 [54], a dysgranular region that degenerates in mild bvFTD [38•].

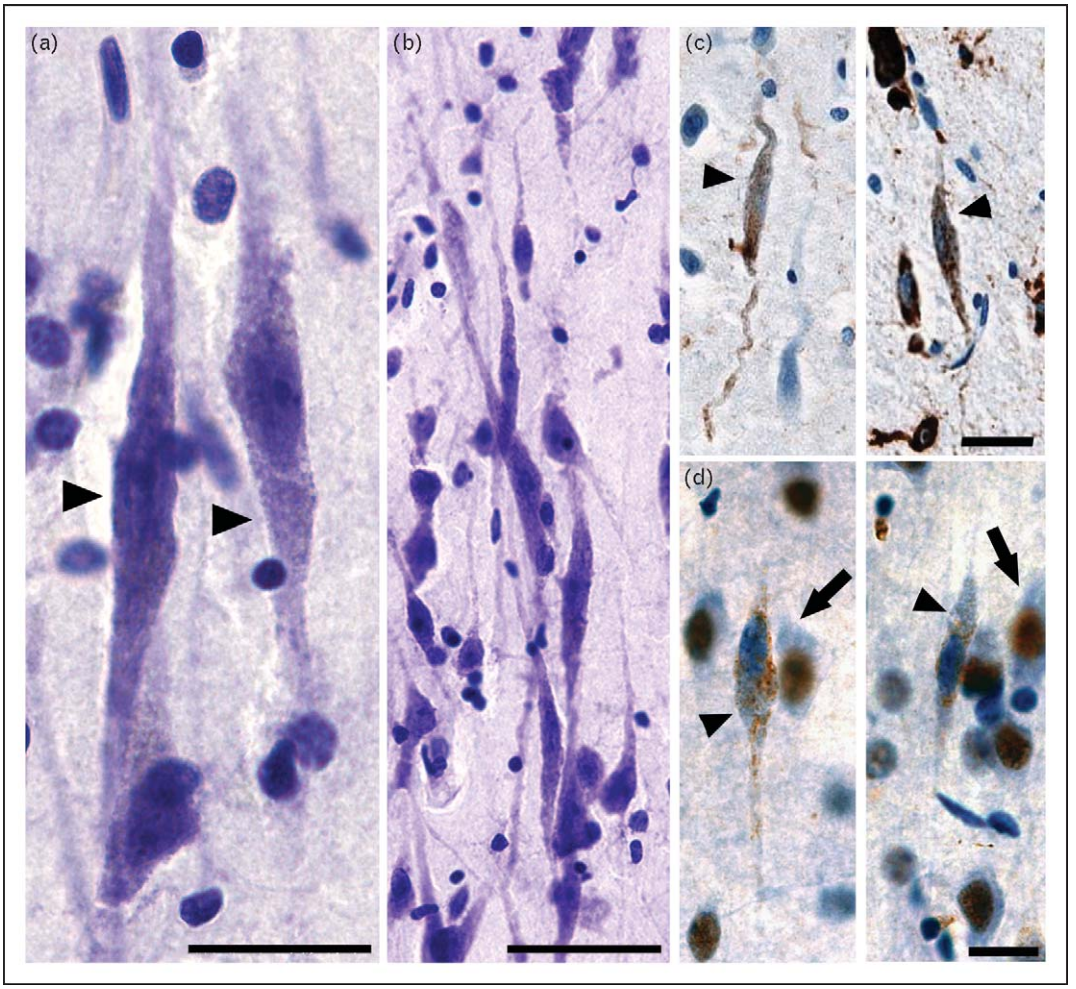
To clarify VEN phylogeny, Nimchinsky *et al.* [55] examined ACC and frontal insula homologues in a diverse array of mammals, including Old and New World monkeys, and identified VENs in only five species: orangutans (few), gorillas (more), common chimpanzees (many), bonobos (frequent, clustered), and humans (abundant, clustered). Selected cetaceans also show VEN-like cells in ACC, frontal insula, and frontal pole [56•] and, most recently, VENs were discovered in ACC–frontal insula homologues of the African elephant [57]. These comparative findings suggest parallel evolution within the most encephalized, socially complex members of three separate mammalian lineages. Most likely, an ancestor common to all VEN-containing species possessed an ACC–frontal insula layer 5 neuronal precursor that can be cued, by specific epigenetic or developmental factors, to differentiate into the VEN morphotype in selected organisms.

VENs are large, bipolar layer 5b neurons whose size and shape distinguish them from neighboring layer 5 pyramidal neurons (Fig. 2a). VEN silver impregnations reveal elongated, sparsely branching apical and basal dendrites, suggesting that VEN clusters may sample from within narrow ACC–frontal insula minicolumns (Fig. 2b) [42,58]. In primates, VENs are 30% more abundant in the right hemisphere, especially in right frontal insula [59•], further supporting a role for these cells in social–emotional function. In light of these findings, we and others have extended prevailing ACC–frontal insula network models to suggest that this circuit has undergone recent evolution and right-lateralization in primates to support conscious bodily self-representation [46] and social–emotional salience processing [23,45•,46,60••,61]. In this model, we revise previous concepts of ACC and frontal insula as primitive or 'ancient' regions and suggest that escalating hominoid social selective pressures have driven recent ACC–frontal insula neuronal and functional specialization.

Early von Economo neuron loss in behavioral variant frontotemporal dementia

We hypothesize that VENs, a neuronal class restricted to the ACC–frontal insula network, may represent an initial

Figure 2 Normal von Economo neuron morphology and inclusion pathology in behavioral variant frontotemporal dementia

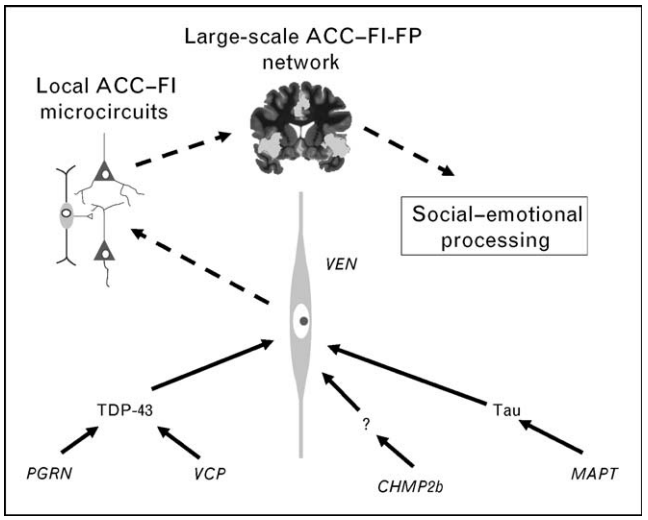


VENs are large bipolar projection neurons (a) that often form vertical clusters of three to six cells (b). Neurologically unaffected control, cresyl violet stain. In patients with bvFTD, (c) Pick's disease (CP-13 antibody for hyperphosphorylated tau) and (d) FTLD-U (TDP-43 antibody) cause similar diffusely speckled disease protein aggregates in VENs (arrowheads in c and d). Surrounding layer 5 pyramidal neurons (arrows in d) show normal nuclear TDP-43 immunoreactivity, which is lost in inclusion-bearing VENs. Scale bars indicate 25 μm (a), 50 μm (b), and 20 μm (c and d). bvFTD, behavioral variant of frontotemporal dementia; FTLD, frontotemporal lobar degeneration; VEN, von Economo neurons.

target in bvFTD, a syndrome associated with focal ACC–frontal insula injury. To begin to test this hypothesis, we performed a quantitative neuroanatomical study of the left ACC [60••]. In bvFTD, we found a 69% reduction in VEN counts after controlling for neighboring layer 5 neuron loss. This VEN selectivity was seen even in patients with early-stage disease. In contrast to bvFTD, late stage AD (Braak stage VI) showed no selective ACC VEN loss, and we have yet to observe VEN NFT formation.

Immunohistochemical studies have begun to reveal an intriguing pattern of FTLD disease protein aggregation in surviving VENs. In Pick's disease, VENs often show swollen somata and diffuse cytoplasmic hyperphosphorylated tau aggregation (Fig. 2c) unlike the spherical Pick bodies seen in small superficial pyramidal neurons. In FTLD-U, initial efforts to identify VEN inclusions were unsuccessful [60••], but recent experiments using thicker (40–50 μm) sections and antibodies to TDP-43 have revealed a striking pattern in which VENs show diffuse, speckled cytoplasmic aggregates with similar morphology to those seen in Pick's disease (Gaus *et al.*, unpublished data; Fig. 2d). These findings suggest that ACC VENs are susceptible to both major FTLD pathological subtypes but are less vulnerable, or perhaps even resistant, to AD pathology. In a subsequent study [23], we used archival whole-brain coronal sections to compare bilateral ACC and frontal insula in two patients, one with mild bvFTD and another with late-stage AD. Summing across all VEN-containing regions, we found a 70% VEN reduction in bvFTD versus AD.

Figure 3 Emerging behavioral variant frontotemporal dementia selective vulnerability model



Diverse molecular abnormalities may converge on a core set of selectively vulnerable neurons, the VENs of the ACC and frontal insula, which anchor dynamic local microcircuits that participate in a large-scale distributed social–emotional processing network. FTLD molecular pathophysiologies may target this system through one or several VEN characteristics that promote their vulnerability. Treatment strategies could be directed toward neuronal or circuit-level survival mechanisms, as well as upstream disease proteins (e.g. TDP-43, tau) and gene products (*PGRN, VCP, CHMP2b*). Dashed lines represent progressive system dysfunction expected to arise from VEN molecular pathophyiology. ACC, anterior cingulate cortex; FI, frontal insula; FP, frontal pole; FTLD, frontotemporal lobar degeneration; VEN, von Economo neurons.

Conclusion

Recent findings have begun to suggest a novel framework for understanding bvFTD selective vulnerability (Fig. 3). Further work is needed to confirm early VEN loss in frontal insula, assess laterality and stage effects, and explore the relationship between VEN loss and pathology in superficial layers, where VEN apical dendrites ramify. Quantitative TDP-43 and tau immunohistochemical studies may clarify the stage at which VENs first manifest selective vulnerability and identify symptoms that accompany these incipient pathological changes. Cell-specific gene and protein expression profiling in humans could help to define ACC–frontal insula VEN homologues in species that lack VENs but remain more amenable to basic biological and disease-modeling approaches. Broadly, neurodegenerative disease models will benefit from keen attention to the genetic, molecular, and environmental factors that build neural systems during development and render them vulnerable to neurodegenerative disease.

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I have no conflicts of interest or other relevant disclosures.

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- •• of outstanding interest

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