Executive functions can help when deciding on the frontotemporal dementia diagnosis

David P. Salmon, PhD
Donald T. Stuss, PhD

Correspondence to
Dr. Salmon:
dsalmon@ucsd.edu

Neurology® 2013;80:2174–2175

Frontotemporal degeneration (FTD) is the overarching label used to describe a spectrum of neurodegenerative disorders characterized by relatively circumscribed frontal and temporal lobar atrophy that leads to profound changes in personality, behavior, or language. The dementia syndrome associated with FTD is usually divided into 2 broad categories: a language-based variant referred to as primary progressive aphasia[1] and a behavioral variant frontotemporal dementia (bvFTD) in which changes in social cognition, behavior, and personality are the earliest and most prominent features.[2] Although not as common as Alzheimer disease (AD), FTD is not rare and accounts for about 9% of all cases of dementia, and is particularly prevalent when the age at onset of dementia is younger than 65 years.[3]

Recent research has made great progress in differentiating the molecular pathology of FTD from that of AD. In contrast to the ubiquitous β-amyloid plaque and neurofibrillary tangle pathology of AD, FTD is characterized by heterogeneous pathology that includes tau pathology with or without Pick bodies (i.e., Pick disease), tarDNA binding protein (TDP-43) inclusions, and fused-in-sarcoma protein (FUS) inclusions.[4] In a small number of cases, FTD may lack distinctive histopathology. There has been progress in clinically differentiating between FTD and AD during life. There are recently revised clinical criteria for both language[5] and behavioral[2] variants of FTD, and in the case of bvFTD, these have been validated against pathologically verified disease.[2]

The revised clinical criteria for bvFTD emphasize the preeminence of behavioral changes in the clinical presentation of the disease. The emergence of personality and behavioral changes such as inappropriate social conduct, inertia and apathy, disinhibition, perseverative behavior, loss of insight, diminished empathy, and hyperorality form the core criteria for the diagnosis of the disease. The veracity of the clinical diagnosis is strengthened when these core behavioral features are supported by neuroimaging evidence of bilateral frontal and anterior temporal atrophy and hypometabolism that is distinct from the medial temporal lobe atrophy and temporo-parietal hypometabolism associated with AD.[6,7]

Neuropsychological testing can provide additional support for the clinical diagnosis of bvFTD. Studies using batteries of neuropsychological tests suggest that FTD and AD are associated with distinct cognitive profiles that might aid the differential diagnosis (for review, see reference 8). Particularly compelling are retrospective studies that demonstrated a double dissociation, in which patients with mild to moderate dementia with autopsy-confirmed FTD are more impaired than those with autopsy-confirmed AD on executive function tests sensitive to frontal lobe dysfunction, but less impaired on tests of memory and visuospatial abilities sensitive to dysfunction of medial temporal and parietal association cortices (e.g., reference 9). Executive functions refer to high-level cognitive functions such as planning, initiation, purposive action, self-monitoring, and self-regulation that are involved in the control and direction of lower-level functions.[10] These abilities are often affected by damage to the frontal lobes, and their dysfunction can be demonstrated on cognitive tests that require problem solving, shifting of cognitive set, initiation of behavior (as during rapid word generation), inhibition of inappropriate responses, working memory, or control of attention.[10] Although patients with FTD perform worse than patients with AD on many of these tests, some tests of frontal lobe function are equally affected in the 2 disorders, reducing their usefulness for differential diagnosis.

In this issue of *Neurology*®, Possin et al.[11] report a study that compared the performances of patients with bvFTD and patients with AD on a newly developed battery of executive function tests known as EXAMINER. The investigators proposed that some of the "frontal lobe function" tests in the EXAMINER battery actually engage fronto-parietal networks and may be similarly impaired in patients with bvFTD and AD, whereas others are more circumscribed in engaging the frontal lobes (and particularly ventral regions such as the orbitofrontal cortex) and may be more severely impaired in bvFTD than in

See page 2180

From the Department of Neurosciences (D.P.S.), University of California, San Diego; and the Ontario Brain Institute (D.T.S.), Rotman Research Institute of Baycrest, University of Toronto, Toronto, Canada.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the editorial.

AD. The results supported their hypothesis, with patients with bvFTD more impaired (relative to the performance of healthy elderly individuals) than patients with AD on the frontal tasks (i.e., Anti-Saccade Test, Letter Fluency Test, Social Norms Questionnaire, Behavioral Rating Scale), and patients with bvFTD and patients with AD impaired to a similar degree on the fronto-parietal tasks (i.e., Set-Shifting Test, Flanker Test, Spatial 1-Back Test, Dot Counting Test, Category Fluency Test). A discriminant function analysis showed that the 4 frontal tasks correctly classified 13/20 patients with bvFTD and 19/24 patients with AD, for an overall classification accuracy of 73%. Thus, patients with bvFTD show pervasive dysfunction on the EXAMINER battery and are more impaired than patients with AD specifically on those tasks that primarily engage frontal lobe function. The results suggest that frontal-specific tests, possibly targeting specific frontal lobe regions, can assist in differential diagnosis of these 2 disorders.

Because accurate differential diagnosis is crucial given potential differences in prognosis and appropriate pharmacologic and behavioral management strategies for bvFTD and AD,[2] it is important to determine how cognitive testing can support this effort. The study by Possin et al.[11] makes important progress toward this goal by showing that tests that presumably engage circumscribed frontal lobe circuits (particularly those of the ventral aspects of the frontal lobes[10]) can distinguish between FTD and AD, while those that presumably engage fronto-parietal circuits affected in both disorders do not. Future research is needed to determine the added value that these distinct patterns of executive function deficits provide to differential diagnosis that is currently based largely on changes in personality and behavior.

AUTHOR CONTRIBUTIONS

David P. Salmon: drafting/revising the manuscript. Donald T. Stuss: drafting/revising the manuscript.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

D. Salmon serves as a consultant for Bristol-Myers Squibb. D. Stuss reports no disclosures. Go to Neurology.org for full disclosures.

REFERENCES

1. Mesulam M. Primary progressive aphasia: a language-based dementia. N Engl J Med 2003;349:1535–1542.
2. Rascovsky K, Hodges JR, Knopman D, et al. Sensitivity of revised diagnostic criteria for the behavioral variant of frontotemporal dementia. Brain 2011;134:2456–2477.
3. Neary D, Snowden J, Mann D. Frontotemporal dementia. Lancet Neurol 2005;4:771–780.
4. Mackenzie IR, Neumann M, Bigio EH, et al. Nomenclature and nosology for neuropathologic subtypes of frontotemporal lobar degeneration: an update. Acta Neuropathol 2010;119:1–4.
5. Gorno-Tempini ML, Hillis AE, Weintraub S, et al. Classification of primary progressive aphasia and its variants. Neurology 2011;76:1006–1014.
6. Foster N, Heidebrink JL, Clark CM, et al. FDG-PET improves accuracy in distinguishing frontotemporal dementia and Alzheimer's disease. Brain 2007;130:2616–2635.
7. Grossman M. Biomarkers in frontotemporal lobar degeneration. Curr Opin Neurol 2010;23:643–648.
8. Wittenberg D, Possin KL, Rascovsky K, et al. The early neuropsychological and behavioral characteristics of frontotemporal dementia. Neuropsychol Rev 2008;18:91–102.
9. Rascovsky K, Salmon DP, Ho GJ, et al. Cognitive profiles differ in autopsy-confirmed frontotemporal dementia and AD. Neurology 2002;58:1801–1808.
10. Stuss DT. Function of frontal lobes: relation to executive functions. J Int Neuropsychol Soc 2011;17:759–765.
11. Possin KL, Feigenbaum D, Rankin KP, et al. Dissociable executive functions in behavioral variant frontotemporal and Alzheimer dementias. Neurology 2013;80:2180–2185.