Handbook of Clinical Neurology, 3rd Series

Title: Neurodegenerative disorders of the human frontal lobes

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Abstract

The frontal lobes play an integral role in human socioemotional and cognitive function. Sense-of-self, moral decisions, empathy, and behavioral monitoring of goal-states all depend on key nodes within frontal cortex. While several neurodegenerative diseases can affect frontal function, frontotemporal dementia (FTD) has particularly serious and specific effects, which thus provide insights into the role of frontal circuits in homeostasis and adaptive behavior. FTD represents a collection of disorders with specific clinical-pathologic correlates, imaging, and genetics. Patients with FTD and initial prefrontal degeneration often present with neuropsychiatric symptoms such as loss of social decorum, new obsessions, or lack of empathy. In those patients with early anterior temporal degeneration, language (particularly in patients with left-predominant disease) and socioemotional changes (particularly in patients with right-predominant disease) precede eventual frontal dysregulation. Herein, we review a brief history of FTD, initial clinical descriptions and the evolution of nomenclature. Next, we consider clinical features, neuropathology, imaging, and genetics in FTD-spectrum disorders in relation to the integrity of frontal circuits. In particular, we focus our discussion on behavioral variant FTD given its profound impact on cortical and subcortical frontal structures. This review highlights the clinical heterogeneity of behavioral phenotypes as well as the clinical-anatomic convergence of varying proteinopathies at the neuronal, regional, and network level. Recent neuroimaging and modeling approaches in FTD reveal varying network dysfunction centered on frontal-insular cortices, which underscores the role of the human frontal lobes in complex behaviors. We conclude the chapter reviewing the cognitive and behavioral neuroscience findings furnished from studies in FTD related to executive and socio-emotional function, reward-processing, decision-making, and sense-of-self.

Introduction

Many neurodegenerative diseases affect human frontal lobe function to varying degrees. Among neurodegenerative disorders, the most profound insult to prefrontal function occurs in frontotemporal dementia (FTD), which is a collection of disorders with specific clinical-pathologic correlates, imaging, and genetics (Miller, 2014). Behavioral and cognitive changes in FTD yield insights into the neurologic basis of socioemotional function, theory-of-mind, and decision-making. Patients with initial frontal lobe degeneration present with neuropsychiatric symptoms such as diminished emotional responsiveness, social dysdecorum, or new obsessions. In those with initial temporal lobe lesions, dominant anterior temporal involvement leads to loss of semantic knowledge while non-dominant anterior temporal disease is associated with social-behavioral changes. Core FTD-spectrum disorders include: behavioral variant frontotemporal dementia (bvFTD), semantic variant primary progressive aphasia (svPPA, also called semantic dementia), and nonfluent/agrammatic primary progressive aphasia (nfvPPA).

Neurodegenerative diseases generally involve ineluctable and targeted spread of misfolded proteins with associated inclusions, synaptic dysfunction and loss, and neuronal loss. However, despite many overlapping and shared mechanisms the underlying pathological causes are variable both within and across clinical syndromes. For example, at least 15 different pathologies have been associated with bvFTD (Seeley, 2017). Frontotemporal lobar degeneration (FTLD) refers to these heterogenous neuropathologic entities that cause degeneration of the frontal and/or temporal lobes. FTLD is a neuropathologic term used to describe the underlying neurodegenerative process, while the term FTD describes the clinical syndromes. The nomenclature requires separation given the phenotypic diversity and neuropathologic heterogeneity across conditions. Herein we focus our review on frontal and frontotemporal

variants with concise mention of other neurodegenerative conditions to impact frontal circuit function, such as Alzheimer's disease (AD) and FTD-spectrum conditions such as frontotemporal dementia with motor neuron disease, progressive supranuclear palsy, and corticobasal syndrome.

After a brief historical introduction to FTD, we review the epidemiology, cardinal clinical features, imaging, neuropathology, and genetics of FTD. This review highlights the clinical heterogeneity of behavioral phenotypes as well as the clinical-anatomic convergence of varying proteinopathies at either the neuronal, regional, or network level. Recent neuroimaging and modeling approaches in FTD reveal varying network dysfunction centered on frontal-insular cortices. Brain connectivity studies in conjunction with behavioral and pathologic correlations have led to the development of testable models of functional-anatomic deficits and new insights for the cognitive neurosciences. We conclude by surveying these insights furnished by FTD research related to executive and socio-emotional function, reward-processing, decision-making, and sense-of-self.

Brief History of FTD

The Czech neurologist Arnold Pick first described FTD in 1892 (Pick, 1892). In a series of publications he described patients with focal lesions of the frontal and temporal lobes that impacted language and behavior. Pick's initial case descriptions led a paradigm shift in the scientific understanding of dementia, which held the cause of all dementia to be a senile process (Thibodeau and Miller, 2013). By 1911, Alois Alzheimer identified unique neuropathologic substrates in Pick's original cases by describing "balloon cells" and argyrophilic neuronal

inclusions in patients with so-called “Pick’s disease” (Alzheimer, 1991). Pick’s pupils later histologically differentiated Pick bodies from Pick balloon cells (Onari and Spatz, 1926; see *Figure 21.1*). By the late 1920s additional cases of Pick’s disease were described with more behavioral features, such as apathy, inertia, and impulsivity (Schneider, 1927; Schneider, 1929).

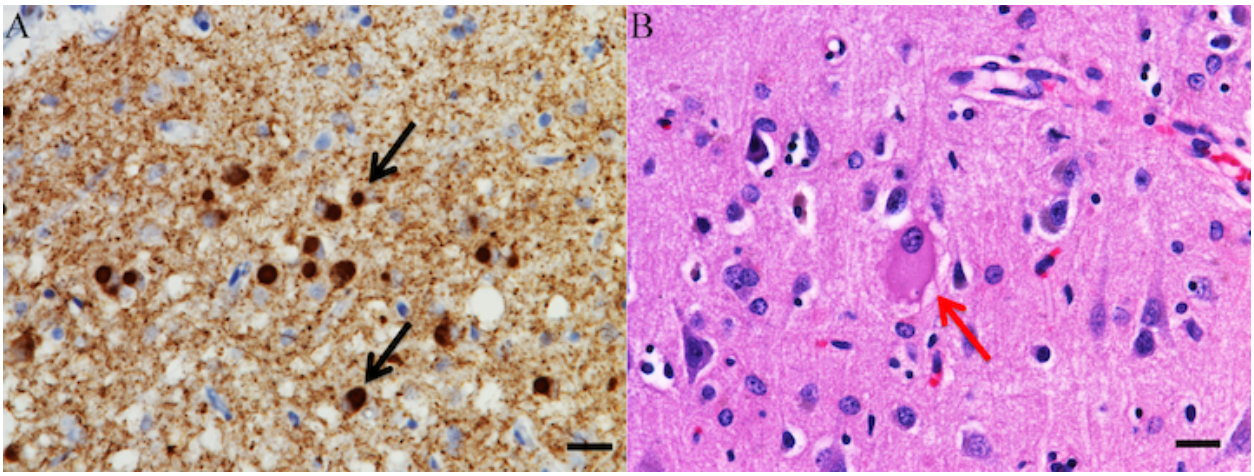

Fig. 21.1. Neuropathologic slides showing Pick cells and Pick bodies. Panel (A) demonstrates Pick bodies (black arrow), which are 3R tau-containing cytoplasmic inclusions that also demonstrate positive silver staining. Panel (B) displays a swollen neuron, also described as a balloon cell (red arrow). The ballooned neuron is from the middle frontal gyrus of a recent case with corticobasal degeneration. Bar¼25mm. Pathology pictures are courtesy of Salvatore Spina, MD, PhD, Memory and Aging Center, UCSF

A seminal article from 1957 published in French by Delay, Brion, and Escourolle made clear anatomical and clinical distinctions between FTD and AD (Thibodeau and Miller, 2013). These authors were amongst the first to detail FTD subtypes, time frames for clinical progression, and etiopathogenesis. The advent of neuroimaging techniques increased the scientific understanding of FTD. For example, regional cerebral blood flow was shown to be decreased in the frontal lobes of patients with neuropsychiatric symptoms and progressive

cognitive decline (Ingvar and Gustafson, 1970; Brun, 1987). Marcel Mesulam identified subtypes of FTD patients with language deficits and coined the term "primary progressive aphasia" (Mesulam, 1982, 2001). The first research criteria for FTD were developed in the 1990s with classifications for bvFTD, svPPA, and nfvPPA (Neary *et al.*, 1998). Additional advances in genetics, neuroimaging and clinical-pathological correlates led to the most recent revised FTD-criteria (Gorno-Tempini *et al.*, 2011; Rascovsky *et al.*, 2011).

The development of reliable diagnostic clinical criteria helped adumbrate FTD's epidemiologic landscape. While AD is the most common cause of neurodegenerative disease in patients over the age of 65, FTD rivals AD for incidence and prevalence in patients ages 45-64 years (Ratnavalli *et al.*, 2002; Goldman *et al.*, 2005; Mercy *et al.*, 2008). The annual incidence of FTD is between 1.6-4.1 cases per 100,000 individuals (Coyle-gilchrist *et al.*, 2016). The prevalence is estimated at 10-20 per 100,000 (Onyike and Diehl-Schmid, 2013). Important to note, however, these numbers likely underestimate the true incidence/prevalence given the under-diagnosis of FTD due to overlap with other more common neuropsychiatric illnesses (Woolley *et al.*, 2011). Typical range for age-of-onset in FTD is from 45-64 years with cases described in younger and older individuals (Snowden, Neary and Mann, 2002; Neary, Snowden and Mann, 2005). Men and women are equally affected by FTD (Hogan *et al.*, 2016). In comparing frequency of FTD subtypes, bvFTD is three to four times more prevalent than PPA.

Behavioral variant frontotemporal dementia

Patients with bvFTD are typically brought to the attention of clinicians by family members concerned by changes in personal conduct and behavior. The condition steadily

undermines normal emotional reactivity, social behavior, and decision-making. Consider the following case: A right-handed, highly educated male presented with changes in behavior beginning in his early 50s which led to significant financial troubles for his family. He shifted away from a life-long history of measured financial prudence to that of gullibility and erratic spending. He succumbed to "get-rich-quick" schemes, hoarded flea-market castoffs and eventually bankrupted his family without insight into the implications of his decisions. In time he became emotionally distant and apathetic. Neuroimaging demonstrated focal frontal and temporal lobe atrophy in the right greater than left hemisphere (see *Figure 21.2).*

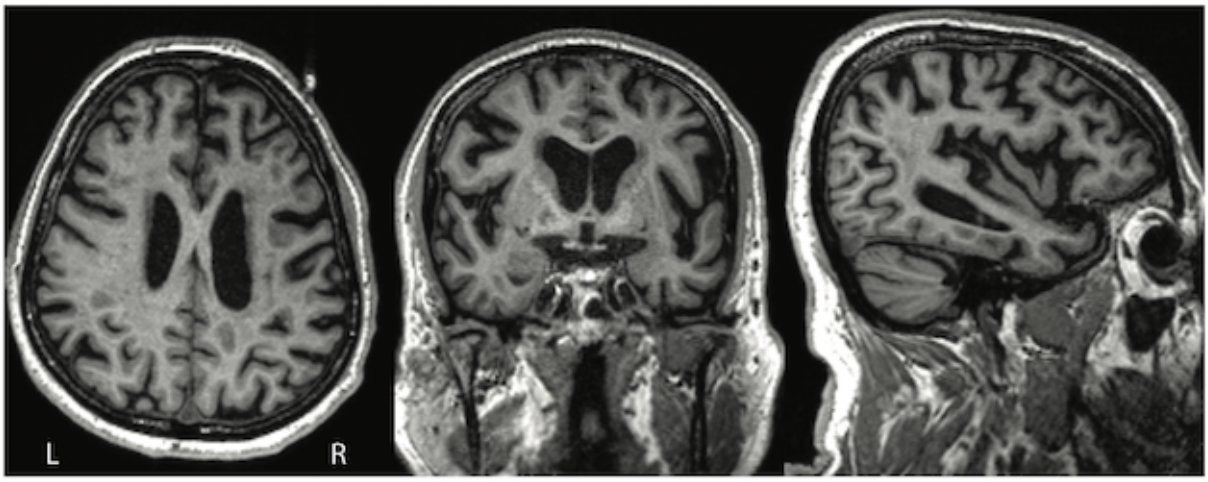

Fig. 21.2. MRI scan of a patient with bvFTD. T-1 weighted axial, coronal, and sagittal MRI images of a right-handed man in his early 60s who presented initially with loss of empathy, compulsive purchasing of books and kitchenware at garage sales, and increased gullibility, giving money away to "get-rich-quick" schemes. Note the loss of frontal volume, slightly worse on the right than left. Right–left orientation is in neurologic convention. Per imaging protocol, a small, hyperintense extracranial vitamin E capsule (seen on the axial scan) was used to mark the direction of the scan.

Table 21.1 Diagnostic criteria for behavioral variant frontotemporal dementia (Rascovsky *et al.*, 2011)

Diagnostic Criteria for behavioral variant frontotemporal dementia

I. Possible bvFTD: Three or more of the following (a-f) must be present, persistent or recurrent with progressive deterioration in behavior and/or cognition based on observation or history

- a. Early behavioral disinhibition
  - a.1. Socially inappropriate behavior
  - a.2. Loss of manners or decorum
  - a.3. Impulsive, rash or careless actions
- b. Early apathy or inertia
- c. Early loss of sympathy or empathy
  - c.1. Diminished response to other people's needs and feelings
  - c.2. Diminished social interest, interrelatedness or personal warmth
- d. Early perseverative, stereotyped, or compulsive/ritualistic behavior
  - d.1. Simple repetitive movements
  - d.2. Complex, compulsive, or ritualistic behaviors
  - d.3. Stereotypy of speech
- e. Hyperorality and dietary changes
  - e.1. Altered food preference
  - e.2. Binge eating, increased consumption of alcohol or cigarettes
  - e.3. Oral exploration or consumption of inedible objects
- f. Neuropsychological profile: executive/generation deficits with relative sparing of memory and visuospatial functions
  - f.1. Deficits in executive tasks
  - f.2. Relative sparing of episodic memory
  - f.3. Relative sparing of visuospatial skills

II. Probable bvFTD: All of the following symptoms must be present

- a. Meets criteria for "Possible bvFTD"
- b. Exhibits significant functional decline by caregiver report or clinician assessment
- c. Imaging results consistent with bvFTD
  - c.1. Frontal and/or anterior temporal atrophy on MRI or CT
  - c.2. Frontal and/or anterior temporal hypoperfusion or hypometabolism on PET or SPECT

III. Definite bvFTD with FTLD pathology: Criterion "a" and either "b" or "c" must be present

- a. Meets criteria for "Possible" or "Probable" bvFTD
- b. Histopathological evidence of FTLD on biopsy or at postmortem
- d. Presence of known pathogenic mutation

IV. Exclusionary criteria for bvFTD: Criterion "a" and "b" must be answered negatively for any diagnosis. Criterion "c" can be positive for possible bvFTD but must be negative for probable bvFTD.

- a. Pattern of deficits is better accounted for by other non-degenerative neurologic or medical illness
- b. Behavioral disturbance is better accounted for by a psychiatric illness
- c. Biomarkers strongly indicate Alzheimer's disease or other neurodegenerative process

Patients with bvFTD exhibit progressive decline in social, emotional and cognitive function. Eventually social, professional, and familial connections are compromised due to the patient's lack of concern for others, loss of social decorum (despite, in many cases, retained knowledge of social mores), and loss of interest in previously valued goals. bvFTD neurodegeneration begins in the pregenual anterior cingulate cortex and frontoinsular cortex (Kim *et al.*, 2012) with accompanying atrophy in the dorsomedial prefrontal cortex, frontal pole, striatum and thalamus (Broe *et al.*, 2003; Seeley *et al.*, 2008).

Clinical criteria for diagnosis of bvFTD (see *Table 21.1*) include early changes in behavior, personality, emotions, and executive control. Cardinal features include early behavioral disinhibition, apathy, loss of sympathy or empathy, perseverative/compulsive behaviors and a shift in eating behaviors. Behavioral disinhibition manifests as social dysdecorum or loss of implicit social knowledge (e.g. overfamiliarity with strangers, telling off-color jokes, or interrupting the minister during a funeral). Other examples of disinhibition include impulsive, rash and careless decision-making with limited regard for enduring consequences. New criminal behaviors are not uncommonly seen in patients with bvFTD (e.g. shoplifting, credit fraud) and are reported in 30-50% of cases (Diehl-Schmid *et al.*, 2013; Liljegren *et al.*, 2015). Dramatic loss of insight regarding the implications of poor decision-making typically accompanies these changes in behavior in patients with bvFTD. The most consistent neuroanatomical correlate of behavioral inhibition is atrophy within the right orbitofrontal cortex (Holroyd *et al.*, 2005).

Apathy in bvFTD may have emotional, cognitive and/or motor aspects. Patients become emotionally indifferent or do not respond to the typical emotional cues from loved ones. Individuals often require prompting from caretakers to start chores or complete activities of daily living. There can be decrease in goal-oriented behaviors or initiative to engage previously

enjoyed tasks. Apathy is easily misdiagnosed as clinical depression. Atrophy with anterior cingulate and medial prefrontal structures correlates with apathy in bvFTD (Rosen *et al.*, 2002; Holroyd *et al.*, 2005).

Patients with bvFTD develop loss of empathy and sympathy. Caretakers describe a loss of personal warmth, decline in displays of spontaneous affection, and selfish behaviors without regard for the feelings of others. Patients appear unaffected by emotional displays of even their closest family. Loss of empathy correlates with degeneration of several key nodes, including the right anterior temporal lobe (non-dominant hemisphere), right frontoinsular cortex, and right subgenual cingulate and ventral striatum (Rankin *et al.*, 2006; Seeley, 2010).

bvFTD is associated with perseverative, stereotyped, or compulsive behaviors. These behaviors range from simple, repeated motor movements, such as finger tapping or scratching, to more complex rituals (e.g. avoiding cracks in the concrete when walking). Stereotypies of speech with repeated, empty "stock phrases" (e.g. "Sure, why not?") occur as the disease progresses. Ritualistic behaviors may involve altered belief states associated with reward. For example, a patient with bvFTD sat for hours each day by the window awaiting the delivery of mail with the hope the *Publishers Clearing House* sweepstakes team would arrive with prize winnings. Voxel-based morphometry studies comparing patients and controls demonstrate that obsessive-compulsive behaviors correlate with bilateral globus pallidus, left putamen, and right greater than left anterolateral temporal cortices (Perry *et al.*, 2012). Repetitive motor behavior correlates with right dorsal anterior cingulate, bilateral premotor and supplementary motor cortices (Holroyd *et al.*, 2005). Degeneration of the striatum is associated with simple motor stereotypies (Josephs *et al.*, 2008).

Eating behaviors frequently shift in the setting of bvFTD illness. The most common change is a shift toward sweets/carbohydrates or other quick sources of calories. Patients often gain weight. In other cases patients exhibit unrestrained eating behaviors apparently lacking the able to modulate behavior based on negative reward signals (Woolley *et al.*, 2007a; Perry *et al.*, 2012). Other changes in eating behavior include: indiscriminate eating, grabbing food from the plates of others, hastily eating without use of utensils, and hyperorality with oral exploration of non-edible objects. Shift in dietary preference and eating behaviors are correlated with regional neuronal loss within the orbitofrontal (right>left), right insula, striatum, and hypothalamus (Woolley *et al.*, 2007b; Piguet, 2011). Changes in eating behavior can overlap with symptoms of obsessions/compulsions. For example, patients' food repertoire may narrow with rigid focus on certain meals (e.g. fruit smoothie for breakfast daily for months). Atrophy of right anterior temporal structures is correlated with ritualistic and focused food interests (Henry *et al.*, 2014).

Given the clinical and pathologic heterogeneity of FTD, regions of initial focal atrophy help with correlation of symptoms. Structural neuroimaging with MRI and/or CT in bvFTD demonstrates symmetric or asymmetric frontal and/or anterior temporal atrophy. Hypoperfusion or hypometabolism of frontal or anterior temporal regions can be apparent on single photon emission computed tomography (SPECT) or positron emission tomography (PET) imaging, respectively (Suárez *et al.*, 2009). In subclinical and early clinical stages of disease however, circuit dysfunction at the cellular level typically lacks identifiable structural neuroimaging correlates based visual inspection or voxel-based comparisons with controls (Seeley, Zhou and Kim, 2012). Dystrophic neurites and local synapse loss elude radiographic detection. As the disease progresses, macroscopic patterns of atrophy emerge (see *Figure 21.2*).

Neuropsychological testing early in the bvFTD disease course often times merely shows subtle dysexecutive function (Gregory, Serra-Mestres and Hodges, 1999). As frontal lobe disease and circuit dysfunction progress, cognitive impairment is mediated by dorsolateral prefrontal, anterior cingulate, and frontostriatal loop dysfunction (Kramer *et al.*, 2003). Degree of deficits in composite measures of executive function and episodic memory on neuropsychological testing may aid in distinguishing between bvFTD and atypical AD (Ossenkoppele *et al.*, 2015).

Primary progressive aphasias

Patients with slowly progressive language dysfunction and degeneration of dominant hemisphere fronto-temporal structures exhibit symptoms of the less common subtype of FTD, known as primary progressive aphasia (Mesulam, 1982). Based on work from Mesalum, Gorno-Tempini and others, the primary progressive aphasias have been divided clinically into semantic variant primary progressive aphasia (svPPA), non-fluent/agrammatic variant primary progressive aphasia (nfvPPA), and logopenic variant primary progressive aphasia (lvPPA) (Gorno-Tempini *et al.*, 2004, 2011). lvPPA patients is nearly always caused by Alzheimer's pathology with focal degeneration of the dominant hemisphere posterior temporal/inferior parietal areas (Mesulam *et al.*, 2008; Rabinovici *et al.*, 2008). Patients present with word-finding trouble and later develop deficits in repetition and comprehension with preservation of motor speech (Mesulam *et al.*, 2008). Given the connection between lvPPA and AD with more posterior dominant hemisphere atrophy, then this chapter will focus more on the progressive aphasias with greater impact on human frontal and temporal lobe function. As subtypes of FTD, svPPA and nfvPPA are discussed in greater detail below.

Semantic variant primary progressive aphasia

The original FTD patient described by Pick in the late 19th century would likely be diagnosed as svPPA with today's nomenclature. Early deficits in patients with svPPA include word-finding trouble, object naming deficits, and loss of comprehension of uncommon concepts (e.g. dromedary camel vs. dog) (Gorno-Tempini *et al.*, 2011). A slowly progressive loss of semantic knowledge ensues over months to years with loss of anterior and inferior temporal structures of the dominant hemisphere (see *Figure 21.3*).

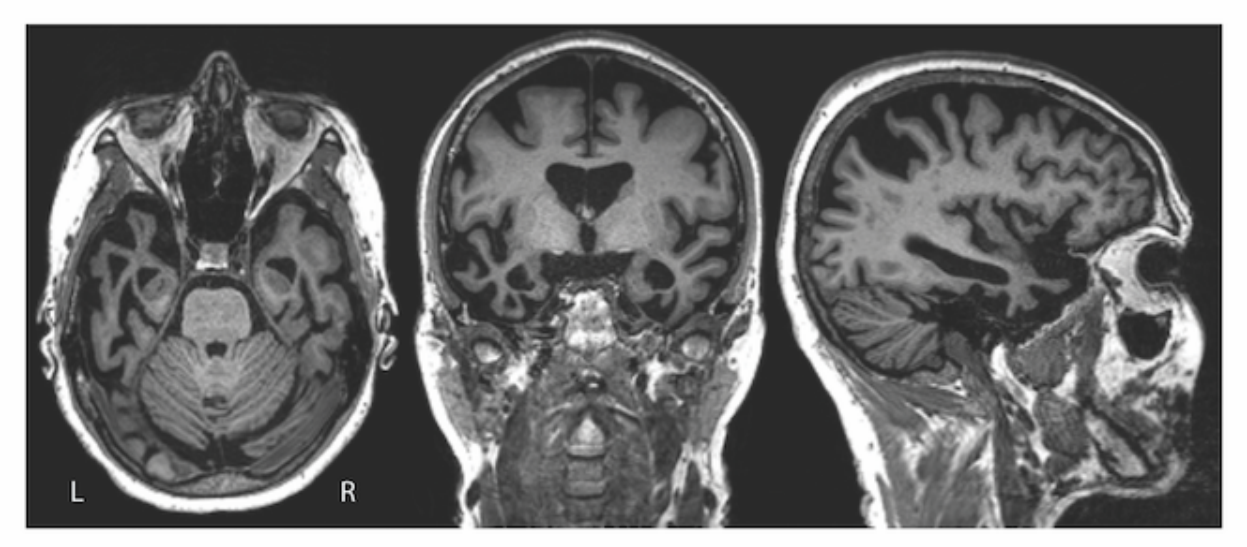

Fig. 21.3. MRI scan of a patient with semantic variant PPA. T-1 weighted axial, coronal, and sagittal MRI images of a 65-year-old right-handed woman who presented with 4 years of language problems marked initially by word-finding and naming difficulties (e.g., calling a "cow" a "bull") progressing to trouble comprehending the meaning of certain concepts. Note the prominent left anterior and inferior temporal atrophy. Note right–left orientation is in neurologic convention.

Table 21.2 Diagnostic criteria for semantic variant primary progressive aphasia (Gorno-Tempini *et al.*, 2011)

Diagnostic Criteria for semantic variant primary progressive aphasia
I. Clinical diagnosis of semantic variant PPA Both a and b must be present a. Impaired confrontation naming b. Impaired single-word comprehension At least 3 of c-f must be present c. Impaired object knowledge, particularly for low frequency words d. Surface dyslexia or dysgraphia e. Spared repetition f. Spared motor speech production and grammar
II. Imaging supported semantic variant PPA Both a and b must be present a. Clinical diagnosis of semantic variant PPA b. Imaging must show at least one of the following: b.1. Predominant anterior temporal lobe atrophy b.2. Predominant anterior temporal hypoperfusion or hypometabolism on SPECT or PET
III. Semantic variant PPA with definite pathology Criterion "a" plus either "b" or "c" must be present a. Clinical diagnosis of semantic variant PPA b. Histo pathological evidence of a specific neurodegenerative pathology (e.g. FTLD-tau, FTLD-TDP) c. Presence of known pathogenic mutation

Table 21.2 reviews the diagnostic criteria for svPPA. A slowly progressive anomia is the cardinal feature of svPPA with relative preservation of verbal fluency. Confrontation naming deficits are present typically without significant improvement from phonemic or semantic cueing on tests such as the Boston Naming or Neuropsychological Assessment Battery (Kramer *et al.*, 2003). Comprehension of single words is impaired usually with loss of object knowledge for

lower frequency items first. Many svPPA patients exhibit surface dyslexia or dysgraphia (Gorno-Tempini *et al.*, 2011). Surface dyslexia is loss of knowledge of pronunciation for irregularly spelled terms, such as "gnat" or "knight." Patients default to core phonetic rules, such as pronouncing "gnat" as "gah-nat." Surface dysgraphia is the inability to spell irregular terms, such as spelling "yacht" as "yot." Patients largely retain motor speech function and echoic memory with preservation of phrase repetition (Gorno-Tempini *et al.*, 2004).

Compared to other types of FTD, svPPA progresses more slowly with on average five to seven years of left anterior temporal degeneration before left frontal and contralateral frontotemporal structures are significantly compromised (Seeley *et al.*, 2005). Mean survival for svPPA patients is nine to ten years following diagnosis, which is notably longer than with other FTD syndromes (Coyle-gilchrist *et al.*, 2016). Handedness and/or learning disabilities may play a role in susceptibility to svPPA. Rates of left handedness or ambidexterity are over-represented in svPPA compared to that expected by chance (Miller *et al.*, 2013). A neurodevelopmental vulnerability to language circuit dysfunction or variations in cerebral lateralization might be an intrinsic risk factor for neurodegeneration within dominant hemisphere language networks. Interestingly, svPPA is the least heritable FTD subtype with rare reports of first- or second-degree relatives with neurodegenerative illness (Hodges *et al.*, 2010).

Neuroimaging shows predominant left anterior temporal atrophy initially (see *Figure 21.3*) and in time inferior and posterior temporal cortices degenerate alongside left-sided frontoinsular and ventromedial frontal cortex. After several years of initial symptoms and focal dominant hemisphere parenchymal volume loss, then contralateral structural neurodegeneration leads to behavioral symptoms, such as compulsions, impaired facial recognition, disinhibition, and altered food preference (Seeley *et al.*, 2005). Obsessions typically revolve around

visual/tactile stimuli rather than verbal/semantic activities. For example, patients can become obsessed with collecting objects like coins or postcards, exhibit new artistic/aesthetic interests such as with painting or sculpting, or adopt new hobbies like gardening or woodworking (Miller *et al.*, 1998; Miller *et al.*, 2000; Seeley, Matthews, *et al.*, 2008).

In temporal variant FTD symptoms can initially differ based on side of onset, but will eventually converge after sufficient time with contralateral spread and degeneration. FTD patients with initial focused atrophy in dominant (left) hemisphere anterior temporal structures exhibit primary language deficits (see *svPPA* above) whereas initial right anterior temporal degeneration causes behavioral changes. Right temporal variant, non-dominant hemisphere FTD patients exhibit early loss of empathy, emotional distancing, mood irritability, and shift toward rigid fixations in appetitive feeding or sexual behaviors (Seeley *et al.*, 2005). Alongside the decline in empathy is loss of social pragmatics, such as difficulty reading other's interest in a conversation and detecting non-verbal cues of disinterest (Rosen *et al.*, 2002). After initial anterior temporal atrophy, dysfunction within ventromedial frontal, insular, and inferior temporal cortices follows and spreads to contralateral cerebral structures of the dominant hemisphere. Right temporal variant FTD patients can display heightened interest in games with words or symbols (Seeley *et al.*, 2005) possibly due to imbalance in hemispheric function with a left temporal "release phenomenon." Evidence from case-control studies suggest two distinct clinical subtypes of right temporal variant FTD might predict underlying pathology (Josephs and Knopman, 2009). Right temporal variant patients to present with personality changes and socially inappropriate behaviors are more likely on neuroimaging to demonstrate greater right frontoinsular and temporal atrophy due to neurodegeneration from tau-proteinopathy (Josephs and Knopman, 2009). Right temporal variant FTD patients who present with prosopagnosia

(facial recognition deficits), word-finding and comprehension trouble, and/or topographagnosia (inability to spatially orient by landmarks) are more likely on neuroimaging to exhibit prominent right anterior temporal and fusiform atrophy and underlying neurodegeneration due to transactive response DNA binding protein 43 (TDP-43) positive inclusions and proteinopathy. This finding converges and overlaps with svPPA neuropathology (see *Neuropathology of FTLD* below).

Non-fluent/agrammatic variant primary progressive aphasia

Whereas motor speech abilities are relatively preserved in svPPA, difficulties with verbal fluency are the presenting features in nfvPPA. Initially, nfvPPA patients experience non-specific word-finding difficulties with pauses and hesitation in speech. Within months to years of sub-clinical language changes patients exhibit errors in expressive speech function marked by slowed or effortful speech often times with speech sound errors (e.g. "*gar*" substituted for "*car*") and altered prosody (Rosen *et al.*, 2002; Gorno-Tempini *et al.*, 2004).

Clinical criteria for diagnosis of nfvPPA are listed in *Table 21.3*. Patients display progressive decline in expressive language function with preservation of object knowledge. Deficits on confrontational naming tasks are aided by cues with phonemic or semantic information, suggesting relatively preserved semantic networks. Simplified and/or agrammatic speech, apraxia of speech, and speech distortions are variably present in patients' spontaneous language. Sentences and utterances shorten and syntax becomes simplified. Missing connector phrases (e.g. *within* or *atop*) and pronoun substitutions (e.g. *him* instead of *her*) give way to altered verb conjugation. Eventually comprehension of syntactically complex sentences declines.

Table 21.3 Diagnostic criteria for nonfluent/agrammatic variant PPA (Gorno-Tempini *et al.*, 2011)

Diagnostic Criteria for nonfluent/agrammatic variant primary progressive aphasia
IV. Clinical diagnosis of nonfluent/agrammatic variant PPA At least one of the following core features must be present a. Agrammatism in language production b. Effortful, halting speech with inconsistent speech sound errors and distortions (e.g. apraxia of speech) At least 2 of 3 must be present c. Impaired comprehension for syntactically complex sentences d. Spared single-word comprehension e. Spared object knowledge
V. Imaging supported nonfluent/agrammatic variant PPA Both a and b must be present c. Clinical diagnosis of nonfluent/agrammatic variant PPA d. Imaging must show at least one of the following: b.1. Predominant left posterior frontoinsular atrophy on MRI b.2. Predominant left posterior frontoinsular hypoperfusion or hypometabolism on SPECT or PET
VI. Nonfluent/agrammatic variant PPA with definite pathology Criterion "a" plus either "b" or "c" must be present a. Clinical diagnosis of nonfluent/agrammatic variant PPA b. Histopathological evidence of a specific neurodegenerative pathology (e.g. FTLD-tau, FTLD-TDP) c. Presence of known pathogenic mutation

Neuroimaging with MRI or CT shows focal degeneration in dominant hemisphere inferior frontal and frontoinsular cortices (see *Figure 21.4*). Hypometabolism or hypoperfusion in atrophic regions of left frontoinsular cortex is apparent on fludeoxyglucose (FDG) PET or SPECT imaging, respectively (Mesulam, 2003).

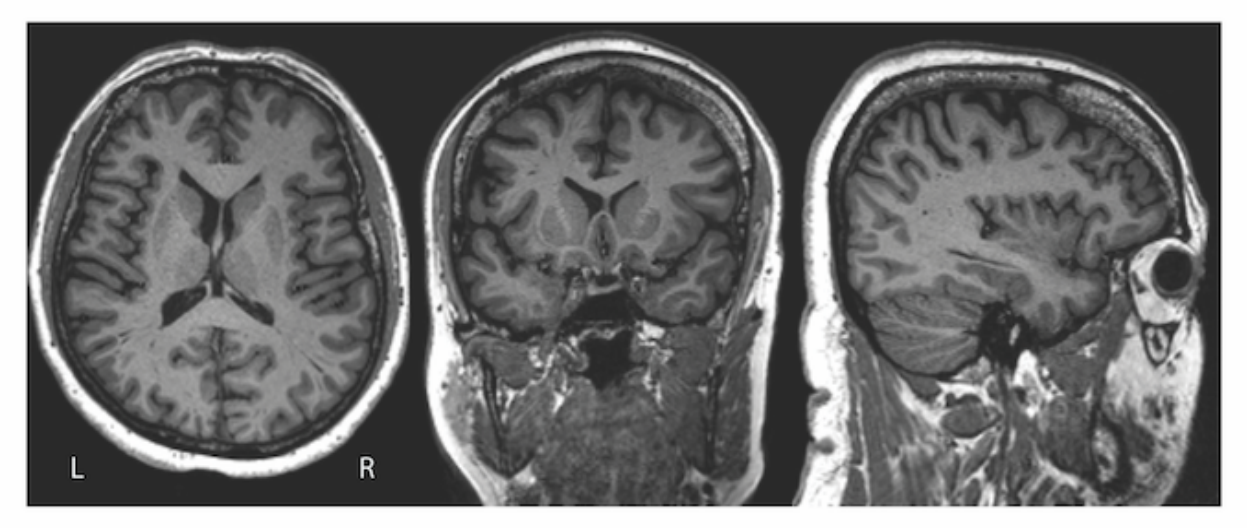

Fig. 21.4. MRI scan of a patient with nonfluent/agrammatic variant PPA. T-1 weighted axial, coronal, and sagittal MRI images of a 66-year-old right-handed man who presented with 6 years of progressive decline in expressive language ability. At first he experienced word-finding trouble and mixed up verb tenses (e.g., "he goed" rather than "he went") and within 5 years became virtually mute. The MRI demonstrates notable atrophy in the left frontoinsular cortices. Note right–left orientation is by neurologic convention.

Neuropathology of FTLD

FTLD pathology involves targeted protein dysfunction and spread which results in gliosis, microvacuolation, synaptic loss and neuronal loss (Brun, 1987). Approximately 90% of FTLD cases are caused by misfolding and protein aggregation of either tau (FTLD-tau) or transactive response DNA binding protein 43-kilodaltons (FTLD-TDP-43) with immunoreactive inclusions (Snowden, Neary and Mann, 2007).

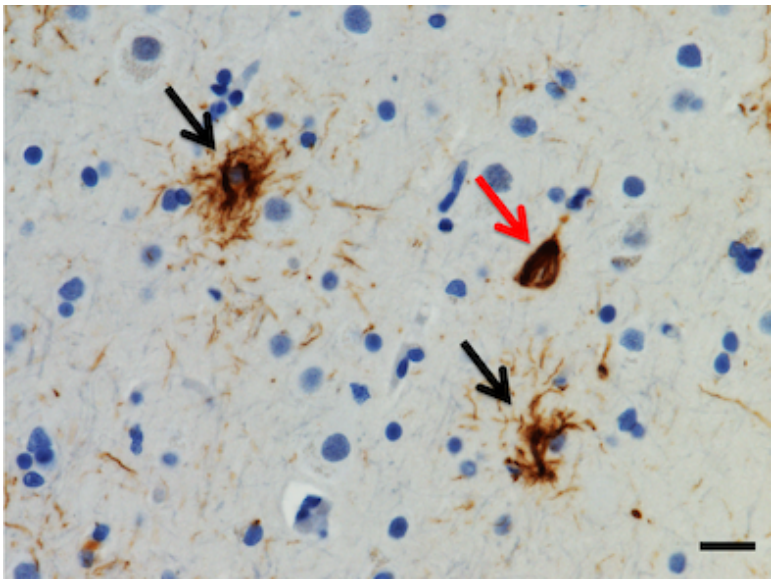

Fig. 21.5. 4R tau with PSP neuropathology. Tufted astrocytes (black arrows) demonstrate 4R tau immunoreactive inclusions proximal to the nuclei. A 4R tau immunoreactive neuronal cytoplasmic inclusion (PSP tangle, red arrow) is adjacent to the tufted astrocytes. 4R-tau inclusions are found in PSP, CBD, argyrophilic grain disease, and globular glial tauopathy. Bar¼25mm. Pathology picture is courtesy of Salvatore Spina, MD, PhD, Memory and Aging Center, UCSF.

Tauopathies are associated with FTLD. Tau is a microtubule-associated protein (MAPT) which plays a fundamental neuropathogenic role in several neurodegenerative diseases. The human brain expresses 6 isoforms of the tau gene product based on alternate splicing in exon 10 of pre-messenger RNA with variable numbers of amino acid repeat. Three-repeat (3R) and four-repeat (4R) isoforms define neuropathologic features of many cases of FTLD (Cairns *et al.*, 2007). For example, Pick's disease is marked by the presence of ballooned neurons known as Pick's cells and so-called Pick's bodies, which are large intraneuronal, round argyrophilic

cytoplasmic 3R tau inclusions (see *Figure 21.1*). 4R-tauopathies include progressive supranuclear palsy, corticobasal degeneration and argyrophilic grain disease (see *Figure 21.5*).

Dysfunctional TDP-43 is the primary proteinopathy in tau-negative, ubiquitin positive FTLD as well as in amyotrophic lateral sclerosis (Arai *et al.*, 2006; Neumann *et al.*, 2006). TDP-43 is a member of the heterogeneous nuclear ribonuclear proteins with features of nucleic acid binding, transcriptional repression, splicing, and translational regulation (Sephton *et al.*, 2011). In neurodegenerative disease, pathologic TDP-43 is in a form that is hyper-phosphorylated, ubiquinated and cleaved. Pathogenic TDP-43 positive inclusions are further classified into four types – Type A-D, in order of incidence type (e.g. Type A is most frequent) and associated cortical layer pathology (Mackenzie *et al.*, 2011). To illustrate, TDP-43 Type C is associated with many long dystrophic neurites in upper cortical layers (II) and relatively few neuronal cytoplasmic inclusions. Type C is associated with svPPA (~90% of cases in UCSF autopsy cohort), which is without known genetic predispositions (see *Figure 21.6*).

While at least 15 types of neuropathological entities are associated with FTLD, most remaining cases are due to protein Fused-in-Sarcoma (FUS; see *Figure 21.6*) with ubiquitin positive, basophilic, or neuronal intermediate filament inclusions (Munoz *et al.*, 2009; Neumann, Rademakers, *et al.*, 2009; Neumann, Roeber, *et al.*, 2009; Urwin *et al.*, 2010). Uncommonly, AD pathology is associated with a bvFTD clinical syndrome.

Genetic Contributions to FTD

Genetics play a prominent role in the cause of FTD. Family history of neurocognitive and psychiatric illness is found in approximately 40% of FTD cases with 10% of cases demonstrating

first-degree relative autosomal dominant inheritance patterns (Chow *et al.*, 1999; Goldman *et al.*, 2005). Mutations coding for the microtubule associated tau protein (MAPT), progranulin (GRN), and C9 open-reading frame 72 (C9orf72) are the most common genes to cause autosomal dominant FTD (Seelaar *et al.*, 2008). Less common causes related to familial FTD include mutations in TARDBP (TDP-43 gene), exostosin glycosyltransferase 2 (EXT2), TANK binding kinase 1 (TBK1), sequestosome 1 (SQSTM1), charged multivesicular body protein 2B (CHMP2B), and valosin-containing protein (VCP), and FUS (Gydesen *et al.*, 2002; Johnson *et al.*, 2010; Fecto, 2011; Mosca *et al.*, 2012; Freischmidt *et al.*, 2015; Pottier *et al.*, 2015).

MAPT mutations in FTD are associated with younger age of symptom onset with relatively symmetric cerebral atrophy often targeting the temporal lobes (Josephs *et al.*, 2009; Whitwell *et al.*, 2012). GRN mutations in FTD are associated with progranulin haploinsufficiency, which is associated with cellular inflammatory/stress response, lysosomal function, and neuronal growth (Ward and Miller, 2011; Petkau and Leavitt, 2014). GRN mutations are associated with later age of onset of FTD symptoms (mean=60 years) with apathy as a prominent symptom, and neuroimaging showing asymmetric frontotemporoparietal atrophy (Rohrer and Warren, 2011; Snowden *et al.*, 2015). GRN carriers most often develop bvFTD, however, nfPPA, corticobasal, and AD clinical phenotypes have been reported (Le Ber *et al.*, 2008). C9orf72 mutations with pathologic hexanucleotide repeat expansions (typically hundreds rather than normal range of 2-23 repeats) are the most frequent cause of inherited FTD-MND (Hosler *et al.*, 2000; Renton *et al.*, 2011). Abnormal hexanucleotide expansion leads to dipeptides and toxic RNA foci which are suspected to contribute to neurodegeneration (DeJesus-Hernandez *et al.*, 2011; Freibaum *et al.*, 2017). C9orf72 mutations are associated with TDP-43 Type B pathology (Mackenzie *et al.*, 2013; Snowden *et al.*, 2015). Mutation carriers may exhibit

psychotic symptoms such as delusions with relative preservation of social pragmatics (Snowden *et al.*, 2012, 2015). Compared to other causes of FTD, C9orf72-related FTD is correlated with atrophy in dorsal frontal, parietal, thalamus, and cerebellum (Sharon *et al.*, 2012; Whitwell *et al.*, 2012).

Changes in brain connectivity in FTD

Patterns of neurodegenerative disease starting with preclinical stages, symptom onset and then progression have neuroanatomic correlates and impact on local and large-scale brain networks. Initially axonal tracer studies in animal models of neurodegenerative disease showed patterns of spreading proteinopathies and neuronal loss, providing early hints about pathophysiological mechanisms (Prusiner, 1984, 2012; Saper, Wainer and Germanii, 1987). Each syndrome features characteristic forms of network-based neurodegeneration (Braak and Braak, 1991). bvFTD selectively impacts frontal function and is associated with changes in frontal network connectivity (Seeley, Zhou and Kim, 2012). In bvFTD, focal degeneration begins in the pregenual anterior cingulate cortex (pACC) and insular cortex (Broe *et al.*, 2003; Seeley, Crawford, *et al.*, 2008). Specifically the cell-types to first manifest changes in bvFTD are von Economo and fork cell neurons of cortical layer five in the pACC and frontoinsular regions in right greater than left (Seeley *et al.*, 2007; Seeley, 2008). By way of comparison, early AD pathology shows neurofibrillary changes in layer two stellate pyramidal neurons of the entorhinal cortex (Braak and Braak, 1995). Comparative animal studies demonstrate that von Economo neurons are distinctive of large-brain social mammalian species, such as cetaceans and simians (Nimchinsky *et al.*, 1999; Hakeem *et al.*, 2009). Not surprising then, early symptoms of bvFTD

are associated with social-emotional dysfunction. Von Economo frontoinsular cell loss correlates with clinical severity and right-sided neuronal injury predicts social and behavioral disinhibition (Seeley, Zhou and Kim, 2012).

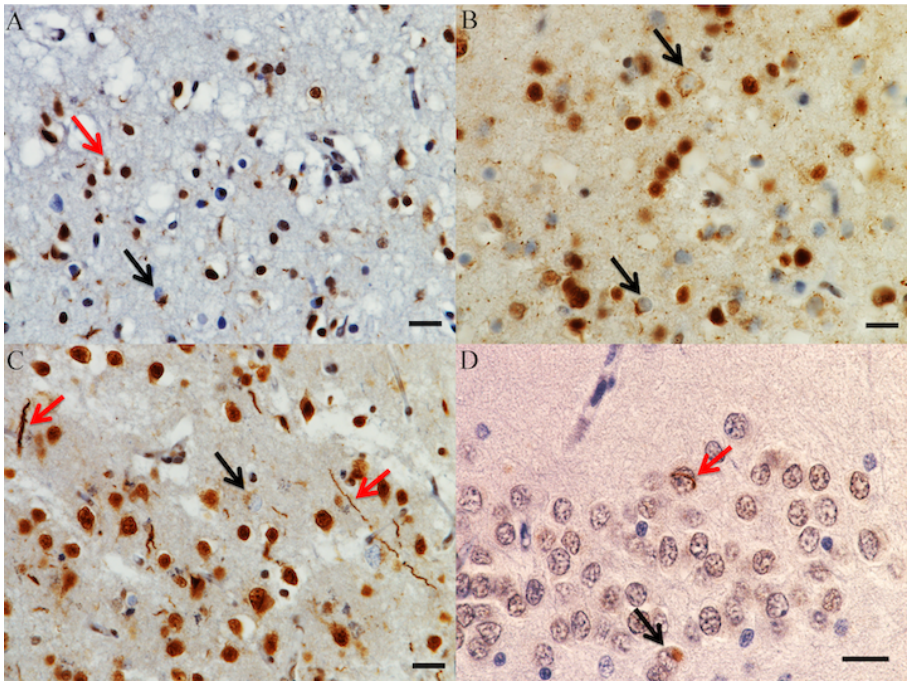

Fig. 21.6. TDP-43 neuropathologic subtypes. (A) TDP-43 type A pathology is depicted, which predominately impacts layer II with many neural cytoplasmic inclusions (black arrow) and short dystrophic neurites (red arrow). (B) In type B, there is a moderate number of "granular" neuronal cytoplasmic inclusions (black arrow) and few dystrophic neurites. (C) Type C pathology is characterized by many long dystrophic neurites (red arrow) and a few neural cytoplasmic inclusions in cortical layer 2. (D) FTLD-U with fused in sarcoma (FUS) pathology demonstrated by FUS immunohistochemistry. Two neurons in the dentate gyrus of a case with sporadic frontotemporal lobar degeneration: one shows a rod-like intranuclear inclusion (red arrow) and the second one a round cytoplasmic inclusion (black arrow). Bar¼25mm. Pathology pictures are courtesy of Salvatore Spina, MD, PhD, Memory and Aging Center, UCSF.

Techniques in structural and functional connectivity analysis have developed in recent years, in parallel with advances in our understanding of bvFTD neuropathology and anatomy (Greicius *et al.*, 2003; Fox and Raichle, 2007). The field of "connectomics" focuses on building brain maps based on structural and functional data to model networks as graphs, representing brain areas (nodes) and connections (edges) (Sporns, Tononi and Kötter, 2005). Major approaches to date include intrinsic connectivity, structural covariance, and structural connectivity (e.g. diffusion weighted imaging). Intrinsic connectivity is established by task-free functional MRI scans (fMRI) to identify temporally synchronous distributed networks based on statistical dependencies of spontaneous, low frequency blood oxygen level-dependent (BOLD) signal changes (Biswal *et al.*, 1995; Raichle *et al.*, 2001; Fox and Raichle, 2007).

fMRI studies of healthy individuals at rest helped demarcate a group of widely replicated networks, including the default mode, salience, dorsal attention, visual, sensorimotor, auditory, and control executive network (Beckmann *et al.*, 2005; Damoiseaux *et al.*, 2006; Seeley *et al.*, 2006, 2009). The salience network was described and explored in healthy neurotypicals, guided in part by focal patterns of atrophy seen in bvFTD in frontoinsular and ACC regions (Seeley *et al.*, 2007). Intrinsic connectivity network maps in healthy young individuals described the so-called salience network, as revealed by the temporal correlation of right insula activity with activity in the bilateral ACC, left frontoinsular, subcortical, limbic, and brainstem areas. This intrinsic functional connectivity matched well with known structural connections established by animal axonal tracer studies (Mesulam and Mufson, 1982; Ongür and Price, 2000). Given previous research showing ACC and insular activity in relation to emotional stimuli, embarrassment, pain perception, disgust, and social cognition, the term "salience network" was adopted for this network (Craig, 2002, 2009a; 2009b; Seeley, Zhou and Kim, 2012).

bvFTD and AD exhibit divergent patterns of salience and default mode network activity (Zhou *et al.*, 2010). Salience network function is disrupted in bvFTD and enhanced in AD, whereas default mode activity is enhanced in parietal regions in bvFTD but weaker in AD. Arterial spin labeled perfusion MRI in FTD (including PPA) shows decreased perfusion in the right frontoinsular area with increased perfusion in biparietal and posterior cingulate cortices (Hu *et al.*, 2010). In patients with AD, perfusion data demonstrate an inverted pattern compared to those with FTD. Default mode and salience network activity are anti-correlated at rest versus tasks, and in FTD and AD there appears to be a reciprocal pattern of relative network change which accentuates with disease progression. Salience network connectivity declines in FTD as a function of disease progression and default mode connectivity increases. In AD, salience network connectivity increases while default mode activity declines. These patterns match with the areas of selectively targeted neuronal loss in early and mid-pathologic stages of the disease (Kim *et al.*, 2012; Seeley, Zhou and Kim, 2012). The structural and functional changes in FTD and AD align with expected clinical deficits from lesions in these areas. AD patients exhibit preservation or even enhancement of personal warmth while this social connectedness and ability to empathize are lost in FTD and bvFTD in particular (Rankin *et al.*, 2006; Mendez and Shapira, 2009). Parietal lobe functions are lost in AD but intact and sometimes enhanced in FTD, such as heightened visuospatial interest, artistic capacities, or spatial orientation (Miller *et al.*, 1998; Seeley, Crawford, *et al.*, 2008; Viskontas *et al.*, 2011).

Brain connectivity studies in conjunction with behavioral and pathologic correlations led to the development of testable models of functional-anatomic deficits in bvFTD (Seeley, Zhou and Kim, 2012). In this view, early neuronal changes in layer five von Economo and fork cell neurons in right more than left frontoinsular and bilateral ACC exert changes over salience

network function and the relative inhibitory balance between default mode and salience networks is disrupted. bvFTD initially impacts pivotal centers for the processing of social, emotional, interoceptive and autonomic information. Moment by moment ascending input feeds into key salience structures (e.g. anterior insular) and is processed in relation to circuits that construct, interpret and weigh the value (hedonic or otherwise) of stimuli (Craig, 2002; Saper, 2002). These constantly updated feeling-states are represented in the frontoinsular cortex in a posterior to anterior gradient (Craig, 2009b) with primary interoceptive data processed in the dorsal posterior insula with increasing energy efficient homeostatic representations extending anteriorly with successive integration of past, present and future goal-states (Craig, 2009a). The efferent limb of the salience network rooted in the pregenual ACC functions to activate visceral and autonomic response (e.g. *dorsal motor nucleus of the vagus nerve*, or *interomediolateral nucleus*) to salient stimuli and mobilize executive control networks (e.g. dorsolateral prefrontal) to guide the individual toward desired goal states without interruption from inhibitory influences of the default mode network (Heimer and Van Hoesen, 2006; Dosenbach *et al.*, 2007; Seeley, Zhou and Kim, 2012).

Loss of connectivity (right>left) from frontoinsular to pACC in bvFTD correlates with disinhibited behavioral patterns (Kim *et al.*, 2012). Breakdown in pACC to frontoinsular reciprocal processing may underlie changes in ability for bvFTD patients to efficiently update feeling-states in order guide behavior appropriately in social contexts. As frontoinsular salience network sites become increasing disconnected from value and context appraisal systems (e.g. *basolateral amygdala, ventral striatum, medial OFC, temporal pole*) then loss of empathy follows especially when the right hemisphere is more impacted. When efferent pACC signals deteriorate then disinhibition gives way to apathy when expected social or emotional stimuli fail

to engender the appropriate visceromotor responses. Additionally loss of pACC to default mode network inhibitory interaction leads to increased default mode baseline activity and impaired attention to the emotional moment (Zhou *et al.*, 2010).

Cognitive and Behavioral Neuroscience of FTD

FTD impacts social, emotional, and executive function. In particular,within the past ten years the behavioral neuroscience of bvFTD has begun to identify neuroanatomic correlates for deficits in theory of mind, reward behavior, language, neuroeconomics and moral decision-making, sense-of-self, and executive function. In this final section we summarize some of the most pertinent findings from the cognitive and behavioral neurosciences to study FTD patients.

Social and Emotional Function in FTD

Change in social comportment is a defining characteristic in bvFTD. The degree of change in social and emotional cognition varies and demonstrates phenotypic heterogeneity. Patients can be divided into subgroups based on initial regional differences in atrophy patterns, including frontal/frontoinsular/temporal (salience network), anterior temporal (limbic/semantic appraisal network), and frontal-subcortical. Patients with salience network and limbic/semantic appraisal network degeneration nearly all exhibit deficits on tasks of social cognition. Patients with greater atrophy in the semantic appraisal network demonstrate trouble with sarcasm detection. Subcortical and frontal-based salience network groups show diminished empathic perspective taking, empathic concern, and personal warmth (Ranasinghe *et al.*, 2016).

Theory of mind (ToM) refers to the capacity to represent and understand mental and emotional states of conspecifics (Premack and Woodruff, 1978). Deficits in ToM in bvFTD is an oft-reported finding with correlates on batteries of social cognition (Henry, Phillips and Von Hippel, 2014). Key nodes to ToM function include medial and lateral prefrontal cortex, temporal-parietal junction, and anterior temporal regions (Carrington and Bailey, 2009).

Critical to ToM abilities, include the ability to detect and represent emotional states of others and couple this with prosocial motivation and appropriate interpersonal behavior to respond to affect sharing. These components to ToM are at least partly dissociable neuroanatomically. Emotion detection, recognition and awareness depend on right>left medial and lateral temporal lobes, amygdala, and insula. Prosocial motivation requires intact nucleus accumbens, caudate head and inferior frontal function (Shdo *et al.*, 2017). Detection of emotions in others presupposes the capability of accurate identification of emotional state in oneself. Dysfunction in bvFTD patient emotional and physiologic reactivity is well documented. For example, when viewing embarrassing or sad video clips, bvFTD patients show attenuated physiologic (e.g. *heart rate, blood pressure, sweat conduction, etc*.) and behavioral emotional reactivity (Sturm *et al.*, 2013). Reduced right-sided pregenual ACC volume in bvFTD patients predicts the degree of deficits in self- versus non-self-conscious emotional reactivity. Insular atrophy correlates with deficits in visceromotor reactivity to disgust in bvFTD patients compared to AD and controls (Verstaen *et al.*, 2016). bvFTD causes abnormalities in detection and response to positive, negative, and self-conscious emotions (Sturm *et al.*, 2008; Goodkind *et al.*, 2015).

Reading emotions of others depends on interest/motivation for mutual face gaze, recognition, and processing of changes in facial expression. Distinct frontal and temporal regions

underlie facial processing (Haxby, Hoffman and Gobbini, 2000). In bvFTD it is unclear whether difficulties in expression recognition are due to perceptual or conceptual dysfunction. In other words abnormal processing might involve aberrant perception and efficient detection of relevant facial expressions or in the conceptual ability to understand meaning of emotional content. The perceptual side at a minimum involves the visual information initially processed in the inferior occipital gyri (early perceptual facial feature detection), superior temporal sulcus (detection of eye or lip movement), and lateral fusiform gyrus (unique facial characteristics). This early perceptual system interfaces with an extended system which includes the intraparietal sulcus (spatially oriented information), auditory cortex (speech perception), limbic system (emotion detection), and anterior temporal (personal identity and biographical information) (Haxby, Hoffman and Gobbini, 2000). Behavioral and neuroimaging evidence from bvFTD suggest the breakdown in facial emotional processing occurs at the level of the extended system rather than at early perceptual levels (Hutchings *et al.*, 2017).

Sense-of-self in FTD

The "self" is a complex concept which has enthralled philosophers and thinkers for centuries. More recently the idea of the self has received attention from neuroscientists. Several neurologic and psychiatric conditions impact patients' sense-of-self, which depends on abstract information about personal attributes extracted from concrete episodic experiences in autobiographic memory and the motivation/desire to maintain a given self-schema (Lewis and Brooks-Gunn, 1979). Development of the self depends largely on frontal lobe function and parallels the maturation and myelination of frontal structures (Stuss and Benson, 1986; Sowell *et al.*, 1999).

Most patients with bvFTD display shifts in personalities with alterations in long-standing values and behavioral patterns. FTD patients with asymmetric loss of right more than left (nondominant) frontal lobe volume exhibit the greatest change in sense-of-self evidenced by dramatic change in well-established patterns of dress, religious or political beliefs (Miller *et al.*, 2001). More specifically, patients with distinct lack of awareness of self and deficits in self-appraisal have greater atrophy within right ventromedial prefrontal cortex (Rosen *et al.*, 2010; Shany-Ur *et al.*, 2014). Patients demonstrate limited insight, concern or understanding regarding their cognitive and emotional deficits (Banks and Weintraub, 2009). Anosognosia and changes in sense-of-self raise ethical concerns about autonomy, decision-making, and moral responsibility as patient expression of values and preference change in time (Chiong, 2013).

Executive Function in FTD

Early in bvFTD, routine clinical neuropsychological batteries may not detect differences in major cognitive domains (e.g. visuospatial, memory, or attention). These measures do not necessarily predict degree of dysfunction in everyday life and raise the question of ecological validity. In a cohort of 104 patients meeting clinical and neuroimaging criteria for bvFTD, 73% presented with initial behavioral symptoms, 1% with motor change, and 26% with cognitive trouble (Ranasinghe *et al.*, 2016). The 26% of cases with initial cognitive complaints were comprised of 16% executive trouble, 6% memory and 4% language changes.

Whether behavioral or cognitive complaints come first in bvFTD patients, the progression of disease exhibits a distinct profile of cognitive decline. At the earliest stages of disease (e.g. Clinical Dementia Rating [CDR] scores of 0.5 or less), bvFTD patients show insensitivity to errors on cognitive testing (error-monitoring), decreased semantic fluency, slower

response times and trouble with confrontational naming with relative preservation of short-term memory, free recall, visuospatial function, attention span, and facial affect naming. As the disease progresses to CDR scores of 1, step-wise decline in error monitoring, semantic fluency, and naming with added trouble emerging in set-shifting, free recall, emotion naming, calculations, and verbal agility (Ranasinghe *et al.*, 2016). Compared to patients with AD, bvFTD patients outperform on tests of episodic memory and set-shifting while underperforming on emotion naming, error monitoring, and lexical fluency. When comparing patients with so-called frontal variant atypical AD compared to bvFTD, AD patients display greater memory and executive function deficits (Ossenkoppele *et al.*, 2015).

Reward Processing and Decision-Making in FTD

The neural representation of value is a complex process that involves a widely distributed network in the brain contingent on the representation and updating of reward value. The idea of reward entails anything that an individual will direct energies and behaviors toward in order to obtain. Primary rewards include food, drink, and sex. Secondary reward such as money is pursued as instrumental to gain primary rewards. Punishments are stimuli that individuals work to avoid. Reward processing is pivotal to decision-making and goal directed behavior (Bermudez and Schultz, 2010). Reward processing interfaces with decision-making, which are the cognitive processes that result in the selection of a belief-state or course of action amongst vying possibilities.

bvFTD impacts both reward and decision-making systems. For example, patients exhibit shifts in dietary preference, eating sweet foods without restraint, suggesting some change in underlying primary reward processing. In other instances, patients develop new hobbies or

intensify previous interests and devote large amounts of time in pursuing related activities (e.g. hours per day spent on organizing coin collection). In both examples, the landscape for the patient's decision-making is drastically altered compared to what was previously known as emblematic of an individual's values. Altered decision-making in patients often carries legal or moral implications.

The neuroanatomy of reward processing involves various regions as based on human and animal studies (Haber and Knutson, 2010). Both primary and secondary reward representation involve orbitofrontal cortex with medial areas encoding the positive reward and lateral demarking punishment or negative consequences (Anderson *et al.*, 2003). The reward value, intensity and valence are encoded in the amygdala (Bermudez and Schultz, 2010). The ventral striatum is an important area for modeling possible reward prediction signals (Sutton and Barto, 1998; Frank, 2006; Maia and Frank, 2011). Prediction errors mark the difference between observed and expected outcomes with positive prediction error signals representing an outcome that was better than anticipated and a negative prediction error being worse than expected (Maia and Frank, 2011). Based on phasic dopamine release quantities, midbrain dopamine neurons encode reward prediction error signals (Bayer and Glimcher, 2005). Dopamine encoded prediction error signals are utilized to learn the value of stimuli or situations, which can be applied to optimize action selection (Sutton and Barto, 1998). Dopamine-dependent learning through prediction error signals also serves a pivotal role in complex, hierarchical goal-structuring (Badre and Frank, 2012; Frank and Badre, 2012). Contextual representations of higher-order, abstract goal-states in rostral PFC influence the gating of states in more caudal PFC regions. Temporal discounting experiments (ability to discount an immediate sensory state in

order to attain a long-term goal) also show a rostral-to-caudal PFC and striatal activation pattern during long- versus short- term goal states (McClure *et al.*, 2004).

bvFTD impacts key nodes in reward processing and decision-making (Perry and Kramer 2014). Deficits in cognitive control are present in bvFTD and might explain some of the alterations (Krueger *et al.*, 2009) in particular due to abnormal lateral orbitofrontal activity (Luks *et al.*, 2007). In tests of primary reward processing, bvFTD patients overeat sweet snacks with neuroanatomical correlates in the right anterior and ventral insula, right orbitofrontal cortex, and right ventral striatum (Woolley *et al.*, 2007a).

With regard to decision-making, one paradoxical finding is that while bvFTD patients often make disastrous decisions in real life, in laboratory settings their decision-making is often more "classically rational" (i.e., in utilitarian terms) than that of controls. As one well-documented example, patients with bvFTD make more utility-maximizing choices in hypothetical personal moral dilemmas than healthy older controls and patients with AD (Mendez and Shapira, 2009; Chiong *et al.*, 2016). In another recent neuroeconomic study, patients with bvFTD made fewer inconsistent choices in the Allais paradox than healthy older controls and patients with AD (Bertoux *et al.*, 2014). The Allais paradox is a violation of expected utility theory in which a subject's preference for gamble A over gamble B is reversed by the inclusion of an additional probabilistic outcome that is the same for each gamble. Finally, bvFTD patients were less averse to losses than controls, patients with AD, and patients with svPPA, as manifested in their willingness to enter 50-50 mixed gambles when the amount that could be won was only slightly larger than the amount that could be lost (Chiong *et al.*, 2016). This strategy maximizes expected monetary value, and is therefore the most rational strategy on

classical models of economic rationality given conservative assumptions about the curvature of the utility function over the relatively small monetary amounts involved in this study.

Loss aversion, the Allais paradox, and non-utilitarian judgment in personal moral dilemmas are often conceptualized as cases in which normal subjects make classically irrational decisions due to the influence of illogical emotional influences (Coricelli, Dolan and Sirigu, 2007; Greene, 2007; Sokol-Hessner *et al.*, 2009). In these experimental paradigms, patients with bvFTD behave in patterns endorsed by classical models of economic rationality; yet they also make very bad decisions in the real world. Further examination of this tension in bvFTD may help us to understand the appropriate normative role of emotions in human decision-making.

Conclusion

The human frontal lobes are vital to socioemotional function, cooperation in groups, language, self-concept, reward processing, and decision-making. When key nodes, such as frontoinsular or ACC, break down as in FTD, then alterations in behavior ensue. Of the FTD subtypes, bvFTD is particularly injurious to social function namely because of early changes in the salience network, centered on right>left insular and pregenual ACC degeneration. FTD exhibits clinical heterogeneity in terms of behavioral phenotypes yet displays clinical-anatomic convergence given differing proteinopathies similarly arrest neuronal circuit function at regional and network levels. Recent neuroimaging and modeling approaches in bvFTD reveal patterns of network dysfunction centered on frontal-insular cortices. These findings reveal novel insights about the behavioral and cognitive neuroscience of ToM, reward processing, self-consciousness, and decision-making.

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