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The Early Neuropsychological and Behavioral Characteristics of Frontotemporal Dementia

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Abstract

Frontotemporal lobe dementias (FTLD) represent a constellation of disorders that may be overlooked or misdiagnosed, despite being a fairly common presenile neurodegenerative diseases. Although the cognitive disorder can be difficult to document, particularly early in the dementia course, neuropsychological evaluation can assist in the diagnosis. Neuropsychologists are in an excellent position to draw from related disciplines like personality theory and social psychology to better assess the types of changes that characterize the prodromal and early phases of the disease. This review summarizes the current state of the field in the diagnosis of FTLD and discusses the emerging role of neuropsychology in elucidating the brain organization of complex processes including empathy, behavioral control and inhibition, reward systems, appetitive behaviors, emotional regulation, and goal-orientation. As this review underscores, FTD remains a powerful model for studying brain-behavior relationships.

Frontotemporal lobar degeneration (FTLD) refers to a set of neurodegenerative disorders arising from relatively circumscribed frontal and temporal lobar atrophy. Characterized by troubling and progressive changes in behavior, personality, judgment, language, and cognition, the disorder compromises individuals while still in their productive years and may initially be mistaken as a psychiatric disorder. As with other degenerative dementias, a goal is to identify these disorders early with the intent of intervening before the disease has fully expressed in brain. Although no pharmacological treatments are yet available to prevent the disease progression, there are treatments that help alleviate symptoms and nonpharmacological interventions to deal with problem behaviors, coping, and adjustment. From a cognitive neuroscience perspective, the FTLD dementias with their effects on some of the core features of human personality and cognition offer an opportunity to better understand how these fundamental processes of human existence are functionally organized, both the processes involved as well as the brain systems that mediate them. This review article discusses the clinical presentation of the FTLD dementias with an emphasis on its early expression. We propose that by applying a theoretical framework of human behavior from social psychology and constructs from personality theory to the study of FTLD, neuropsychology is ideally positioned to elucidate some of the brain mechanisms underlying a range of complex human behaviors, emotions, and social cognition.

Clinical and Neuropathological Expression of FTLD

The first mention of FTLD as a syndrome was in 1892 when Arnold Pick, a neurologist at the University of Prague, described the clinical and pathological features of one of his patients. He reported an aphasic presentation that progressed over three years in a 71-year-old individual. Upon autopsy, there was found to be significant frontal and temporal lobe atrophy in the diseased brain. Pick's clinical description of his patients with this frontal and temporal atrophy pattern provided diagnostic value that continues to inform diagnostic criteria. The pathology and histology of the presenting disease was actually described by Alois Alzheimer several years later. Alzheimer described the histological characteristics as

"spongy cortical wasting, ballooned cells, and argentophilic globes in neuronal cytoplasm" (Alzheimer, Forstl, & Levy, 1911). These ballooned neurons, or Pick bodies, are globose tau-positive neuronal cytoplasmic inclusions (Cairns et al., 2007), and the term "Pick's disease" was used for several years to refer to the clinical syndrome.

Subsequent reports showed that FTLD was both clinically and pathologically heterogeneous. The clinical presentation of FTLD can include aberrations in language, social function, cognition, and behavior. Most diagnostic criteria now separate the language and behavioral variants of FTLD. The behavioral variant is typically referred to as frontotemporal dementia (FTD), behavioral variant FTD, or frontal variant FTD. Frontal atrophy is more prominent than temporal atrophy, and while the atrophy is bilateral, some reports suggest that the right-hemisphere is more involved than the left (Perry et al., 2006; Rosen et al., 2002). The behavioral variant of FTLD, referred to here as FTD, will be the primary focus of this review.

The FTLD syndrome also includes two language variants. These progressive aphasias are semantic dementia (SD) and progressive non-fluent aphasia (PNFA). SD is characterized by a gradual loss of word meaning and semantic knowledge. Word finding and single-word comprehension problems are typically the first and ultimately the most severe symptoms, even while speech is fairly fluent and grammatical form and repetition are preserved. SD is associated with bilateral anterior temporal lobe atrophy. When the disorder is predominately left-sided, patients primarily present with language deficits, although behavioral abnormalities include compulsions and impairments in emotional processing (K. P. Rankin, Baldwin, Pace-Savitsky, Kramer, & Miller, 2005). Predominant right-temporal involvement is associated with difficulty recognizing faces and social dysfunction. PNFA is characterized by an early disturbance in motor speech, repetition, and syntax. Oftentimes, the patients themselves are the first to be aware of changes, complaining of subtle declines in the ability to articulate and express themselves. Although expressive speech is the most dramatic symptom early in the disease course, impairments in syntactical processing are also evident when written language and comprehension are carefully assessed. Neuroimaging studies indicate that PNFA is characterized by left inferior frontal and insular atrophy.

FTLD is also characterized by pathological heterogeneity, to the point that it may be most useful to conceptualize FTLD as an umbrella term that describes several neurodegenerative syndromes that differentially affect the frontal and temporal lobes. In fact, most cases of FTLD do not actually have Pick bodies. While microvacuolation and neuronal loss are typically seen on H&E staining, immunohistochemistry has led to a much better understanding of the molecular basis of FTLD-related neurodegeneration (Cairns et al., 2007). Pick bodies are now referred to as tau-positive inclusions with a preponderance of 3R tau. The majority of FTLD cases, however, are tau-negative and ubiquitin-positive. More recent studies have identified the presence of a TAR-DNA binding protein (TDP-43) that may be the primary disease protein underlying the ubiquitin-positive cases (Amador-Ortiz et al., 2007; Cairns et al., 2007; Neumann, et al., 2007). Associations between specific pathologies and clinical syndromes are also beginning to emerge; tau and ubiquitin pathology are both seen in FTD, whereas tauopathies more often underlie PNFA, and ubiquitin is much more frequent in SD.

Etiology of FTLD

Identifying the underlying neurobiological causes of FTLD and the antecedent factors that may influence its expression are areas of active investigation. FTLD is the third most common neurodegenerative syndrome behind Alzheimer's disease (AD) and dementia with Lewy bodies (Cairns et al., 2007). It is proportionately more common in the presenium, with

an average age of onset in the late 50's (Johnson et al., 2005). Ratnavalli et al. (Ratnavalli, Brayne, Dawson, & Hodges, 2002) reported that the prevalence of FTLD and AD were similar prior to the age of 64, and FTLD accounts for 10-20% of all early-onset dementias (Ratnavalli et al., 2002; Snowden et al., 2001).

The majority of FTLD cases are probably sporadic, although 30-40% of cases have a positive family history (Josephs, 2007; Sikkink, Rollinson, & Pickering-Brown, 2007), and several autosomal dominant variants have been identified. Chow et al. (Chow, Miller, Hayashi, & Geschwind, 1999) investigated the frequency of familial FTD by looking for FTLD-related symptoms in the families of 42 index cases of FTD. After excluding family members with depression, they found familial cases in 40%, of whom the majority showed a dominant transmission pattern. The initial presentations mostly consisted of personality and behavioral changes that preceded cognitive impairment. Amyotrophic lateral sclerosis was found in 11%.

Two genes on chromosome 17, microtubule-associated protein tau (MAPT) and progranulin, may account for 20% of all familial cases, and genes on chromosomes 3 and 9 have also been identified (Sikkink et al., 2007). The MAPT gene is associated with frontotemporal atrophy and tau inclusions at autopsy. Several mutations in the progranulin gene have also been identified, although these cases are linked to tau-negative, ubiquitin-positive pathology. Genetics is vitally important for early detection of FTLD because by prospectively studying families with a likely FTLD-associated gene, we can begin to describe the types of abnormalities that might signal an incipient neurodegenerative disorder. Clinical experience with these families has suggested a higher incidence of academic underachievement, psychiatric disturbance, and personality disorders beginning well before the onset of FTLD, and early signs of prodromal change include personality and behavior change (Chow et al., 1999). In addition, a study of one family with a known mutation in chromosome 17 showed presymptomatic carriers demonstrated cognitive dysfunction that was not present in 6 nonmutation-carrying relatives. Frontal-executive dysfunction was prominent even in some of the youngest mutation carriers (Geschwind et al., 2001).

In addition to FTD, SD, and PNFA, several other related clinical syndromes potentially fall under the FTLD spectrum. Two atypical parkinsonian disorders, progressive supranuclear palsy (PSP) and corticobasal syndrome (CBS), are clinically and pathologically related to FTLD (Kertesz & Munoz, 2003) Both disorders are neurodegenerative diseases that present with behavioral symptoms and frontal-executive difficulties (Belfor et al., 2006; Kaat et al., 2007) and are tauopathies, although the pathological molecule is 4R tau. In addition, patients with PNFA frequently progress to PSP and CBS, even in the absence of early motor findings (Ferrer et al., 2003; Josephs et al., 2006). The last decade has also clearly documented an extensive overlap between FTLD and ALS. Several reported autosomal dominant FTLD families contain numerous cases of ALS or combined FTD/ALS (Hosler et al., 2000; Valdmanis et al., 2007; Wilhelmsen et al., 2004). In addition, Lomen-Hoerth (Lomen-Hoerth, 2004) noted overlap between ALS and FTD in sporadic cases. Of the 20 consecutive FTD patients studied with detailed neuromuscular examination and electromyography, the investigators found none had a family history of ALS but three patients met criteria for the diagnosis of definite ALS and six additional patients met criteria for possible ALS. The presence of FTLD symptoms in a large percentage of ALS patients further supports the view that these disorders share a common neuroanatomy (Chang et al., 2005; Murphy et al., 2007). Studying ALS patients prospectively is also important for identifying prodromal symptoms because they are at increased risk of developing FTLD.

Diagnostic Criteria

Three sets of diagnostic criteria have been published since 1994 that reflect our evolving knowledge of what FTLD is and how it presents (Brun et al., 1994; McKhann et al., 2001; Neary et al., 1998). The Neary criteria (1998) are the most widely used at present, and helped formalize the distinctions between FTD, SD, and PNFA. The criteria for FTD include onset before 65, insidious onset and gradual progression, early decline in social interpersonal conduct, early impairments in regulation of personal conduct, early emotional blunting, and early loss of insight. Numerous supportive features were also specified, including decline in hygiene, mental rigidity, hyperorality, and perseverative behavior. Exclusionary criteria include early amnesia and spatial disorientation.

Recently, Rascovksy et al. (Rascovsky, Hodges et al., 2007) detailed several limitations of the Neary criteria for FTD. In particular, they noted that the large number of features in the Neary criteria make them difficult to use in routine clinical practice, the inclusion criteria may be unduly restrictive and insensitive to very early stages, the exclusion criteria (e.g., amnesia) are overly restrictive and may exclude some FTD patients, key aspects of the criteria are not well defined, they do not allow for level of diagnostic certainty (e.g., probable versus possible), base rates for several of the behavioral symptoms are very low, and neuroimaging and genetic information are not sufficiently incorporated. An international consortium has now been established to revise the diagnostic and research criteria for FTD and the other FTLD syndromes.

Neurobehavioral features of FTD

The initial symptoms of FTD may reflect the early involvement of orbitofrontal cortex as well as the disruption of an associated network involving the insula, striatum, and medial frontal lobes. As noted in the diagnostic criteria, these patients often present with marked changes in behavior and personality. Behavioral disturbances vary among patients and frequently include apathy, irritability, disinhibition, poor insight, aberrant motor behavior, and loss of personal and social awareness. Snowden and colleagues (Snowden et al., 2001) described two distinct behavioral syndromes: an apathetic subtype, characterized by a generalized loss of interest in activities and volition, loss of social emotions, and decreased pain response; and a disinhibited subtype, characterized by hyperorality, an increased preference for sweet foods, exaggerated sensory responses, repetitive motor behavior, and increased apathy. Patients with FTD commonly violate social norms, for example, by making sexually inappropriate comments, stealing, or publically urinating (Miller et al., 1991). Stereotyped or ritualized behaviors may include repetition of a story or phrase, collecting or hoarding, and repetitive organization of objects. Patients may show changes in their personality and be perceived as more submissive and rigid. A shift in the patient's attitudes or values, such as a change in religious beliefs, can also occur (Miller et al., 2001; Rankin, Kramer, Mychack, & Miller, 2003; Rankin et al., 2004). Often, these early changes are misinterpreted as something psychiatric or as a 'mid-life crisis'. Cognitive impairment is not as pronounced as behavioral changes early in the disease process when many patients perform within normal limits on traditional neuropsychological tests. As the disease progresses, the number and severity of behavioral impairments increase, and cognitive impairments, especially with regard to executive functioning emerge (Diehl-Schmid, Pohl, Perneczky, Forstl, & Kurz, 2006; Hodges et al., 1999; Kramer et al., 2003).

Neurocognitive features of FTD

There are several challenges facing anyone attempting to draw inferences about FTD from the existing neuropsychological literature. First, the diagnostic criteria for FTD have evolved over the past two decades, and the lack of a single, universally applied set of diagnostic

criteria limits comparability. In addition, not all published studies describe their diagnostic criteria (Hutchinson & Mathias, 2007). Second, variability in terminology can be confusing. Some studies used the term 'FTD' to refer to the entire set of FTLD syndromes. In addition, some groups divide FTLD into frontal and temporal variants, some dichotomize along the behavioral versus language spectrum, and groups that follow the Neary criteria separate FTLD according to the clinical syndromes of FTD (frontal variant), PNFA (left-frontal), and SD (left-temporal). Patients with extensive right-temporal involvement and relatively subtle language deficits early on may be classified as behavioral variant rather than language variant. Third, sample sizes are often small, leading to some discrepant findings in the literature. Fourth, many published studies combine behavioral and language variant patients. While this helps address the problem of small sample sizes, studying a heterogeneous group of patients can lead to spurious findings that to not generalize. Fifth, any research comparing FTD with other neurodegenerative disorders must face the problem of how to equate for severity. Scales like the Mini-Mental State Exam and Dementia Rating Scale are widely used to match dementia groups on severity. These scales were developed for AD, however, and their emphasis on episodic memory may make them less sensitive to the behavioral dysfunction in FTD (Gregory, Serra-Mestres, & Hodges, 1999). Rosen et al. (Rosen, Narvaez et al., 2004) examined the Clinical Dementia Rating scale (CDR), a functional measure of severity, in patients with AD, FTD, and SD who were matched for age and MMSE scores. They found that total CDR scores were significantly worse in the FTD group compared with the AD and SD patients, indicating that FTD patients have greater functional impairments than AD or SD patients with an equivalent MMSE score. FTD typically progresses more rapidly than AD, so matching for duration of illness may yield a more severely impaired FTD group. Sixth, FTD patients tend to be younger than typical AD patients, so researchers must choose between covarying for age statistically or using earlier age-of-onset AD patients. Finally, researchers and clinicians working with FTD patients need to consider the possibility that impaired test performance is due to factors other than a deficit in the construct the test is designed to measure. For example, FTD patients may have below average performances on measures of episodic memory because of inattention or poor organization rather than a memory deficit per se.

Neuropsychological studies of FTD have typically focused on episodic memory, semantic memory, working memory, executive functioning, and visuospatial ability (Hodges et al., 1999; Hutchinson & Mathias, 2007). Perhaps the most consistent finding is the relative preservation of episodic memory in FTD relative to other neurodegenerative patients (Harciarek & Jodzio, 2005; Hutchinson & Mathias, 2007; Kramer et al., 2003; Perry & Hodges, 2000). To some degree, this finding is circular, since absence of early amnesia is one of the diagnostic criteria for FTD. Nonetheless, studies of episodic memory have suggested that this construct may be particularly helpful for differential diagnosis, and inclusion of semantic memory tasks further improves separation between groups. Hodges et al. (1999) reported that FTD patients were less impaired in episodic memory than SD and AD patients and had normal semantic memory, whereas SD and AD patients were impaired in both. Glosser et al. (2002) also found that FTD patients obtained higher free recall, cued recall, and recognition scores than AD patients. They further reported that serial-order recall was more common in FTD, suggesting less efficient learning strategies. Kramer et al.(2003) found that their AD and SD groups were significantly impaired relative to FTD on verbal memory, whereas only the AD group was impaired on visual memory, suggesting that measuring memory in both verbal and spatial modalities is valuable. Importantly, the relative preservation of memory in FTD has also been reported in autopsy-confirmed cases (Rascovsky et al., 2002). When examining cognitive test performance at baseline, FTD patients (n = 14) had higher scores on the Dementia Rating Scale memory subscale that AD patients (n = 28) after controlling for age, education, and level of dementia.

Although group studies support the view that episodic memory is preserved in FTD, severe amnesia can be present early in the disease. Graham et al. (2005) describe eight cases of pathologically confirmed FTD cases whose initial symptoms included significant memory impairments. Some overlap between dementia with hippocampal sclerosis and FTD has also been suggested that might explain the early memory deficits (Hatanpaa et al., 2004).

Semantic memory also tends to be intact in FTD patients, whereas deficits are apparent in both SD and AD (Rogers, Ivanoiu, Patterson, & Hodges, 2006). Rascovsky et al. (2007) studied 16 autopsy-confirmed FTD and 32 AD patients with phonemic and semantic category fluency tasks. Despite being matched on age, education, and dementia severity, FTD patients performed worse overall and showed similar impairment in letter and semantic category fluency, whereas AD patients showed greater impairment in semantic category than letter fluency. A measure of the disparity between letter and semantic category fluency (the semantic index) was effective in differentiating FTD from AD patients. FTD patients also perform better than SD patients on semantic memory tasks like autobiographical memory and naming (Hou, Miller, & Kramer, 2005; Kramer et al., 2003).

Given the widespread frontal atrophy and behavioral disinhibition that characterizes FTD, impairments in executive functioning have been surprisingly difficult to measure (Nedjam, Devouche, & Dalla Barba, 2004). In fact, early FTD patients often perform in the normal range on traditional ‘frontal-executive’ tests measuring working memory, planning, mental flexibility, response inhibition, and concept formation (Gregory & Hodges, 1996). In a recent meta-analysis of neuropsychological deficits in FTD. Hutchinson and Mathias (Hutchinson & Mathias, 2007) reported that none of the measures of concept formation, reasoning, or executive functioning (e.g., Wisconsin Card Sort) showed large group differences between FTD and AD. Collette et al. (2007) also reported similar degrees of impairment between FTD and AD on the Stroop and Go/No-go tasks.

Studies that have investigated the patterns of relative impairment in FTD versus other dementias have yielded more consistent positive findings. Pachana et al. (1996), for example, noted that FTD patients were relatively more impaired on executive tasks and relatively less impaired in memory that AD patients, and Kramer et al. (2003) reported that the relative patterns of impairment on executive, language, and memory measures were more discriminating than any individual test.

Experimental paradigms have shown subtle impairments in executive control in FTD versus controls, but extensive comparisons with other patient groups are lacking. Using the attentional set-shifting paradigm from the CANTAB, for example, Rahman et al. (1999) showed that FTD patients had difficulty in reversing previously learned visual discriminations. Kramer et al. (2007) used a flanker paradigm to study a small group of FTD patients who performed within normal limits standard frontal-executive tests like Stroop and Trails. Participants were required to indicate the direction of a centrally presented arrow as quickly and accurately as possible. The central arrow was flanked on both sides by arrows either pointing in the same direction (congruent condition) or opposite direction (incongruent condition). A significant group X condition interaction effect indicated that the FTD patients were disproportionately slowed on the incongruent trials relative to controls, suggesting a subtle impairment in inhibiting attention or response to the irrelevant stimuli.

Self-monitoring is another facet of executive functioning that may be specifically disrupted in FTD. Carey et al. (2007) studied 44 FTD, 30 AD, and 27 control subjects with the Delis-Kaplan Executive Function System Tower task. A subset of patients underwent structural magnetic resonance imaging to obtain regional measures of cortical volumes. FTD and AD groups demonstrated significantly poorer overall achievement scores on the Tower test

relative to controls, but did not differ from one another. In contrast, the FTD group committed significantly more rule violation errors than the control and AD groups, indicating poorer performance monitoring. In addition, the overall achievement scores correlated with brain volumes in several regions, whereas an increased number of rule violations correlated specifically with decreased bilateral frontal volume. Both left and right frontal volumes remained significant predictors of rule violation errors after controlling for the contribution of overall achievement on the task and all other brain regions.

Thompson and colleagues (2005) also highlight the potential utility of error scores. They found that while achievement scores on tests of sentence repetition, metaphor interpretation, visual construction, recall of celebrities, and immediate and delayed story recall correctly classified 71% of 38 FTD patients and 93% of 73 AD patients, adding qualitative variables to the logistic regression model increased the number of FTD patients correctly classified to 96%. The qualitative variables that suggested greater impairment in the FTD group included perseverative errors on a naming test, organizational and perseverative errors on a visual construction task or overelaborated copies, and concrete responses during metaphor interpretation.

Follow-up studies are now beginning to characterize longitudinal change in FTD (Chow, Hynan, & Lipton, 2006). Rascovsky et al. (2005) compared rates of cognitive decline in 70 patients with autopsy-confirmed FTD and 70 with AD matched for overall age, education, and MMSE score at initial evaluation Patients with FTD had significantly shorter survival from initial evaluation to death than patients with AD (FTD = 4.2 years, AD = 6.0 years), and they declined significantly faster over one year on the MMSE (mean annual rate of change: -6.7 points for FTD vs -2.3 points for AD). These results suggest shorter survival and faster rates of decline in patients with FTD. Wittenberg et al. (2008) compared rates of decline on verbal episodic memory, working memory, and spatial abilities in 23 FTD and 32 AD subjects. Mean follow-up interval was 13.6 months. The California Verbal Learning Task – Short Form, backward digit span, and a design copying task were administered at each time point to measure episodic memory, working memory, and spatial abilities, respectively. There was a significant three-way Diagnosis X Time X Task interaction. Post-hoc analyses indicated that FTD subjects showed a greater rate of decline on backward digit span relative to AD, whereas there were no differences in rates of decline in verbal episodic memory or spatial function.

Non-cognitive domains

FTD is primarily a behavioral disorder, and the current diagnostic criteria make very little mention of cognitive functioning. It is not surprising, therefore, that attempts to sharply define the neurocognitive features of FTD have not been very successful. Studies examining behavioral and social changes are increasingly the focus of research in FTD, particularly early in the disease when cognition is still relatively preserved. Levy et al. (1996) were among the first to use the Neuropsychiatric Inventory (NPI), an informant-based measure, to characterize behavioral change in 22 FTD and 30 AD patients. Patients with FTD exhibited more apathy, disinhibition, euphoria, and aberrant motor behavior and relatively lower levels of depression than AD patients. Rankin et al (in press) set out to quantify spontaneous social behavior during subject interview to discriminate FTD from SD and other dementias. Following a one-hour interaction during which cognitive tests were administered, clinicians rated subjects on how often they engaged in abnormal social behavior, such as interrupting the examiner, perseverating on a specific topic, ignoring personal boundaries, or making personal comments. They found that FTD patients demonstrated specific social behaviors during clinical interactions that helped to discriminate them from other dementias and normal controls. FTD individuals were more likely to be rated as tending to exhibit an

unusual calmness or ease during the evaluation, and a subset of the FTD patients demonstrated disinhibited behavior such as crossing personal boundaries. They also were more likely to be perseverative, becoming fixated on a certain topic or stimulus that prevented the examiner from continuing the assessment. In contrast, individuals with AD were similar to normal controls on the clinician rating scales. Further, the behaviors displayed by the FTD subjects allowed the examiners to differentiate them from psychiatric patients. This differentiation is very important because early FTD patients are often referred for psychiatric care by their primary care physicians due to behavioral and personality changes that are generally most prominent before cognitive changes can be noted.

Important insights into FTD have been obtained from studies measuring change in social functioning. Rankin et al (2003), for example, obtained premorbid and current first-degree relative ratings of social behavior using an established measure of interpersonal functioning, the Interpersonal Adjectives Scales, to measure personality change in 16 patients with FTD, 13 with SD, and 16 with AD. All three groups showed significant change over time in multiple domains, including increased introversion and submissiveness. However, patients with FTD evidenced significantly greater increases in overall interpersonal pathology than patients with AD. Patients with FTD showed a large increase in submissiveness, whereas patients with SD showed a significant increase in cold-heartedness. FTD patients also demonstrate minimal insight into their personality changes (Salmon et al., 2007), exaggerating their positive qualities and minimizing their negative qualities, whereas patients with AD showed accurate self awareness in all personality dimensions except submissiveness and extraversion (Rankin et al., 2005).

Differentiation of FTD from AD

Using neurocognitive assessment to differentiate between FTD and AD is often difficult, in part because FTD is primarily a behavioral disorder. In addition, neuropsychological deficits are driven by neuroanatomy rather than pathology, and there is some overlap in the atrophy patterns across neurodegenerative syndromes. As previously noted, FTD can be associated with hippocampal injury (Grossman et al., 2007; Hatanpaa et al., 2004), and frontal variants of AD have been identified (Johnson, Head, Kim, Starr, & Cotman, 1999).

Despite these challenges, some studies have demonstrated reasonable success at differential diagnosis. In their meta-analysis of 94 studies and over 4600 FTD and AD patients, Hutchinson and Mathias (2007) reported that measures of orientation, memory, language, visuomotor function, and general cognitive ability were the most discriminating between AD and FTD, although their overall samples were not well matched on age and global cognition (e.g., MMSE) and several studies combined the behavioral and language variants of FTLD. Kramer et al. (2003) assessed the ability of a brief neuropsychological bedside screening battery to discriminate between groups of AD, FTD, and SD patients with comparable age, education, and MMSE score. The neuropsychological screening assessed episodic memory, working memory, executive function, naming, spatial ability, abstract reasoning, and calculations. The FTD group had the best verbal memory but performed significantly worse on backward digit span and made significantly more executive errors, whereas the AD group was impaired on verbal and the SD group was most impaired on verbal memory and confrontation naming. A discriminant function analysis identified that the five most discriminating variables, Boston Naming, recall of the modified Rey figure, CVLT-SF delayed recall, category fluency, and executive errors (rule violations and perseverations) correctly classified 89.2% of cases.

Libon et al (2007) also emphasized the importance of episodic memory and errors. They studied over 100 subjects with a comprehensive neuropsychological battery that yielded

factor scores measuring declarative memory, working memory/visuoconstruction, processing speed/mental flexibility, lexical retrieval, and semantic memory. AD patients did least well on tests of declarative memory and SD patients were particularly impaired in semantic memory. Their FTD group (called "social comportment/dysexecutive patients) actually performed more quickly than the other groups on tests of processing speed/mental flexibility, but made more errors. Rascovsky et al. (2007) found that verbal fluency alone could reliably discriminate between path-confirmed cases FTD and AD. Their subjects were administered three phonemic fluency conditions (letters F-A-S) and three category conditions (animals, fruits, and vegetables). Their primary dependent measure was the semantic ratio, i.e., the proportion of total fluency responses that came from the category fluency trials. As expected, the semantic index was significantly lower in AD than FTD even though overall, FTD patients produced fewer words than patients with AD. A logistic regression showed that an optimal semantic index cutoff score of .552 correctly classified 92.3% of AD patients and 84.6% of FTD patients, for an overall correct discrimination rate of 89.7%.

Mendez et al. (2007) found that neuropsychological measures lacked sensitivity for accurate diagnosis of FTD at initial presentation. However, the pattern of progression on neuropsychological tests was helpful at establishing diagnosis over time, with worsening naming and executive functions and preserved constructional ability noted at follow-up. Some other brief batteries have found moderate success in differentiating early FTLD patients, as a general syndromic group, from early AD patients by focusing on language impairments. However, the language impairments are commonly seen in the aphasic PPA subtypes of FTLD but not in the behavioral variant, therefore, the specificity of the brief batteries is lacking for the former group (Gregory, Orrell, Sahakian, & Hodges, 1997; Liscic, Storandt, Cairns, & Morris, 2007; Mathuranath, Nestor, Berrios, Rakowicz, & Hodges, 2000). These batteries have not been successful at identifying specific objective achievement measures on which early FTD patients perform more poorly than and can be easily discriminated from early AD patients.

Improvements in differential diagnose will likely come from incorporating behavioral and social measures, since these symptoms define the disorder and are the first to emerge. The most common behavioral changes include apathy, disinhibition, and inappropriate social conduct. Some studies have shown that the caretaker report of behavioral change is often the best way to differentiate between FTD and AD (Binetti, Locascio, Corkin, Vonsattel, & Growdon, 2000; Gregory et al., 1997). The hallmarked behavioral and functional changes are identified by the caretakers and quantified through their responses on measures like the NPI, Interpersonal Reactivity Index (IRI), Interpersonal Adjectives Scales, and Clinical Dementia Rating Scale (CDR).

Bozeat et al. (2000) investigated whether changes in mood, personality, and behavior could differentiate between FTD, SD, and AD using a questionnaire designed to assess a wide range of neuropsychiatric symptoms. A factor analysis showed four symptom clusters, stereotypic and eating behavior, executive dysfunction and self care, mood changes, and loss of social awareness. Stereotypic and altered eating behavior and loss of social awareness reliably differentiated AD from FTD with no effect of disease severity. By contrast, executive dysfunction, poor self care, and restlessness showed a significant effect of disease severity only, and changes in mood were found to be equally prevalent in the three patient groups. Discriminant function analysis correctly classified only 71.4% of subjects, however.

Although not the focus of this review, neuroimaging methods are likely to prove an important part of the differential diagnosis of FTD. Mendez et al (2007), for example, concluded that neuroimaging, particularly functional brain studies, greatly increased the

sensitivity of detecting FTD over what was possible with neuropsychological measures. Atrophy patterns in FTD are predominately frontal, but extend well beyond the frontal lobes and are more evident in some frontal regions than others. Cardenas et al. (2007) used deformation-based morphometry methods to analyze the structural MRIs of 22 subjects with FTD and 22 cognitively normal, age-matched controls. Patients with FTD showed extensive frontal atrophy affecting both gray matter and white matter. There was a smaller degree of atrophy bilaterally in the anterior temporal lobes. Subcortical and midbrain regions, including the thalamus, pons, and superior and inferior colliculi also showed significant atrophy, although to a lesser degree than cortical regions. Volume loss is initially seen in the orbitofrontal cortex before frontal atrophy becomes more widespread and includes dorsolateral regions (Perry et al., 2006). Significant atrophy has also been reported in the ventromedial and posterior orbital frontal regions as well as the insula and the anterior cingulate cortex (Rosen et al., 2002). MRI-perfusion has also shown hypoperfusion in right frontal regions in FTD patients relative to controls, and higher perfusion than AD in the parietal lobes and posterior cingulate. Frontal hypoperfusion in FTD correlated with deficits in judgment and problem solving. Adding frontal perfusion to gray matter (GM) atrophy significantly improved the classification of FTD from normal aging to 74%, and adding parietal perfusion to gray matter atrophy significantly improved the classification of FTD from AD to 75%. Combining frontal and parietal lobe perfusion further improved the classification of FTD from AD to 87% (Du et al., 2006).

The recent development of PIB, a PET tracer with amyloid binding properties that enable in vivo measurement of cerebral amyloid load, also has tremendous potential for differential diagnosis. Because amyloid deposition is a marker of AD, but is not characteristic of FTD, PIB scanning could dramatically reduce the number of misdiagnosed patients. Several studies have already shown that clinically diagnosed FTD patients are much less likely to show amyloid deposition relative to AD patients (Engler et al., 2008; Rabinovici, Furst et al., 2007; Rowe et al., 2007).

Contributions to cognitive neuroscience

Patients with FTD offer a unique opportunity to study brain-behavior relationships. The constellation of social and behavioral changes typical of FTD are rarely seen in other disorders, and the relatively focal pattern of atrophy and hypoperfusion offers a window into understanding what role these anterior structures play in cognition and complex social behavior.

FTD has been a useful working model of the importance of the right-hemisphere in behavioral control. For example, Mychack et al. (2001) tested the hypothesis that right-sided FTD is associated with socially undesirable behavior. Based on visual inspection of SPECT scans, 12 patients were classified as having predominantly right-sided and 19 patients were classified as having predominantly left-sided FTD. A clinician blinded to the imaging data reviewed medical records to tabulate the frequency of the following socially undesirable behaviors: criminal behavior, aggression, loss of job, alienation from family/friends, financial recklessness, sexually deviant behavior, and abnormal response to spousal crisis. Eleven of 12 right-sided but only 2 of 19 left-sided FTD patients had socially undesirable behavior as an early presenting symptom, highlighting the importance of the right hemisphere in mediating social behavior. Rosen et al. (2005) used voxel-based morphometry to identify relationships between structural MRI and neuropsychiatric symptoms. Four of the 12 behaviors studied, apathy, disinhibition, eating disorders and aberrant motor behavior, showed clear correlations with brain regions, all of which were in the right hemisphere.

Studies of FTD have been particularly useful in learning how specific brain regions might mediate certain aspects of social behavior. In the Rosen et al. (2005) study, apathy was independently associated with tissue loss in the right ventromedial superior frontal gyrus, disinhibition with tissue loss in the right subgenual cingulate gyrus in the ventromedial prefrontal cortex, and aberrant motor behavior with tissue loss in the right dorsal anterior cingulate and left premotor cortex. These results are of particular importance in that they highlight the importance of the medial wall of the right frontal lobe in behavioral regulation.

Insights into the neuroanatomy of empathy have also been garnered from FTD patient groups. Severe empathy loss is a common feature in both FTD and SD. In one study, the Interpersonal Reactivity Index (IRI) Empathic Concern and Perspective taking scores were correlated with structural MRI brain volume using voxel-based morphometry (Rankin et al., 2006). Voxels in the right temporal pole, the right fusiform gyrus, the right caudate and right subcallosal gyrus correlated significantly with total empathy score after whole-brain correction for multiple comparisons. These findings are consistent with previous research suggesting that a primarily right frontotemporal network of brain regions is involved in emotion processing, and highlights the roles of the right temporal pole and inferior frontal/striatal regions in regulating complex social interactions.

Several studies of FTD patients have also suggested neuroanatomical models of emotion processing. Rosen et al. (2006) reported that a region in the right lateral inferior temporal gyrus (Brodman's area 20) extending into the right middle temporal gyrus (BA 21) was correlated with accuracy of emotion recognition. This effect appeared to be strongest for sadness, which was also independently correlated with atrophy in the superior temporal gyrus. These data suggest that regions in the right lateral and inferolateral temporal lobe are important for visual processing of negative emotions from faces and that functioning of this right temporal network is most critical for recognition of sad faces. A significant role for the right amygdala in recognition of negative facial affect has also been reported (Rosen, Pace-Savitsky et al., 2004). Werner et al. (2007) examined two aspects of emotional processing (emotional reactivity and emotion recognition) in FTLD subjects using measures of self-reported emotional experience, emotional facial behavior, autonomic nervous system response to film stimuli, ability to identify a target emotion of fear, happy, or sad experienced by film characters. FTLD patients were significantly impaired compared with controls in emotion recognition for the fear and sad film clips. MRI volumetrics revealed that deficits in emotion recognition were associated with decreased frontal and temporal lobar volumes.

In an excellent review, Viskontas (2007) described several ways in which studies of FTD have elucidated the role of orbitofrontal cortex (OFC) in social and emotional behavior. The OFC is involved early in FTD along with an associated network involving the insula, striatum, and medial frontal lobes. This network is likely the neuroanatomical substrate for the observed impairments involving stimulus-reward reversal learning, response inhibition, and ability to judge the appropriateness of their behavior in the social context. Also, deficits in emotion recognition and empathy have been directly linked to OFC atrophy in these patients, even in very early FTD when cognitive skills are still relatively intact. Disruption to this orbitofrontal-insular-striatal circuit may also contribute to the hyperorality and weight gain commonly observed in FTD. Woolley et al (2007) performed a free-feeding study of 18 healthy control subjects and 32 patients with neurodegenerative disease, most of whom fell in the FTLD spectrum. Despite normal taste recognition, 6 of 32 patients compulsively binged, consuming large quantities of food after reporting appropriate satiety. All six patients who overate were clinically diagnosed with FTD. Voxel-based morphometry indicated that the binge-eating patients had significantly greater atrophy in the right ventral

insula, striatum, and orbitofrontal cortex, further supporting a model in which right-sided ventral insular and orbitofrontal cortices play a pivotal role in behavioral regulation.

Studies using FTLD subjects have also contributed to the literature on the relationships between cognition and brain structure. Set-shifting, for example, has been linked to bilateral frontal volumes, even after carefully controlling for all component cognitive skills involved in the shifting task and after controlling for the contributions of non-frontal brain regions (Kramer, Quitania et al., 2007). A specific relationship has also been found between rule violations on cognitive tests and right dorsolateral prefrontal cortex (Possin et al., 2008). In this study, MRI images and neuropsychological test data were collected from a heterogeneous sample of 118 subjects. A principal components analysis showed that rule violation errors made across four subtests from the Delis-Kaplan Executive Function System tapped a shared construct separate from repetition errors, and based on these results, rule violation factor scores were generated. The relationship between the factor scores and regional differences in grey matter atrophy was examined using voxel-based morphometry. A covariates-only statistical model was used with age, sex, and MMSE scores entered as nuisance covariates, and total grey matter volume entered as a global covariate. After whole-brain correction for multiple comparisons, a significant relationship was observed between rule violation errors and right dorsolateral prefrontal cortex atrophy.

Conclusions

The FTLD constellation of disorders, and FTD in particular, continue to be underdiagnosed and misdiagnosed, despite being fairly common presenile neurodegenerative diseases. The past decade has seen significant advances in our understanding of the molecular, genetic, imaging, and behavioral changes associated with these syndromes, and the development of methods that can potentially improve early detection. The role of neurocognitive testing for early diagnosis will likely be small in that FTD is fundamentally a behavioral disorder, and cognitive deficits may be difficult to document. Neuropsychologists are in an excellent position, however, to draw from related disciplines like personality theory and social psychology to better assess the types of changes that do characterize the prodromal and early phases of the disease. Investigations of early FTD have taught us the importance of a neural network involving frontal insula, anterior cingulate, orbitofrontal cortex, and striatum, particularly in the right-hemisphere (Rabinovici, Seeley et al., 2007), and have elucidated this network's role in empathy, inhibition, reward systems, appetitive behaviors, emotional regulation, and goal-orientation. Early FTD remains a powerful model for studying brain-behavior relationships.

Clinically, neuroimaging and careful family histories taken from informants will play an increasing role in determining which patients are more likely to have early FTD. Subtle changes in motivation and social interaction can also be found in psychiatric disorders, and the differential diagnosis during prodromal phases is difficult. Although treatments for FTD are not well developed, early and accurate diagnosis remains essential to help patients and families plan for the future and to avoid the tragedy of inappropriate and counterproductive interventions.

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