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CRITICAL REVIEW

Frontotemporal dementia: A review

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Abstract

This review summarizes the clinical, imaging, and pathological features of frontotemporal dementia (FTD). Clinicians have become increasingly sensitive to FTD in the differential diagnosis of Alzheimer's disease. Clinical subgroups of FTD patients have been recognized, including patients with progressive non-fluent aphasia, semantic dementia, and behavioral disorder with executive difficulty. The clinical, neuroimaging and neuropathological profiles associated with these clinically defined subgroups are examined. (*JINS*, 2002, *8*, 566–583.)

Keywords: Frontotemporal dementia, Progressive aphasia, Semantic dementia, Neuropsychiatric impairment

INTRODUCTION

Frontotemporal dementia (FTD) is a progressive neurodegenerative syndrome with diverse clinical presentations. Among the most prominent features are progressive aphasia and bizarre affect with a personality change. The historical literature often refers to these patients with the eponym "Pick's disease" (Gans, 1922; Onari & Spatz, 1926) in honor of Arnold Pick, the Prague neurologist who first described this condition (Pick, 1892, as translated by Girling & Berrios, 1994). Until recently, Pick's elegant descriptions of patients with focal dementias provided the richest clinical characterizations of this condition. Even when recognized clinically, the gross neuropathologic changes associated with Pick's observations could not be assessed by *in vivo* imaging studies until relatively recently. This review summarizes recent clinical and neuroimaging features associated with FTD, emphasizing characteristics useful for clinical diagnosis, and experimental hypotheses assessing the factors underlying these clinical observations. From the perspective of cognitive neuroscience, the unique opportunity to study brain-behavior relationships in FTD should help us advance models concerned with the neural basis for cognition and social/affective functioning.

The microscopic abnormalities of this condition were first reported by Alois Alzheimer (Alzheimer, 1911). He and Altman described argyrophilic inclusions (Pick bodies) and swollen cells (Pick cells) in the atrophic frontal and temporal brain regions that have come to define the pathologic picture of Pick's disease (Altman, 1923). To avoid confusion, I will refer to the clinical syndrome as "frontotemporal dementia (FTD)" and to the microscopic picture of this specific histopathologic condition as "Pick's disease." It has become recognized over the years, moreover, that several different histopathologic conditions may underlie FTD. For example, Constantinidis proposed a tripartite classification scheme for the various microscopic abnormalities associated with FTD (Constantinidis, 1985; Constantinidis et al., 1974; Tissot et al., 1985). All three conditions included neuronal drop-out and microvacuolation. Type A is the classic Pick's disease with Pick bodies and swollen Pick cells. Type B includes only swollen cells, and today would probably be called Corticobasal degeneration (CBD). A discussion of the clinical features of this condition is beyond the scope of this review, although we have seen patients with pathologically-confirmed CBD whose major clinical presentation was a progressive aphasia. Type C of Constantinidis describes a pattern similar to Pick's disease but without the intracytoplasmic inclusions or the swollen cells. These cases would now be labeled *dementia lacking distinctive histopathology* (DLDH; Giannakopoulos et al., 1995; Knopman et al., 1990) or *frontotemporal dementia of the non-Alzheimer's type* (Brun, 1987; Mann et al., 1993; Neary & Snowden, 1996). To help distinguish between the nomenclature used to name the clinical condition of "FTD" and the Type C histopathologic condition, I will refer to this

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pathological entity as *dementia lacking distinctive histopathology* (DLDH). These conditions have been associated more recently with unique biochemical features (Hong et al., 2000). Moreover, these clinical and pathological presentations have been related to a defect on chromosome 17 (Foster et al., 1997). This review will also consider the molecular, biochemical, and histopathological features associated with the clinical presentation of FTD.

CLINICAL FEATURES OF FRONTOTEMPORAL DEMENTIA

FTD is a disorder of language, cognition and behavior that affects older segments of society. FTD occurs on average in patients about a decade earlier than the onset of AD (Brun & Gustafson, 1993; Haase, 1977), with reported cases beginning as early as 21 years of age (Lowenberg et al., 1939) and as late as 80 years of age (Binns & Robertson, 1962). Inspection of the distribution of the age at diagnosis in our series reveals another difference from AD, namely, that the risk of FTD apparently does not increase with age. Instead, we have found a normal, poisson-like distribution of ages at diagnosis in FTD, with onset arrayed around a mean age of about 62 years. This suggests an underlying pathophysiology in FTD that is less tightly governed by age and differs fundamentally from a condition like AD where the risk of the disease accumulates with age.

The frequency of occurrence of FTD is unclear. I am not aware of any published, community-based estimates of FTD, possibly because of the difficulties associated with the accurate diagnosis of FTD. The incidence of FTD within dementia and memory disorders clinics is estimated to range between about 4% and 20% (Gustafson, 1993; Kertesz, 1997). Martin Rossor estimates that 12% of demented patients with an onset before the age of 65 have a frontotemporal form of dementia. Autopsy series have reported rates of occurrence between about 2% and 20% (Gustafson, 1993; Klatka et al., 1996; Knopman et al., 1990).

Neurologic examination of FTD patients typically reveals so-called frontal release signs or primitive reflexes such as a grasp reflex and a palmomental response. Extrapyramidal features such as rigidity and gait instability are not rare. Some FTD patients may have a masked face, micrographia, and other secondary features of a parkinsonian syndrome, but a resting tremor is rare. A small number of FTD patients have fasciculations, muscle wasting, and motor weakness suggestive of motor neuron disease. Swallowing difficulty with an attenuated gag reflex are not uncommon in the subgroup of FTD patients with effortful speech (Turner et al., 1996), and EMG studies in a consecutive series of 10 such patients did not reveal any evidence of motor neuron disease. Disorders of ocular motility, cerebellar abnormalities such as ataxia and dysmetria, and sensory defects are not typically associated with FTD. Neurologic signs are important to identify since they may represent a major cause of morbidity and mortality in FTD. Unfortunately, these are generally subtle, and not sufficient for making a diagnosis of FTD. In the absence of definitive neurological signs, the diagnosis of FTD is typically based on a detailed cognitive and behavioral examination, often supported by a neuroimaging study.

COGNITIVE AND IMAGING CHARACTERISTICS OF FRONTOTEMPORAL DEMENTIA

Clinical Diagnosis of FTD

The clinical diagnosis of FTD is often made on the basis of a detailed cognitive and behavioral assessment. A major thrust has been to distinguish FTD from more common conditions such as AD. Unfortunately, the criteria adopted to identify AD appear to be too broad to assist this effort. For example, a prospective study evaluated the sensitivity and specificity of the consensus criteria of the National Institute of Neurologic and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA; McKhann et al., 1984) for distinguishing AD from FTD among 56 consecutively examined demented patients (Varma et al., 1999). The gold standard for determining a patient's diagnosis was the neuropathologic finding at autopsy. The authors found a sensitivity of .93 for identifying patients with probable AD. However, the specificity was only .23. Twenty of 26 patients with FTD also fulfilled the NINCDS-ADRDA clinical criteria for probable AD. Deficits in the domains of language, attention, and perception as described in the NINCDS-ADRDA statement did not help distinguish AD from FTD clinically. However, the presence of impaired orientation and apraxia increased the likelihood of a patient having AD, while the presence of problem-solving difficulty increased the likelihood of a patient having FTD. A recent postmortem study of 170 patients with the clinical diagnosis of AD found that 12% of the patients were misdiagnosed (Klatka et al., 1996). Many of the misdiagnosed patients in fact had a form of FTD. Litvan and her co-workers assessed the ability of experienced neurologists to make the diagnosis of Pick's disease on the basis of scenarios constructed from patients' charts (Litvan et al., 1997). While there may not be universal agreement on the clinical and pathological criteria that were used, these investigators nevertheless documented frequently inaccurate diagnoses. In another study of 21 patients with the histopathologic diagnosis of Pick's disease, 85% were misdiagnosed during life with another neurodegenerative condition such as Alzheimer's disease (AD) (Mendez et al., 1993).

Perhaps the earliest formal effort at developing diagnostic criteria specific for FTD was published by the Lund group (Gustafson & Nilsson, 1982). Based on their extensive clinical experience with autopsy-proven cases, these investigators attempted to distinguish between FTD and AD by tallying the frequency of intellectual deficits (early amnesia, early disorientation, apraxia, aphasia, and agnosia),

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neurologic signs (increased tone, myoclonus, seizures), behavioral disorders (early loss of insight, Kluver-Bucy syndrome, early signs of disinhibition, irritability, and dysphoria), and temporal progression (slow progression, progressive speech loss) on a 16-point scale. A score of greater than 5 on their scale was associated with a frontotemporal form of dementia. Despite the prescient nature of this instrument, it proved difficult to apply because of its great reliance on the subjective judgment of the clinician.

The research groups from Lund, Sweden and Manchester, UK proposed clinical criteria based on their extensive experience (The Lund and Manchester Groups, 1994). They catalogued the cognitive and behavioral features of FTD. Core diagnostic features for FTD included: insidious onset with slow progression; early loss of personal awareness; early signs of disinhibition; mental rigidity and inflexibility; hyperorality; stereotyped and perseverative behavior; utilization behavior; distractibility, impulsivity, and impersistence; early loss of insight. These investigators also listed additional affective and speech symptoms; physical signs such as primitive reflexes, early incontinence, akinesia, and labile blood pressure; normal spatial and practic functioning; and a variety of exclusionary features. The strength of this approach derives from the skill of these clinicians with perhaps the world's greatest experience in FTD, and the criteria are based on clinical–pathological correlations in over 60 patients. The major weakness includes that the relative importance of the long list of clinical features is not provided. These features may lead to high sensitivity, but are likely to be associated with poor specificity. An assessment of these criteria, using neuroimaging data as the gold standard for establishing the presence of FTD, found selective support for the Lund and Manchester approach (Miller et al., 1997). For example, criteria concerned with "hyperorality," "early loss of social awareness," "stereotyped/perseverative behavior," "progressive reduction of speech," and "preserved spatial orientation and praxis" successfully discriminated between FTD and AD, but criteria such as "depression/anxiety," "hypochondriasis," "mental rigidity," "echolalia," "insidious onset," and "late mutism" were not helpful.

Neary and his colleagues published clinical criteria concerned with identifying three subgroups of FTD patients (Neary et al., 1998). Core diagnostic features and supportive features were similar to those described by the Lund-Manchester group in 1994. Clinical subgroups included (1) *progressive non-fluent aphasia*, a disorder of expressive language characterized by non-fluent spontaneous speech with agrammatism, phonemic paraphasias, and anomia; (2) *semantic aphasia* and *associative agnosia*, an impairment of word meaning and object identity with fluent, empty spontaneous speech and semantic paraphasias that may be accompanied by a perceptual disorder characterized by prosopagnosia or associative agnosia; and (3) *frontotemporal degeneration*, a disorder of character and social conduct that includes early loss of insight, decline in personal hygiene, mental rigidity, distractibility, hyperorality, and perseveration. The outstanding strength of these criteria is that specific cognitive, language, and behavioral components of FTD subgroups are made explicit. An attempt to validate these subgroups clinically in a large cohort of patients was successful in only about two-thirds of the cases (Davis et al., 2001), and modified subgrouping criteria are currently being validated (Price et al., 2001).

Another recent effort, reflecting the great heterogeneity in the clinical presentation of FTD, has attempted to simplify these detailed criteria while joining them with more specific histopathologic and biochemical criteria (McKhann et al., 2001). The clinical features focus on the presence of the two most common characteristics of FTD: progressive aphasia, and neurobehavioral disorder. The pathologic features emphasize the biochemical characteristics of tau and other abnormal accumulations of proteins found in the brains of these patients, and the chromosomal abnormality. This approach requires validation.

Rossor and his colleagues from 12 European centers focused more narrowly on Pick's disease (ECAPD Consortium, 2000; Rossor, 1999). These investigators, using the NINCDS-ADRDA consensus for AD as a model, have drafted specific clinical criteria that correspond to the histopathological appearance of 50 patients with Pick's disease as defined by Constantinidis Type A Pick's disease. The clinical features for probable Pick's disease include: progressive cognitive impairment with or without behavioral change; onset before 70 years of age; and evidence for asymmetry on neuropsychological assessment that may be accompanied by asymmetry on structural imaging. Features consistent with a probable diagnosis of Pick's disease include: progressive language impairment; progressive apraxia without other motor signs; and progressive change in personality and behavior. These criteria are currently undergoing a validation study.

Psychometric approaches to the clinical diagnosis of FTD also have been adopted. The Mini Mental State Examination (Folstein et al., 1975) does not appear to be a useful tool for screening patients with FTD, since profoundly impaired FTD patients can have a normal MMSE (Gregory & Hodges, 1996; Miller et al., 1991). Gregory and her colleagues developed a brief battery of bedside tasks in an attempt to distinguish between FTD patients and AD patients (Gregory et al., 1997). This consisted of frontal release signs, awareness of an ethical dilemma in a short story, and perseverative errors on an oral word fluency test. Unfortunately, this kind of tailored battery was no more successful at identifying patients with FTD. More recently, Hodges and his co-workers have developed another brief battery of tests for identifying demented patients—Addenbrooke's Cognitive Examination (Mathuranath et al., 2000). This instrument consists of 6 components unequally divided across domains of orientation, attention, memory, verbal fluency, language, and visuospatial ability. By calculating (verbal fluency + language)/(orientation + memory), the investigators were able to discriminate FTD from non-FTD with a sensitivity of 58% and a specificity of

97%. As noted in an accompanying editorial, the value of this instrument remains to be established with a wider clinical range of FTD patients.

Detailed neuropsychological test batteries also have been developed in an attempt to distinguish between patients with FTD and AD. However, many of these comparative studies have encountered considerable difficulty distinguishing quantitatively between FTD and AD. Problems have included the particular range of psychometric tools used to assess the patients, and the particular nature of the FTD patients participating in the studies. For example, early investigations failed to find a difference on executive measures when patients with FTD and AD were directly compared (Jagust et al., 1989; Knopman et al., 1989). One study comparing FTD patients with AD patients matched for overall dementia severity with the MMSE found a significant difference only in verbal anterograde memory performance (Frisoni et al., 1995). Several investigations comparing FTD patients and AD patients matched for overall dementia severity on the MMSE found significantly worse performance among AD patients only on non-language measures such as visual constructions, nonverbal memory, and calculations (Mendez et al., 1996; Pachana et al., 1996). Jagust et al. (1989) and Pachana et al. (1996) performed within-group comparisons, and found that FTD patients are more impaired in their executive and language functioning than their memory performance, while AD patients demonstrated the reverse pattern. FTD patients and AD patients were discriminated with 84% accuracy on the basis of performance on the Vocabulary subtest of the Wechsler Adult Intelligence Scale (WAIS), the Block Design subtest of the WAIS, and a paired-associate learning measure (Elfgren et al., 1994). A recent study has found memory difficulties in both AD and FTD, but has shown different patterns of memory impairment (Pasquier et al., 2001). FTD patients benefited more from cues, had better encoding, and demonstrated a slower forgetting rate than AD patients.

Recent work has been more successful at distinguishing consistently between FTD and AD, possibly because of the important focus on specific cognitive and behavioral domains. One clinical feature that has received increasing attention is the bizarre behavior and personality change that can be seen in some FTD patients. Clinical observations by the Lund group have emphasized the prominent behavioral and social disturbances in FTD patients (Gustafson et al., 1992). Using the Neuropsychiatric Inventory developed by Jeffrey Cummings (Cummings et al., 1994), Bruce Miller and his colleagues quantified the personality and behavioral characteristics of 22 FTD patients and 30 AD patients (Levy et al., 1996). Compared to AD patients, FTD patients demonstrated greater neuropsychiatric morbidity, including greater apathy, disinhibition, euphoria, and aberrant motor behavior, although AD patients were more depressed. Based on disinhibition, apathy, and depression scores, 77% of FTD patients and 77% of AD patients were correctly assigned to their diagnostic category. Another study comparing 20 FTD patients and 40 AD patients matched for overall dementia severity demonstrated greater depression, anxiety, agitation, irritability, disinhibition, mood lability, and anergia in FTD than AD (Lopez et al., 1996).

Other work has focused on the language disturbances seen so commonly as an early feature of FTD (Snowden et al., 1992; Snowden & Neary, 1994). One study demonstrated relative difficulty on measures of expressive speech in FTD compared to AD (Johanson & Hagberg, 1989). More recently, 28 FTD patients and 67 AD patients matched for overall dementia severity and demographic features were compared on measures assessing grammatical aspects of sentence comprehension and semantic aspects of single word comprehension (Grossman et al., 1996a). These investigators found that FTD patients differ significantly from control subjects only for grammatical aspects of sentence comprehension, but that AD patients differ from control subjects only for semantic memory judgments associated with single words.

One recent study has illustrated the usefulness of combining language and behavioral assessments. Fourteen FTD patients and 15 AD patients matched in overall dementia severity according to the MMSE were found to differ in their performance on a controlled oral word association test (FAS word fluency), free recall performance on a supra-span word learning task, behavioral observations of executive dysfunction in the real world such as lack of insight and rule-breaking, and emotional observations such as inappropriate euphoria and adjustment difficulties (Lindau et al., 1998). AD and FTD patients were classified with 90% accuracy based on neuropsychological performance (FAS word fluency, free recall, and "hits" from the recognition portion of the memory assessment); behavioral and emotional observations (lack of insight, rule-breaking, adjustment difficulties, and euphoria) distinguished between FTD and AD patients with 97% accuracy.

Subgroups of FTD patients often present with progressive aphasia or a behavioral disturbance (Davis et al., 2001; Neary et al., 1998; Price et al., 2001). While these presentations often are not restricted to a single domain of impaired functioning, the overwhelming clinical character of the impairment represents an important clue to the underlying nature of a dementing patient's decline. Moreover, detailed studies of these patients can provide important insights into the neural basis for higher cognitive and behavioral functioning. These subgroups are described in more detail below.

Progressive Non-Fluent Aphasia

Clinical characteristics

Arnold Pick's early clinical description of this disease included a woman whose speech became progressively effortful and eventually led to complete muteness (Pick, 1892, as translated by Girling et al., 1994). More recently, Mesulam introduced the concept of Primary Progressive Aphasia (Mesulam, 1982). He described several individuals presenting

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with an anomic aphasia but no evidence of dementia whose speech worsened insidiously over time. Three of these patients had progressive loss of speech output and impaired repetition, despite relatively preserved aural comprehension of single words. CT scan showed atrophy in the region of the left Sylvian fissure. A PET scan performed on one of these patients showed a defect of glucose metabolism in the left hemisphere (Chawluk et al., 1986).

Several clinical descriptions have since provided a detailed characterization of progressive non-fluent aphasia (PNFA), one form of progressive aphasia evident in Pick's series of reports. For example, one of Kempler's three progressive aphasic patients (Case 2) presented with slow, dysprosodic, and hypophonic speech production (Kempler et al., 1990). He had difficulty understanding and repeating sentences, but confrontation naming was relatively preserved. Delecluse and her co-workers described a patient with impaired spontaneous speech due to compromised fluency, prosody, and articulation (Delecluse et al., 1990). There was also impaired repetition, reading, and naming, but relatively preserved single word comprehension. Tyrrell and his co-workers described a subject with progressively reduced speech output that was effortful and halting (Tyrrell et al., 1990a). Naming was quite impaired. This was associated with orofacial dyspraxia as well as limb apraxia. Another subject presented with naming difficulty and impaired sentence construction, but his memory and reasoning were intact. Speech became progressively limited, with utterances becoming shortened to single words and ultimately limited to grunting. He could not understand speech, but he could communicate in writing at the time of examination. Caselli described three patients with non-fluent speech, phonemic paraphasic errors, and impaired sentence repetition (Caselli & Jack, 1992). Comprehension on the Token Test was impaired, but confrontation naming otherwise was quite good.

Detailed longitudinal studies have underlined core clinical characteristics of PNFA. One report described the longitudinal course of three PNFA patients who exhibited an unrelenting decline on measures such as the Token Test, repetition (particularly for sentences), and the Boston Naming Test (Weintraub et al., 1990). Declines on measures of buccofacial praxis and reading were relatively modest, and performance was stable over time on measures such as orientation, design recall, line orientation, face recognition, and Raven's Progressive Matrices. Another report described the longitudinal course of 10 primary progressive aphasics and 10 AD patients on the Western Aphasia Battery (Karbe et al., 1993). Speech fluency and oral expression declined together with repetition and confrontation naming. The decline in comprehension was more modest, possibly because the comprehension subtest of the Western Aphasia Battery does not emphasize grammatical aspects of sentences. Grossman and his co-workers provided a longitudinal characterization of 4 PNFA patients in comparison to 25 patients with Alzheimer's disease (Grossman et al., 1996b). The speech of the PNFA patients became progressively less fluent, and their naming and repetition declined over several years. Ultimately these patients were mute. Comprehension of sentences also decayed throughout the disease process, while comprehension of single words declined only late in the patients' course.

Some researchers have begun to investigate the basis for the language deficit in PNFA. The critical feature appears to be a grammatical impairment that interferes with expression, distinguishing PNFA patients from semantic dementia patients whose speech may appear non-fluent at times due to frequent word-finding pauses, and from patients with a dysexecutive syndrome who are mute due to an apathetic, amotivational state (see below). Most PNFA patients have grammatical comprehension difficulty in sentences as well. For example, two PNFA patients were examined on a wide variety of language and cognitive measures (Hodges & Patterson, 1996). Impairments were seen on measures of sentence comprehension and sentence-picture matching that require an appreciation of grammatical relationships in sentences, as well as modest difficulty on measures of confrontation naming, repetition, and phoneme discrimination. Their comprehension of single words on word–picture matching tasks and reading of regular words was relatively preserved. In another report, four PNFA patients were shown to be impaired in their comprehension of grammatically complex sentences compared to grammatically simple sentences on measures of sentence-picture matching and responding to oral probes of sentences (Grossman et al., 1996b). A parallel expressive deficit was seen on a sentence completion task, where the PNFA patients encountered considerable difficulty describing pictures that require grammatical phrasing such as the passive voice. Given the central role of verbs in sentences, it is not surprising that verb naming difficulty has been reported in FTD as well (Cappa et al., 1998), and a recent study also has described a verb comprehension deficit in these patients (Rhee & Grossman, 2001).

Perhaps the most convincing evidence for a grammatical processing deficit in PNFA has come from detailed experimental studies (Grossman et al., 2001; Tyler et al., 1997). These investigators reported impairments during off-line assessments of syntax in sentences, and this was correlated with a short-term memory deficit on a forward digit span task. The patients' performance during an on-line measure of grammatical processing with a word monitoring technique demonstrated insensitivity to several kinds of grammatical relationships in sentences. While this insensitivity to grammatical agreement violations occurred in the temporal window during which a grammatical agreement is normally activated for processing, Grossman et al. showed that these patients are sensitive to the agreement following a delay that is beyond the temporal window during which a grammatical agreement is normally activated. The authors speculated that sentence information held in a short-term memory buffer during sentence processing becomes degraded while grammatical agreement knowledge is slowly activated.

Neuroimaging features

A pattern of reduced cortical activity has emerged in many functional neuroimaging studies of PNFA suggesting a defect in the inferior and dorsolateral prefrontal regions extending into the superior temporal area of the left hemisphere. A PET scan of Kempler's PNFA patient (Case 2) revealed hypometabolism in left frontal regions that extended into adjacent superior temporal and inferior parietal regions (Kempler et al., 1990). The PET scans of Tyrrell's PNFA patients showed defects in the left frontal and superior temporal regions (Tyrrell et al., 1990a). In the three PNFA patients described by Caselli, left frontal atrophy was seen on MRI, and SPECT scans demonstrated hypoperfusion centered in the left frontal region (Caselli et al., 1992). The PNFA patient studied by Delecluse and her co-workers had SPECT imaging that showed reduced frontal and temporal perfusion that was more prominent on the left than the right (Delecluse et al., 1990). Grossman et al. associated the pattern of longitudinal impairment seen in 4 PNFA patients with a PET defect in the middle frontal, inferior frontal, and superior temporal regions of the left hemisphere (Grossman et al., 1996b).

More recently, the relationship between a left frontal cortical defect and impaired sentence comprehension has been reinforced by a direct correlation between cognitive performance and SPECT imaging (Grossman et al., 1998). This study found a significant correlation between impaired grammatical comprehension and reduced dorsolateral and inferior frontal activity on SPECT. A perfusion fMRI study using an arterial spin labeling technique recently confirmed this correlative observation in FTD, and the absence of a similar correlation in AD underlined the specificity of the relationship between grammatical processing and left inferior and dorsolateral prefrontal cortex in FTD (Alsop et al., 2001). It is difficult to assert that a correlative frontal perfusion defect is specific for a grammatical impairment, however, since imaging studies in patients with dysarthric speech also showed a left frontal defect (Kartsounis et al., 1991; Tyrrell et al., 1991). Analysis of PNFA patients' pattern of neural activation monitored by BOLD fMRI during a sentence comprehension challenge has provided additional evidence consistent with a grammatical deficit in these patients (Cooke et al., 2001). FTD patients read grammatically simple sentences (with subject-relative center-embedded constructions such as "The boy from Boston that chased the girl with brown hair was friendly") and grammatically complex sentences (with object-relative center-embedded constructions such as "The boy that Amy chased with brown hair was friendly"). Half of each type of sentence had a brief (three-word) antecedent noun–gap linkage as above, and half had a lengthy (seven-word) linkage such as "The boy from New York with brown hair that chased Amy was friendly"). Healthy control subjects recruited both ventral and dorsal portions of left inferior frontal cortex during comprehension of object-relative sentences with a long linkage. However, PNFA patients did not recruit the ventral left inferior frontal region during these grammatically-demanding sentences, although dorsal inferior frontal cortex was recruited.

Taken together, these observations suggest a core deficit in PNFA consisting of effortful, non-fluent speech. Most of these patients also appear to have a grammatical comprehension impairment. Neuroimaging findings suggest that compromised left inferior frontal cortex plays a crucial role in the impaired language profile of PNFA patients.

Semantic Dementia

Clinical characteristics

Another form of progressive aphasia has been described that is quite different from the non-fluent aphasic syndrome described above. Pick described 3 cases of progressive fluent aphasia associated with atrophy of inferior regions of the temporal lobe (Pick, 1904, as translated by Girling & Berrios, 1997). A contemporary of Arnold Pick, Max Rosenfeld, also provided an early description of a patient who presented with word-finding difficulty and semantic paraphasic errors in spontaneous speech (Rosenfeld, 1909, as described in Luzzatti & Poeck, 1991). There was a striking verbal amnesia for the names of objects, with frequent circumlocutions when a name could not be retrieved.

Modern descriptions of this syndrome were first provided by Warrington, who presented 3 patients with impaired semantic memory (Warrington, 1975). These patients had empty, circumlocutory spontaneous speech with frequent paraphasias. They had difficulty on language expression tasks dependent on semantic memory such as defining words and confrontation naming. Their comprehension of single words also was impaired, associated with impoverished knowledge of the semantic features linked to words. The central, semantically based nature of these deficits was emphasized by two additional observations: They had difficulty in other modalities of stimulus presentation such as recognizing visually presented objects, despite no apparent visual–perceptual deficits; and their semantic memory impairment disproportionately affected a specific category of knowledge (natural kinds such as animals) compared to other categories (manufactured artifacts such as tools). Surface dyslexia and surface dysgraphia with regularization errors were present. Syntax and repetition were relatively preserved.

Patients such as these have been consolidated into an entity known as *semantic dementia* (SD) in a seminal article written by Hodges and his co-workers (Hodges et al., 1992), based on a term first introduced by Snowden (Snowden et al., 1989). Patients with this fluent form of progressive aphasia have frequent circumlocutions, word-finding pauses, and semantic paraphasic errors in their spontaneous speech, as well as considerable confrontation naming difficulty (Edwards-Lee et al., 1997; Kempler et al., 1990; Mesulam, 1982; Poeck & Luzzatti, 1988; Snowden et al., 1992; Tyrrell et al., 1990a). They have comprehension difficulty for single words, but syntax and phonology are rel-

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atively preserved. Some progressive fluent aphasics also have difficulty recognizing objects, despite normal performance on visual–perceptual measures that required matching and copying. It is also important to note that PNFA and SD may represent two poles of a spectrum language disorder, and a subgroup of progressive mixed aphasics manifests difficulty with both semantic memory and the grammatical organization of language (Davis et al., 2001; Price et al., 2001).

Additional studies have been conducted to investigate the basis for the semantic memory impairment in SD. Hodges and his co-workers demonstrated that these patients have relatively impoverished knowledge of features associated with word meaning (e.g., impoverished knowledge of whether a deer is domestic or gives milk) despite relatively preserved superordinate knowledge (e.g., they know that a deer is a kind of animal; Hodges et al., 1992). Moreover, this limitation in semantic memory was evident in multiple modalities of stimulus presentation, emphasizing the central, semantically-based nature of their deficit. SD patients are impaired on other measures dependent on semantic memory such as naming to description, word-picture matching, knowledge of semantic features associated with a word, sorting pictured objects based on characteristic features, and anomaly judgments of visually presented chimeric combinations of two objects (Hodges et al., 1996, 1999). Patients with left-lateralized disease may have naming difficulty that is most prominent, while right-lateralized disease may interfere with visual-perceptual processing for meaning; true SD with a multi-modal semantic impairment may depend on the presence of bilateral disease (Lambon Ralph et al., 2001; Snowden, 1999). In this context, the semantic memory impairment in some SD patients appears to be most prominent for natural kinds such as animals compared to manufactured artifacts such as tools. This has been seen on measures such as picture confrontation naming, recognition picture naming, and defining single words (Basso et al., 1988; Parkin, 1993; Tyrrell et al., 1990a; Warrington, 1975). Taken together, this approach suggests the degradation of a distinct set of semantic features—in particular, features representing visual–perceptual knowledge.

Impaired semantic memory in SD appears to have significant consequences for other forms of memory as well (Murre et al., 2001). Assessments of autobiographical memory have revealed that SD patients have relatively better recall of recent events than remote events, although they are impaired at recalling all time intervals (Graham & Hodges, 1997; Graham et al., 1998; Hodges & Graham, 1998; Snowden et al., 1994). SD patients also appear to demonstrate the same gradient (recent events recalled more accurately than remote events) for non-personal, factual events, although these are not recalled as well as personal events (Snowden et al., 1994, 1996a). Both Graham and Snowden have emphasized the important relationship between semantic memory and the forms of anterograde and remote memory needed to represent various forms of knowledge over the long term (Graham et al., 1997; Snowden et al., 1996a). Graham and her colleagues have hypothesized that the relatively intact hippocampus mediating episodic memory allows SD patients to acquire new information, but that dysfunctional temporal neocortex limits the ability of SD patients to represent autobiographical and remote factual information in semantic memory. This possibility is supported by the observation that patients with SD apparently are able to reacquire information such as the names of objects and to improve performance on measures such as category naming fluency with extensive practice (Graham et al., 1999). By comparison, Snowden and her colleagues have proposed that impaired semantic memory has unequal consequences for autobiographical and factual forms of remote memory in SD since these remote forms of memory are dissociable and have distinct neural representations in temporal neocortex. This view converges with other recent evidence suggesting an alternate account—that the breakdown of semantic memory in SD represents a regression from context-free meaning to highly specific, personal, and context-dependent meaning (Funnell, 2001).

Another consequence of the semantic memory impairment in SD is concerned with reading. Many SD patients have a surface dyslexia. This is manifested as difficulty pronouncing irregularly spelled words together with regularization errors (Hodges et al., 1992; Noble et al., 2000; Patterson et al., 1994; Rozzini et al., 1997). Patterson has associated the surface dyslexia of SD patients with their semantic impairment, arguing that semantic memory is necessary to bind together the sublexical elements of sight vocabulary words so that they can be pronounced without grapheme–phoneme correspondence rules (Patterson et al., 1994; Patterson & Hodges, 1992). One alternate account has attributed surface dyslexia and regularization errors to difficulty accessing phonology from semantics (Watt et al., 1997). A second possibility is related to the specific neuroanatomic distribution of disease in these patients. Noble and her colleagues described reading difficulty in SD that progresses from surface dyslexia to letter-by-letter reading, a form of reading difficulty related to impoverished letter recognition regardless of semantic memory status (Noble et al., 2000). Temporal brain regions important for word meaning are adjacent to temporal-occipital cortex that mediates letter form recognition, and these investigators argued that the pattern of reading difficulty in SD reflects the anatomic distribution of disease as the condition progresses. Evidence supporting Patterson's original claim comes from the observation of similar phenomena in other contexts. For example, Parkin's patient had a surface dysgraphia, with frequent errors spelling irregular words such as "colonel" (spelled "curnal") and "soldiers" (spelled "solgers") that consisted of regularizations (Parkin, 1993). Others have described a patient with a "surface dysphasia" wherein repetition is performed in a manner mediated by the phonologic system and without semantic support (McCarthy & Warrington, 2001). A similar effect may be present in the short-term memory of SD patients as well. SD patients' short-term memory for word lists thus was

better for known words than unknown words, and the SD patients produced many phonological errors consistent with reduced binding of sublexical elements by semantic "glue" (Knott et al., 1997).

Several reports have described progressive syndromes associated with focal right hemisphere degeneration. Among these have been patients with progressive prosopagnosia who developed loss of personal semantic knowledge that was associated with anterior right temporal lobe disease on structural or functional neuroimaging (Evans et al., 1995; Tyrrell et al., 1990b). Two patients have been described with progressive visual agnosia (De Renzi, 1986). A case report of progressive amusia and aprosodia suggests one way in which a right frontal neurodegenerative condition can present (Confavreux et al., 1992).

These observations have been confirmed by several recent group studies. In one report, 11 patients with right-sided FTD were compared to 11 patients with left-sided FTD on a battery of neuropsychological measures (Boone et al., 1999). Patients with right-sided FTD had worse Performance IQs than Verbal IQs. The right FTD subgroup demonstrated consistently worse performance on nonverbal executive measures such as design fluency and picture arrangement compared to their verbal analogs, while the left FTD subgroup demonstrated the reverse pattern of worse performance on verbal measures. Right FTD patients also demonstrated more perseverative responses and poorer conceptual level responses on the Wisconsin Card Sorting Test. Glosser and her colleagues developed a battery of low-level tasks (e.g., contrast sensitivity) and intermediate-level tasks (e.g., spatial localization, object discrimination, and unfamiliar face perception) that assess visual functioning in a manner that minimizes task-related resource demands (Gallo et al., 2001). These investigators reported that FTD patients have significant visual perceptual deficits on object and face recognition measures. Another study, comparing right FTD patients, left FTD patients, and AD patients, found the greatest visual–constructional difficulty in AD compared to the two FTD subgroups. The right-FTD group was most notable for their perseverative behavior on measures such as the Wisconsin Card Sorting Task, emphasizing a limitation in the processes that these patients can bring to bear when approaching material in the visual modality.

Neuroimaging features

Early CT imaging studies of Warrington's (1975) and Mesulam's (1982) semantically impaired patients revealed some non-specific atrophy that was greater on the left than the right. Unfortunately, this imaging modality provides only limited structural detail and has significant artifact in the ventral temporal region that prevents adequate imaging of the temporal lobe. One of Warrington's (1975) patients has been re-imaged with MRI, revealing left-sided peri-Sylvian and temporal atrophy (Tyrrell et al., 1990a). Structural neuroimaging studies with MRI in other progressive fluent aphasics also have demonstrated left temporal lobe atrophy (Neary, 1997; Snowden et al., 1996b). Visual inspection and voxel-based structural morphometry has indicated anterior temporal atrophy that is often most prominent on the left with relative preservation of hippocampal volume (Galton et al., 2001; Hodges et al., 1996; Mummery et al., 1999).

Functional neuroimaging studies have confirmed the role of the left temporal lobe in this syndrome. A PET study of 1 of Warrington's semantically-impaired patients revealed left-temporal and peri-Sylvian atrophy (Tyrrell et al., 1990a). SPECT imaging in one of Poeck's progressive fluent aphasics revealed left-hemisphere hypoperfusion that appeared to be most evident in the temporal region (Poeck & Luzzatti, 1988). In Snowden's series, 6 progressive fluent aphasics studied with SPECT imaging revealed hypoperfusion anteriorly that involved the left hemisphere in 2 patients and was bilateral in 4 patients (Snowden et al., 1992). The PET scans of Kempler's 2 progressive fluent aphasics showed hypometabolism that was most prominent in the posterior temporal and inferior parietal regions of the left hemisphere (Kempler et al., 1990). PET scans in the 4 progressive fluent aphasics of Tyrrell's series showed significantly reduced oxygen utilization in the left temporal lobe (Tyrrell et al., 1990a). Functional neuroimaging studies of SD at rest with SPECT and PET have revealed reduced perfusion centered in the left temporal lobe that at times has extended into the inferior frontal lobe (Cardebat et al., 1996; Edwards-Lee et al., 1997; Snowden et al., 1996b).

A functional neuroimaging study of 4 SD patients has confirmed the crucial role of the left temporal region in this clinical syndrome by assessing the pattern of cortical activation associated with a semantic decision (Mummery et al., 1999). SD patients demonstrated limited recruitment of the left posterior inferior temporal gyrus, a crucial semantic area that was activated by control subjects during performance of the same semantic decision task. The investigators attributed the pattern of limited activation to a disconnection within the left temporal lobe separating the atrophic anterior temporal regions from the crucial semantic cortices of posterior temporal regions.

Taken together, the core clinical feature of SD is a semantic memory impairment. This results in empty circumlocutory speech and poor comprehension of single words, with deficits on tasks dependent on single word meaning such as naming. There may also be difficulty with reading and writing, and with other forms of remote memory that depend in part on semantic memory. Structural and functional neuroimaging studies have emphasized the crucial role of the left temporal lobe in SD.

Behavioral Disorder and Dysexecutive Syndrome

Clinical characteristics

Another subgroup of FTD patients has changes in behavior and personality. Patients with a behavioral disorder and dysexecutive (BDD) syndrome can demonstrate rigidity and

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inflexibility, disinhibition and impulsivity, distractibility and impersistence, and perseverative behavior (Gustafson, 1987, 1993). Other characteristics have included a lack of empathy, emotional unconcern, apathy, and irritability. Severe personal self-neglect has been described (Orrell et al., 1989). Features of Kluver-Bucy syndrome have emerged in some of these patients, including: hyperoral behavior manifested as gluttony, dietary compulsions, and attempts to consume inedible objects; hypersexual behavior ranging from a preoccupation with sexual jokes to compulsive masturbation; hypervisual behavior that can be manifested as shoplifting small, shiny objects and playing with fire; and unprovoked rage behavior (Cummings & Duchen, 1981; Miller et al., 1995).

These BDD patients also have presented with atypical forms of depression, psychosis, or mania (Gregory & Hodges, 1993; Gregory et al., 1996; Lopez et al., 1996; Mendez et al., 1997; Miller et al., 1991; Neary et al., 1988). For example, a depressed subgroup of FTD patients has been reported to have little apathy despite significant depression on the Neuropsychiatric Inventory, and this may be associated with intermittent outbursts of disinhibited, agitated, and socially inappropriate behavior. They may also exhibit stereotypies and ritualistic behavior. Many of these patients have a severe social disorder (Lough et al., 2001; Miller et al., 1997). Disorders of personality, behavior, and social conduct are maintained when followed longitudinally, remaining relatively isolated and often without cognitive difficulty (Gregory et al., 1999; Mychack et al., 2001). A survey of behavioral features in BDD patients, SD patients, and AD patients identified four symptom clusters: Stereotypic and eating behavior; executive dysfunction and self-care; mood changes; and loss of social awareness (Bozeat et al., 2000). Only eating behavior and social awareness differentiated BDD patients from SD and AD patients.

These behavioral abnormalities may also characterize some of the cognitive difficulties that can emerge in many of these patients. Features such as rigidity and inflexibility, disinhibition and impulsivity, distractibility and impersistence, and perseverative behavior thus may also have a significant impact on cognitive functioning. For example, BDD patients may have significant difficulty modulating their attention. They can become very perseverative, and echolalia and echopraxia often emerge as the disease progresses. Utilization behavior and perceptual boundedness are cognitive features of these patients that may be related to disinhibition (Lhermitte et al., 1986). Features of executive difficulty also can be seen (Johanson & Hagberg, 1989). This includes limited production on category naming fluency tasks (Elfgren et al., 1993; Miller et al., 1991; Pasquier et al., 1995), particularly on category naming fluency measures guided by a letter (Hodges et al., 1999). They may also have impairments on the Wisconsin Card Sorting Task and other measures of executive control such as the Stroop Test and the Trails procedure (Elfgren et al., 1993; Miller et al., 1991; Neary et al., 1988), and they may be quite slowed in the time they require to make a decision (Rahman et al., 1999). A subgroup of these patients may have isolated difficulty with executive functioning (Davis et al., 2001; Price et al., 2001).

Hodges and his co-workers directly contrasted the subgroup of BDD patients with patients suffering from SD or AD (Hodges et al., 1999). BDD patients are generally less impaired than AD patients on anterograde memory measures, although there is some individual variability, and they are less impaired than SD patients on measures of semantic memory. Hodges concluded that it is possible to distinguish between these groups of patients based on their cognitive impairment profiles. Language changes can be seen in BDD patients as well, and may include anomia and echolalia. Muteness may emerge in advanced cases, possibly related to reduced initiative, apathy, and an amotivational state. Other work has emphasized the subtle, resource-dependent language impairments in BDD patients. For example, 10 BDD patients and 8 PNFA patients performed a word–picture matching procedure with verbs and nouns that was administered alone and during concurrent performance of a secondary task (Rhee & Grossman, 2001). The PNFA patients had greater difficulty with verbs than nouns regardless of the condition under which the word–picture matching procedure was administered, consistent with a language-based deficit. However, the BDD patients were equally impaired with nouns and verbs. Their picture–word matching took longer and was less accurate for both word classes during concurrent performance of a secondary task than word–picture matching alone. Moreover, word–picture matching decisions in these patients were correlated with the processing speed needed to perform executive measures sensitive to inhibitory control and planning, emphasizing the resource-dependent nature of BDD patients' language difficulties.

Neuroimaging features

Neary and his co-workers described a series of 9 patients with disorders of social conduct, personality change, and loss of initiative who were impaired on measures of abstraction, planning, and problem-solving (Neary et al., 1987). SPECT scanning showed anterior defects in 7 of the 9 patients, while a posterior defect was seen in only 1 patient. Risberg studied regional cerebral blood flow with the ^{133}Xenon inhalation technique in 9 neuropathologically proven cases of frontal lobe degeneration of the non-Alzheimer type and 4 cases of Pick's disease (Risberg, 1987). Frontal dementia and Pick's disease patients showed significantly reduced cerebral blood flow in dorsolateral frontal regions bilaterally. A longitudinal study of 7 of these frontal dementia patients demonstrated progressively diminished flow in the frontal regions. Caselli described a patient with a 2-year history of reduced initiative, a tendency to repeat herself, and a subtle personality change who was profoundly impaired on tests of cognitive flexibility and executive control (Caselli & Jack, 1992). MRI showed frontal atrophy that was more prominent on the right than the left and that also

extended somewhat into the right temporal lobe. SPECT scan showed hypoperfusion of the frontal lobes bilaterally as well as the right anterior temporal region. Jagust and his co-workers studied 5 patients who presented with poor judgment, irritability, apathy, and behavioral disinhibition (Jagust et al., 1989). SPECT scanning showed reduced perfusion of orbital and dorsolateral frontal regions compared to AD. Starkstein studied 8 patients with a frontal lobe dementia who met the clinical criteria for Pick's disease according to the Gustafson-Nilsson scale (Starkstein et al., 1994). These patients were matched with 8 AD patients on neuropsychological measures of memory, language, attention and executive functioning. SPECT scans demonstrated significantly reduced perfusion in orbital and dorsolateral frontal, anterior temporal, and basal ganglia regions in frontal dementia patients compared to AD patients. Within-group comparisons demonstrated that perfusion was particularly reduced in orbital frontal and anterior temporal regions of the FTD patients.

Miller and his co-workers have tested the hypothesis that a right hemisphere disturbance is particularly associated with a behavioral change (Miller et al., 1993). These investigators found that right anterior hypoperfusion on SPECT imaging was associated with prominent behavioral disturbances. In another study of FTD subgroups defined on the basis of relatively lateralized temporal lobe defects identified by visual inspection of SPECT scans, 5 right-sided FTD patients demonstrated prominent behavioral disorders such as irritability, impulsiveness, bizarre dressing habits, limited mental flexibility, and visual hyperalertness in comparison to five left-sided FTD patients with a progressive aphasia (Edwards-Lee et al., 1997). More recent work has associated right anterior temporal atrophy with difficulty recognizing emotion from faces and speech that was not due to semantic or perceptual difficulties (Perry et al., 2001).

On the basis of imaging studies such as these, some investigators have proposed grouping patients with bizarre behavior and disproportionate executive difficulty into a "frontal lobe variant" of FTD (Gregory et al., 1999; Hodges et al., 1999). This contrasts with a subgroup consisting of progressive aphasics called a "left temporal lobe variant" of FTD. Proposals such as these should be lauded for their attempt to bring order to a confusing area of investigation, but it may be premature to support this specific classification system. For example, non-aphasic patients with predominantly right temporal lobe pathology also appear to have prominent behavioral disorders (Edwards-Lee et al., 1997; Miller et al., 1993; Perry et al., 2001). The cases considered under the "left temporal lobe variant" rubric have consisted almost entirely of the semantic dementia form of progressive aphasia, moreover, and have not included the progressive non-fluent aphasics with left frontal disease (Grossman et al., 1996b; Lieberman et al., 1998; Turner et al., 1996).

In sum, the subgroup of BDD patients presents with an atypical mood disorder and bizarre personality changes that include disinhibition, socially inappropriate behavior, and features of Kluver-Bucy syndrome. An executive disorder is also present in many of these patients, including poor planning, limited inhibitory control, perseveration, and slowed information processing speed. Neuroimaging studies have associated this behavioral disorder with changes in orbital frontal, dorsolateral frontal, and anterior temporal regions that may be more prominent on the right than the left.

PATHOLOGIC FEATURES OF FRONTOTEMPORAL DEMENTIA

Dementia Lacking Distinctive Histopathology (Frontal Lobe Degeneration of the Non-Alzheimer Type)

Several distinct pathological conditions have been associated with FTD, but it has not been possible to map any one of these conditions onto a particular clinical presentation. Perhaps the most common condition underlying FTD is "frontal lobe degeneration of the non-Alzheimer type" (Brun, 1987) that I have referred to as "dementia lacking distinctive histopathology" (DLDH; Knopman et al., 1990) to distinguish the nomenclature used for the pathologic condition from the clinical presentation. This pathological condition has been associated with PNFA, SD, and BDD. In 1 of the 8 patients (Patient 4) reported by Green and his co-workers, for example, PNFA was associated with a histopathologic assessment that revealed neuronal loss with microvacuolation and gliosis that was most prominent in the superficial cortical layers anteriorly (Green et al., 1990). Two of Snowden's non-fluent progressive aphasics were studied histopathologically (Snowden et al., 1992). Spongiform change in superficial cortical layers due to neuronal dropout was present in a frontal, anterior parietal, and anterior temporal distribution more prominently in the left hemisphere than the right hemisphere. Pyramidal cells were severely affected in the deeper cortical layers. Another case with progressively effortful speech and agrammatism had neuronal loss and gliosis with microvacuolation predominantly in the frontal cortices (Lippa et al., 1991). Turner and his colleagues described the clinical, imaging, and pathological features of four patients with progressive non-fluent aphasia (Turner et al., 1996). These patients had progressive decline of their spontaneous speech fluency conjoined with grammatical comprehension difficulty. PET scans demonstrated frontal and anterior superior temporal perfusion defects that were more evident in the left hemisphere than the right hemisphere. Pathologic assessment demonstrated a pattern of neuronal drop-out, gliosis, and microvacuolation in superficial cortical layers anteriorly. Turner and his colleagues surveyed the literature for cases with adequate descriptions to support the clinical diagnosis of PNFA, and evaluated the nature of the histopathologic abnormality in these patients. They found that PNFA is disproportionately associated with non-Alzheimer's forms of dementia such as DLDH.

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SD is also associated frequently with neuronal loss and the microscopic features of DLDH. For example, a patient with fluent but paraphasic spontaneous speech had word-finding difficulty and a lexical comprehension impairment consistent with SD. Bitemporal atrophy was evident on MRI (Scheltens et al., 1990). Histopathologic findings included severe neuronal loss with intense gliosis in the superficial layers of anterior temporal cortices that extended into ventral medial frontal regions (Scheltens et al., 1994). In the series published by Snowden and her co-workers (1992), 1 SD patient demonstrated spongiosis, neuronal loss, and gliosis in the superficial layers of the middle and inferior temporal gyri, with reactive astrocytosis and pyramidal neuron loss in the deeper cortical layers. One patient with a fluent aphasic syndrome and atrophy in a left inferior temporal distribution revealed neuronal loss and spongiform changes in the superficial cortical layers (Kertesz et al., 1994). Case 2 of Poeck and Luzzatti (1988) had clinical features of SD, including fluent, circumlocutory speech with semantic paraphasic substitutions. This patient had profound atrophy of the temporal lobes, moderate atrophy in the frontal association regions, and relatively preserved hippocampal volume (Schwarz et al., 1998). Microscopic evaluation revealed severe spongiform change and neuronal loss in the temporal neocortical regions, as well as some neuronal loss in superficial frontal and insular regions. More recently, 3 cases of SD demonstrated frontal and anterior temporal atrophy with neuronal dropout and gliosis that was most prominent in the superficial cortical layers (Rossor et al., 2000). These cases also contained intracytoplasmic inclusions that stained positively for ubiquitin but negatively for tau.

A similar histopathologic pattern has been seen in BDD patients. One early study described a woman whose most prominent clinical feature was the change in her personality, including hypersexual behavior, loss of social insight, and alternating between inappropriate euphoria, temper outbursts, and assaultive behavior (Malamud & Boyd, 1939). Autopsy revealed atrophy that was more pronounced on the left, particularly in an inferior temporal and orbital frontal distribution, although the hippocampus was relatively preserved. Microscopic evaluation revealed severe neuronal dropout and gliosis in the superficial cortical layers of these atrophic regions. Brun has described the pathological presentation of 16 cases with "frontal lobe degeneration of the non-Alzheimer's type" (Brun, 1987). Gross inspection revealed only mild atrophy. Microscopic changes were most evident in the dorsolateral prefrontal and orbital frontal cortices, and to a lesser extent in the anterior temporal, insula and cingulate regions. Histopathologic abnormalities included neuronal loss, spongiosis, and gliosis in the superficial cortical layers. In a family with disinhibition and progressive mutism, there was frontotemporal atrophy with intraneuronal inclusions that were ubiquitin immunoreactive but tau negative (Kertesz et al., 2000).

The unifying theme of these patients from a biochemical perspective is the remarkably low level of *tau* evident in their brains (Zhukareva et al., 2001). *Tau* is a microtubule-associated protein that contributes to axonal metabolism and the cytoskeletal structure of neurons (Hong et al., 1998). In this context, the frequency of familial FTD has been a topic of intense interest because of the link with the q21–22 portion of chromosome 17 where the *tau* protein is encoded (Bird et al., 1997; Foster et al., 1997; Hutton et al., 1998; Wilhelmsen et al., 1994). Missense or deletion defects have been detected most often in the region of exon 10, a portion of the tau protein that is critical to microtubule binding. Recent surveys have demonstrated a defect of *tau* in about 6% to 18% of patients with non-Alzheimer dementia (Poorkaj et al., 2001; Rizzu et al., 1999). In patients reporting a positive family history, the frequency of a chromosomal tauopathy increases, yet explains less than half of these cases. An important entailment of these observations is that there are likely to be other genetic mechanisms for FTD that will be discovered. For example, a patient with clinical features resembling FTD has been associated with the centromere region of chromosome 3 (Ashworth et al., 1999; Brown et al., 1995). The heterogeneous clinical presentations within families having identical chromosomal defects (Hutton et al., 1998; Poorkaj et al., 1998; Spillantini et al., 1998; Wilhelmsen et al., 1994) raises important questions about the mechanism by which defects on chromosome 17 cause neurological disease. Many patients with sporadic DLDH resemble a subgroup of patients with an inherited tauopathy who have very low levels of *tau* (Zhukareva et al., 2001). Yet these patients have detectable *tau* mRNA, suggesting that the level of *tau* is controlled posttranscriptionally.

One unusual form of FTD that resembles DLDH histopathologically has a markedly worse prognosis. This has been associated clinically with presentations of PNFA or BDD, but I am not aware of any cases presenting with SD (Bak & Hodges, 1999; Bak et al., 2001). For example, some of these patients present with effortful speech, dysarthria, and anomia that is conjoined by weakness, fasciculations, and muscle wasting similar to that seen in motor neuron disease. The condition progresses to severe disability and death over a matter of months (Ferrer et al., 1991; Kirschner et al., 1987). A series of 7 cases with rapidly progressive non-fluent aphasia and motor neuron disease had bilateral frontal and temporal hypoperfusion on functional neuroimaging studies (Caselli et al., 1993). Gross neuropathologic evaluations of these cases revealed frontal and anterior temporal atrophy. Histopathological evaluations demonstrated neuronal loss, gliosis and microvacuolation in the superficial cortical layers of frontal and anterior temporal cortices, as well as neuron loss from motor nuclei in the brain stem such as the hypoglossal nucleus. A behavioral disorder conjoined by motor neuron disease has been described in a series of 4 cases that rapidly progressed to death (Neary et al., 1990). Functional imaging studies revealed reduced signal in a frontal distribution. Histopathologic evaluation revealed vacuolar changes in the superficial cortical layers of the frontal lobe with pyramidal cell dropout in the deeper cortical layers. There were also changes

in the hypoglossal nuclei of the brain stem. In several recently described cases, ubiquitin-positive but tau-negative non-argyrophilic intraneuronal inclusions have been seen in motor neurons as well as surviving neurons in the frontotemporal regions of the brain (Okamato et al., 1991; Wightman et al., 1992). A recent series of 9 cases of PNFA without clinically apparent motor neuron disease has demonstrated these intraneuronal inclusions as well (Jackson et al., 1996).

Pick's Disease

Pick's disease has been associated with PNFA, SD, or BDD as well, although this pathological condition is generally much less common than DLDH. Pick's disease is also a tauopathy, but the biochemical signature of this histopathological entity is quite different from DLDH. The form of *tau* that accumulates in many neurodegenerative conditions, including Pick's disease, is hyperphosphorylated. Isoforms of human *tau* include either three or four consecutive repeat motifs of the microtubule binding region. Pick's disease is relatively unique since it is largely the three-repeat form of hyperphosphorylated *tau* that is found in the brains of these patients (Hong et al., 2000). However, the molecular basis for this condition remains to be elucidated, in part because familial Pick's disease appears to be quite rare (Constantinidis et al., 1974; Gans, 1922; Groen & Endtz, 1982).

In one study, a patient with progressively effortful and dysarthric speech also had grammatical comprehension difficulty suggestive of PNFA (Lieberman et al., 1998). MRI showed profound left frontal and anterior temporal lobar atrophy, and a PET study demonstrated reduced cerebral blood flow at rest that was most prominent in an inferior frontal and superior frontal distribution in the left hemisphere. Histopathological evaluation demonstrated intraneuronal Pick body inclusions, ballooned Pick cells, neuronal drop-out, and gliosis that disproportionately affected frontal and anterior temporal regions. A series of 3 well-characterized cases with progressive non-fluent aphasia had detailed histopathologic evaluations (Kertesz et al., 1994). Two of the cases had ballooned neurons and intraneuronal Pick body inclusions, while the 3rd case only had ballooned neurons. All three cases had neuronal loss, microvacuolation, and gliosis that was most evident in the superficial cortical layers anteriorly. Other cases of PNFA have been reported with histopathologic evidence for Pick's disease (Graff-Radford et al., 1990; Holland et al., 1985). Brun has described the pathological presentation of 4 cases of Pick's disease who presented with behavioral changes (Brun, 1987). The brains of these patients revealed marked frontal and/or temporal atrophy that was asymmetric in 3 of 4 cases. Microscopic changes were most evident in frontal regions, although there were milder changes in anterior parietal and cingulate regions as well. Neuronal loss, gliosis, and spongiosis was evident in the superficial cortical layers, and ballooned cells and intraneuronal inclusions were evident. By comparison, only a very small proportion of reported SD cases have been associated with Pick's disease. One early report described a garrulous patient with fluent spontaneous speech that contained phonemic and semantic paraphasias (Wechsler, 1977). Comprehension and naming errors were prominent. CT scan revealed atrophy of the left peri-Sylvian region. Pathologic evaluation demonstrated significant left temporal atrophy that was most prominent anteriorly and inferiorly as well as some frontal atrophy (Wechsler et al., 1982). Microscopic inspection of these areas demonstrated spongiosis, gliosis, and ballooned cells containing Pick bodies.

Alzheimer's Disease

While the progressive aphasic and behavioral presentations of FTD are relatively distinct, cases of progressive aphasia and behavioral/dysexecutive disorders also have been associated with the histopathological features of AD. For example, a patient with fluent, circumlocutory speech containing paraphasic and paragrammatic errors as well as word finding difficulty had impaired comprehension (Pogacar & Williams, 1984). Visual memory was relatively preserved, and he was able to place locations on a map of the US. Left hemisphere atrophy was seen on a CT scan. Pathologic assessment revealed anterior temporal atrophy that was more prominent on the left than the right as well as left frontal opercular atrophy. Histopathologic evaluation revealed neuronal loss and gliosis that was most prominent in the superficial layers of the temporal and parietal lobes. Neuritic plaques and neurofibrillary tangles were present in areas of atrophy as well as in the hippocampus and the basal forebrain nuclei. Two other patients reportedly presented with non-fluent speech and difficulty understanding grammatically complex sentences, in the context of good memory and single word comprehension (Galton et al., 2000). These patients had the histopathologic features of AD in a superior temporal distribution with relative sparing of entorhinal cortex. One patient in the series reported by Green and his co-workers (Patient 8) had effortful speech with some paraphasic errors but relatively good comprehension and relatively preserved memory (Green et al., 1990). Histopathologic analysis revealed numerous neuritic plaques in the inferior parietal cortex and in hippocampal-associated regions of the subiculum and entorhinal cortex. Neurofibrillary tangles were evident in the CA1 portion of the hippocampus, entorhinal cortex, and neocortical regions. Patients with a "frontal variant" of AD had significantly impaired performance on measures of executive functioning such as the Trail Making Test Part B, FAS word fluency, and the Block Design Test (Binetti et al., 1996; Johnson et al., 1999). Analysis of brain tissue samples in these patients revealed disproportionately greater loads of neurofibrillary tangles in the prefrontal cortices compared to the topographic distribution of histopathologic abnormalities in patients with typical AD.

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SUMMARY

There is now good evidence pointing out the critical clinical features contributing to frontotemporal forms of dementia. While it has proven somewhat difficult to establish a clinical diagnosis of FTD with a traditional neurological or neuropsychological evaluation, recent approaches supplementing these assessments have emphasized careful behavioral observations and detailed language assessments. An extension of this approach has focused on specific FTD subgroups. The agrammatic speech of progressive nonfluent aphasia identifies this FTD subgroup. Semantic dementia is recognizable on clinical grounds because of their difficulty processing single words for meaning. The subgroup of patients with bizarre behavior and executive difficulty can be identified on the basis of their personal and social conduct disorder that may be conjoined with impaired problem-solving. Recent work focusing on these patterns of impairment has begun to investigate the source of the difficulty underlying these clinical presentations.

While focal atrophy can be seen on structural neuroimaging studies of some patients, functional neuroimaging studies have been quite useful in confirming the locus of disease in FTD patients, particularly early in the course of the condition. This has proven to be a valuable adjunct to the clinical assessment. In the context of the known neural connectivity pattern of subdivisions of the frontal lobe, it is possible to hypothesize that degeneration in left inferior frontal cortex and possibly left superior temporal cortex plays an important role in the emergence of PNFA, that anterior–inferior and posterior temporal degeneration contributes to semantic dementia, and that defects in orbital frontal and anterior temporal regions—particularly in the right hemisphere—are implicated in the behavioral difficulties of patients with a behavioral and social disorder. Improved spatial resolution of resting functional neuroimaging techniques and the emergence of activation neuroimaging studies in these patients will contribute greatly to our understanding of the pathophysiology of FTD and the neuroanatomic basis for their cognitive and behavioral disorders. There is a great need for additional detailed clinical and neuroimaging studies in FTD patients with a known histopathological diagnosis. Such work in patients with autopsy-confirmed disease has allowed us to develop hypotheses about the presentation of FTD during life. It is these direct links that will allow us to confirm hypotheses about brain–behavior relationships in FTD.

Based on these observations, a helpful clinical algorithm identifies a clinical pattern consistent with an FTD subgroup, and confirms the frontal–temporal distribution of disease with a functional neuroimage. A structural image demonstrating extensive atrophy would be most consistent with the presence of Pick's disease, particularly in patients with PNFA or with bizarre behavior and executive difficulties. Subgroups of FTD patients may also have a relatively rapid decline with motor system impairments. This would suggest an ALS-dementia syndrome, particularly in patients with PNFA or with bizarre behavior and executive difficulty. The vast majority of the remaining FTD patients are likely to have dementia lacking distinctive histopathology or frontal lobe degeneration of the non-Alzheimer type, although this must be distinguished from the so-called frontal lobe variant of AD. Other neurodegenerative conditions with executive impairments and mild extrapyramidal features should be excluded as well, including corticobasal degeneration, Lewy body dementia, and other akinetic-rigid disorders.

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