Neuropsychology of Frontotemporal Dementia and

Primary Progressive Aphasia

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ABSTRACT

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Scientific background: This paper reviews the neuropsychological features of frontotemporal dementia (FTD) and Primary Progressive Aphasia (PPA). Diagnostic criteria and classification systems, the role of neuropsychological assessment in differential diagnosis, and findings primarily from neuropsychological studies on attention/executive function, memory, language, and visuospatial abilities are covered. Recommended batteries for the assessment and differential diagnosis are also reviewed. An example of neurocognitive profiles from FTD, PPA, and Alzheimer's disease (AD) subjects enrolled in the Northwestern Alzheimer's Disease Center AD is provided to illustrate distinguishing clinical features of these dementia syndromes.

INTRODUCTION

Frontotemporal lobar degeneration (FTLD) refers to a group of non-amnestic degenerative syndromes, characterized primarily by behavioral or language-predominant symptoms at onset.[1] The behavioral variant has been termed frontotemporal dementia (FTD), or frontal lobe dementia (FLD),[2] although both terms are synonymous and refer to a progressive decline in behavior and/or comportment as well as impairments in executive functions.[3, 4] In the Neary et al. classification system, the language variant is subdivided into semantic dementia (SD), a syndrome in which there is a prominent fluent aphasia with impaired single word comprehension and (in some cases) deficits of visual recognition, and progressive non-fluent aphasia (PNFA), used to describe patients with a non-fluent aphasia and relatively preserved comprehension. A similar dementia syndrome of language deterioration in the absence of memory or other cognitive changes, termed primary progressive aphasia (PPA), was first described by Mesulam in 1982,[5] and recently updated.[6] PPA encompasses both PFA and SD without visual agnosia. PPA can be differentiated from the clinical syndrome typical of Alzheimer's disease (AD) by the relative preservation of memory, and from FTD by the relative sparing of frontal lobe functions and appropriateness of behavior.

DIAGNOSTIC TESTS

Magnetic resonance imaging (MRI) is recommended for use in the diagnosis of dementia[7] mainly as a means of excluding other causes such as cerebrovascular disease and space occupying lesions. However, few studies have demonstrated the clinical utility of MRI specifically in the diagnosis of early FTD or PPA. Patients with FTD have been shown to have greater atrophy in the anterior brain regions[8] and different patterns of temporal atrophy[9] compared to AD. PPA patients typically show focal atrophy of the left hemisphere frontal, temporal, insular and parietal components of the language network.[10, 11] Similar to AD subjects, discernable atrophy on MRI is not a consistent finding in the early stages of FTD or PPA. Therefore, the finding of frontal atrophy or focal left hemisphere atrophy may increase the likelihood of a diagnosis of FTD or PPA respectively, the absence of structural abnormalities in the early stages of the disease should not be used to rule out a diagnosis of FTD or PPA.

The pattern of abnormalities seen in functional neuroimaging, such as single photon emission tomography (SPECT) and positron emission tomography (PET), in FTD has also been proposed as a means of differentiating this syndrome from AD. FTD subjects tend to show hypoperfusion of anterior cortex, with relatively normal posterior cortex functioning in SPECT studies.[12, 13] Reduced metabolism in frontotemporal regions as well as basal ganglia and/or parietal lobes in FTD has been shown with PET imaging.[14] In PPA, metabolic abnormalities tend to parallel predominant language dysfunction, in that non-fluent patients have reduced metabolism in left frontal areas, while fluent patients with impairments in comprehension tend to have reduced left temporal metabolism.[15, 16] Despite these relatively focus findings, evidence that functional imaging improves upon diagnostic accuracy based on clinical symptoms alone has not been demonstrated.

Although significant advances have been made recently in understanding genetic factors in FTD and PPA,[17, 18] the neuropsychological profile continues to be one of the most sensitive measures for the early detection and diagnosis of these syndromes.

NEUROPSYCHOLOGICAL ASSESSMENT

Screening tests

In general, neuropsychological assessment combines standardized testing with expert clinical knowledge of principles of brain-behavior relationships and diseases that can impair brain function.[19] Neuropsychological testing can range from simple, brief screening instruments, to extensive testing batteries that may require 8 or more hours to administer. Most of the screening instruments developed to detect dementia have been studied primarily in control subjects or in patients with AD. For example, The Mini Mental State Exam (MMSE),[20] developed as a brief screening test for dementia, has been used frequently in epidemiologic studies as a screening for cognitive impairment,[21] and is often considered a “gold standard” against which to examine validity of novel disease severity instruments.[22, 23] It has been shown to be relatively stable in non-demented elderly (ages 70 – 88),[24] even over a 5-year period.[25] The MMSE has been used

in numerous studies of AD and has been shown to be effective in differentiating AD from non-demented elderly subjects,[26] predicting conversion to AD,[27] and estimating progression rates.[28] The utility of the MMSE in detecting non-AD dementias, and in differentiating between dementia syndromes, has not been demonstrated. Because most of the items on the MMSE are language-based, scores for PPA patients are likely to overestimate their level of impairment. Conversely, the MMSE may underestimate the level of disease severity in FTD patients, many of whom continue to score normally even when requiring nursing home care.[29]

The Addenbrooke's Cognitive Examination (ACE) was developed as a screening measure specifically designed to differentiate FTD from AD.[30] Total administration time is estimated to be between 15-20 minutes. The ACE is comprised of component scores that assess six cognitive domains, including orientation, attention, memory, verbal fluency, language, and visuospatial skills. The sum of the component scores provides a composite score (100 points) and cut-off scores of 88 and 83 have been shown to effectively predict dementia.[31] The ACE is also comprised of a Verbal-Language/Orientation-Memory (VLOM) ratio, which compares language and memory scores [(verbal fluency + language)/ (orientation + memory)], and it is used to determine whether FTD or AD is the more likely clinical diagnosis. A VLOM ratio of < 2.2 was found to be useful for differentiating FTD from non-FTD (sensitivity %58 and specificity %97) and >3.2 for differentiating AD from non-AD (sensitivity %75 and specificity %84). However, a later study suggests the VLOM ratio formula has good specificity (%88), but poor sensitivity (%11.1) in the diagnosis of FTD when a cutoff score < 88 is used.[30]

Comprehensive test batteries

A comprehensive test battery that includes multiple instruments assessing all cognitive domains (i.e., attention, memory, visuospatial abilities, language and executive functioning) is likely to be more effective in early differential diagnosis of FTD and PPA. However, time and labor-intensive comprehensive test batteries are impractical for older adults, especially for those diagnosed with dementia and are in the later stages of the disease process. Therefore, the clinician should focus on cognitive domains that are most relevant for a particular patient's symptom presentation and de-emphasize those that are not.

Using a comprehensive battery allows a profile of primary deficits to be determined and distinguished from secondary deficits that may arise as the result of language or executive function impairments. For example, a PPA patient with a prominent aphasia may score poorly on tests of other cognitive domains that are verbally mediated, such as story or word list learning tests, verbal reasoning tests, orientation measures, etc. In this case, nonverbal measures for memory and other areas would be more likely to provide an accurate assessment of these cognitive functions. Similarly, patients with FTD may demonstrate poor test performance in multiple cognitive domains due to difficulties in sustaining attentional focus, impairments in motivation and task persistence, and poor organizational and problem solving strategies. The expertise of the clinician and availability of a flexible array of instruments appropriate to the patient's symptom presentation are crucial in order to derive an accurate diagnosis.

NEUROPSYCHOLOGICAL PROFILES of FTD and PPA

Table 1. Neuropsychological characteristics of early FTD, PPA and AD

Cognitive Domain	AD	FTD	PPA
Attention			
Attention span	Intact	Intact	Non-verbal intact
Working memory	Intact	Impaired	Reduced
Executive functions	Intact	Impaired	Non-verbal intact
Language			
Naming	Mildly reduced	Intact	Semantic impaired
Verbal fluency	Intact	Reduced	Logopenic impaired
Complex comprehension	Intact	Intact	Agrammatic impaired
Visuospatial	Impaired	Impaired due to executive functions	Intact
Memory			
Orientation	Impaired	Intact	Intact
Verbal	Severely impaired	Impaired encoding intact retention	Impaired, due to language deficits
Visual	Severely impaired	Impaired encoding intact retention	Intact
Behavior	Intact or mildly reduced	Severely impaired	Intact
Mood	Risk of depression	Generally intact	Risk of depression
Insight	Intact or mildly reduced	Severely impaired	Intact
Activities of Daily Living	Mildly reduced	Judgment, decision making impaired	Intact

Table 1 provides a summary of typical impairments in FTD, PPA, and AD in each of the major cognitive domains. It is important to remember that there is a great deal of heterogeneity in symptoms between individual patients, and therefore the presence of any single impairment should not be considered pathognomonic, but rather be considered in the context of the overall neuropsychological evaluation results.

Neurocognitive Profile in FTD

Unlike studies of early AD subjects, where episodic memory is almost universally found to be the primary impairment on neuropsychological testing,[32, 33] studies of neuropsychological functioning in early FTD subjects have yielded more variable results. This may be due to the fact that FTD subjects may show secondary impairments in other cognitive domains as the result of executive function problems. Another potential explanation for the lack of consistent findings is that not all studies differentiate between the behavioral and language subtypes of FTD, which may lead to increased variability within the FTD group and obscure differences between FTD and other groups.

Based on the areas of early degeneration in FTD, predominant deficits would be most likely in the domains of attention/working memory processes and executive functioning (i.e., abstract reasoning, planning, organization, and problem solving). Greater impairment in executive functions in FTD compared to AD has been indicated by some researchers,[31, 34] and other studies have demonstrated the usefulness of tasks of attention and executive function in assisting the early differential diagnosis of FTD and AD.[35-38] However, there have been studies that did not find consistent differences on attention/executive measures when patients with FTD and AD were directly compared.[39, 40] Thompson et al[41] found FTD and AD group differences on a range of neuropsychological test scores across multiple domains, but these differences did not occur consistently across tests within any cognitive domains, with the exception of executive functioning.

Although the majority of studies find FTD subjects less impaired on memory testing relative to AD patient,[19, 36, 37] others have not shown this difference,[42] possibly due to the type of memory testing used. Wicklund et al[43] compared memory performance in FTD and AD and found that FTD patients encoded and recalled more details from a story than AD patients, but no differences in encoding were found on a word list-learning test. However, FTD patients recalled more words after a delay than AD patients, and percent retention on both tasks was greater for the FTD group.

Rascovsky et al[44] retrospectively examined cognitive test scores in autopsy-confirmed FTD and AD. Their results showed FTD subjects performed worse than AD on word generation tasks and better than AD on tests of visuospatial abilities and memory. Various studies have shown that unlike the high correlation between clinical memory impairment and Alzheimer's disease neuropathology, multiple degenerative diseases can be associated with the clinical syndromes of FTD and PPA,[45-48] and no specific clinical findings have been found to predict the underlying neuropathology.[46, 49]

Behavioral Profile in FTD

Alterations in behavior and personality are among the most salient features in FTD and have been shown to be highly specific for differentiating FTD from other forms of dementia,[50] and may often precede the decline in cognition.[29] Information about behavioral changes relies heavily on the availability of a reliable informant and can be difficult to objectively quantify. The use of structured questionnaires, such as the Neuropsychiatric Inventory (NPI)[51] and Frontal Behavioral Inventory (FBI)[52] is helpful in ensuring a comprehensive evaluation of behavioral changes.

The NPI is a caregiver-based questionnaire that evaluates the following behaviors: delusions, hallucinations, dysphoria, anxiety, agitation/aggression, euphoria, disinhibition, irritability/lability, apathy, aberrant motor behavior, sleep and appetite change. If the informant acknowledges the presence of a symptom, the frequency and severity of the behavior are then rated. Total frequency and severity scores can be determined and higher scores are associated with greater abnormality. This questionnaire is unique in that it also estimates the amount of distress or burden that each behavior causes the caregiver.

FTD subjects matched for disease severity have been shown to have higher total NPI scores compared to AD subjects, and to demonstrate greater levels of apathy, disinhibition, euphoria, and

aberrant motor behavior.[53, 54] The NPI been shown to be sensitive to detecting behavioral changes in FTD and PPA and may also be useful in tracking progression or emergence of behavioral symptoms over time.[55]

The FBI includes 24 items that represent both negative and positive behavioral symptoms. The behaviors are rated based on frequency ranging from symptoms "not present" to symptoms that are "severe" or occur "most of the time". Behavioral symptoms include apathy, aspontaneity, emotional indifference, inflexibility, concreteness, personal neglect, distractibility/disorganization, inattention, loss of insight, logopenia, verbal apraxia, alien hand, perseveration, disinhibition/ irritability, jocularity, irresponsibility/poor judgment, social inappropriateness, impulsivity, euphoria/restlessness, aggression, hyperorality, hypersexuality, utilization behavior, and incontinence.

Although there is no normative data available for the FBI, FTD subjects have been found to show significantly higher scores compared to AD, PPA, vascular dementia, and depressive disorder patients.[56] The FBI has also been shown to improve diagnostic accuracy when added to traditional neuropsychological tests. The FBI correctly classified %95 of FTD subjects, while cognitive testing alone was only successful in discriminating %78 from subjects with AD. In addition, a cutoff score of 27 or higher was found to give optimal sensitivity and specificity.[39] The FBI is also useful in tracking progression of behavioral symptoms in FTD over time.[57]

Recommended battery for assessment of FTD

Tests of executive functions should be included in any neuropsychological battery for FTD. Table 2 in Wicklund et al[19] lists a number of possible measures rated according to severity level. In general, however, measures of reasoning and cognitive flexibility (i.e., Wisconsin Card Sort Test[58]), and response inhibition (i.e., Stroop Color Word Test[59]) have been found to be sensitive to frontal lobe dysfunction,[29] and should be included in the assessment of suspected FTD. The Go-NoGo paradigm is another measure of response inhibition that has been shown to be sensitive to subtle changes in frontal lobe functions.[60] Patients with FTD have also been shown to perform poorly on tests of attention and working memory. In particular, the FAS lexical fluency test has been shown to be differentially impaired in FTD in multiple studies.[41, 44, 61] Other measures of attention and working memory include the Digit Span subtest from the Wechsler Adult Intelligence Scale-3rd Edition (WAIS-III)[62] and the Trail Making Test.[63]

Memory tests with repeated learning trials, followed by recognition, such as the California Verbal Learning Test-II (CVLT-II),[64] are useful in providing an accurate examination of the impact of attentional and executive impairments on episodic memory. The CVLT-II is particularly useful because it includes normative data for repetition and intrusion errors, two types of responses that are typically prominent in the profiles of FTD patients. The CVLT-II also allows for the examination of learning strategies that can enhance encoding. Although the 16 words are presented in random order, they can be grouped into four categories (e.g., tools, fruits, insects, and clothing). The patient's use of clustering, an active learning strategy which requires the ability to organize the words into categories for easier recall, can be used as a measure of frontal dysfunction.

Tests of visuoperception and language, although not typically affected by frontal lobe dysfunction, are recommended in the test battery to assist in diagnosis. The Boston Naming Test (BNT)[65] is a

measure of confrontation naming that helps in profiling access to language in FTD. Comprehension can be objectively measured using subtests from a larger aphasia battery, such as the Western Aphasia Battery,[66] or grossly examined by the patient's ability to follow conversation and understand test instructions. A measure of constructional ability such as the Rey Complex Figure Copy,[67] can be useful especially when a qualitative interpretation is included to examine problem solving approach and organizational strategies.

Neurocognitive Profile in PPA

By definition, language disturbances are the most salient feature in the early clinical picture of PPA. In fact, the diagnostic criteria require at least two years of isolated language impairment with relatively intact functioning in other cognitive abilities such as episodic memory, visuospatial skills, reasoning, and comportment.[10] Deficits in other cognitive domains can eventually emerge after the initial few years, but the language dysfunction remains the most salient feature and advances most rapidly, throughout the course of the illness.[6] Primary progressive aphasia is distinct from states of pure progressive dysarthria or phonological disintegration where the articulation rather than usage of words becomes disrupted.[68]

Patients with aphasia resulting from stroke are often characterized as fluent versus non-fluent, based on patterns of spoken language and comprehension deficits. Fluent patients generally produce speech at normal to fast rates and show relatively normal phrase length, but have difficulty with auditory comprehension. Non-fluent patients show slow rates of speech with effortful production, reduced phrase length, and relatively spared auditory comprehension. Although studies have attempted to describe the language disorder in PPA based on these two categories,[69, 70] the clinical symptoms in PPA are quite variable[71] and most do not conform to the traditional anatomical patterns based on stroke subjects.

Gorno-Tempini et al[72] described three subtypes of PPA, *logopenic, agrammatic*, and *semantic*, which correspond to distinctive patterns of brain atrophy. The logopenic variant is characterized by word- difficulties and decreased output, but relatively preserved syntax, grammar and comprehension. The agrammatic subtype, which is similar to the Neary[1] criteria progressive nonfluent aphasia (PNFA) subtype of FTLD, is characterized by labored speech, agrammatism in production and/or comprehension, variable degrees of anomia, and phonemic paraphasias, in the presence of relatively normal word comprehension. Semantic dementia (SD) is characterized by fluent, grammatically correct speech, loss of word and object meaning and surface dyslexia and relatively preserved syntactic comprehension skills.

Patients with early PPA may also show mild ideomotor (usually buccofacial) apraxia, dyscalculia, disinhibition, and constructional deficits.[73] These additional symptoms indicate a progression or spread of dysfunction to prefrontal and parietal cortices immediately adjacent to the language network.

Recommended battery for assessment of PPA

Standardized neuropsychological aphasia batteries such as the Boston Diagnostic Aphasia Examination (BDAE)[74] or the Western Aphasia Battery (WAB)[66] are helpful in characterizing early language impairments in PPA. These two aphasia batteries both include subtests that assess grammar, naming, comprehension, fluency, repetition, reading and writing. Supplemental language

measures of more extensive confrontation naming include the Boston Naming Test,[65] the Object and Action Naming Test[75] and the Verb and Sentence Test.[76] The Pyramids and Palm Trees Test[77] can be administered to assess semantic knowledge, and includes both a verbal and non-verbal component. Subjects are required to match a target object (or word) with the one of two choices that shares some essential feature with the target. A thorough examination of language functioning will not only help to characterize the subtype of PPA, but will also lay the foundation for how to structure an appropriate test battery.

Demonstrating the integrity of non-verbal domains by eliminating the need for verbal mediation on neuropsychological tests is helpful in order to accurately assess other cognitive domains. For example, Wicklund et al[78] compared performance of patients with PPA, AD, FTD, and age-matched controls on the 10 item modified version of the Visual Verbal Test,[79] a nonverbal measure of reasoning and cognitive flexibility. PPA patients and controls performed similarly, while both AD and FTD subjects were found to be significantly impaired.

Although the language disorder in PPA may interfere with the ability to memorize word lists or solve reasoning tasks, the patient typically has no difficulty recalling daily events or behaving with good judgment, indicating that explicit memory, executive functions and social skills remain intact. Non-verbal memory tests, such as the Brief Visuospatial Memory Test[80] are recommended in order to objectively quantify memory functions in patients with PPA rather than relying exclusively on a verbal memory measures where performance could be artificially reduced as the result of primary deficits in language.

DATA FROM SUBJECTS in the NORTHWESTERN ALZHEIMER'S DISEASE CENTER

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Figure 1 shows the neurocognitive profiles from FTD, PPA, and AD subjects enrolled in the Northwestern Alzheimer's Disease Center. All subjects underwent a complete neurological and neuropsychological evaluation as part of their participation. Individuals with AD (N=70) were diagnosed using NINCDS-ADRDA criteria for probable Alzheimer's Disease[81]. The diagnosis of FTD (N=39) was made based on criteria outlined by the consensus statement on frontotemporal lobar degeneration.[1] A diagnosis of PPA (N=43) was made on the basis of Mesulam's criteria.[6] There were no significant differences between groups in duration of illness ($p = .15$), or MMSE score ($p = .10$).

Performance in the four cognitive domains is represented using z-scores computed on the basis of age-matched control subject's scores. The "executive" function score is comprised of performance on Trail Making Test Parts A and B; "language" score is equivalent to performance on the 60-item Boston Naming Test and F-A-S lexical fluency test; "memory" score consists of performance on the CERAD word list recall subtest; and "spatial" score is equivalent to CERAD construction score. As expected, AD subjects performed significantly worse than the other groups on memory recall. Somewhat surprisingly, FTD subjects performed worse than the PPA group, despite the use of a verbal memory measure. On the language measure, PPA subjects performed worse than both FTD and AD who did not differ from each other. The FTD group performed significantly worse than AD and PPA subjects on the executive function and visuospatial measures. Although AD

subjects would be predicted to score worse than the other groups on the visuospatial measure, the fact that we used primarily a measure of construction, rather than other types of visuospatial tasks, may have explained the absence of this finding.

These results, which are based on a preliminary analysis of our data set, generally support the expected areas of focal impairment in FTD and PPA based on literature findings. However, it is important to remember that there is a great deal of heterogeneity within each patient group, and therefore clinical neuropsychological findings should be interpreted within the context of a full neurological and psychosocial evaluation to most accurately arrive at the proper diagnosis.

CONCLUSION

This review of the literature serves as an outline of major neuropsychological findings in FTD and PPA, expected cognitive and behavioral profiles, and recommended test batteries for use in the differential diagnosis. The symptom presentation of FTD typically involves deficits in attention/ working memory processes and executive functioning, as well as behavioral abnormalities. These deficits can cause secondary impairments in other cognitive domains (i.e., memory) and this should always be taken into considered in test interpretation. Language is the most salient feature in the early clinical picture of PPA. Eliminating the need for verbal mediation on neuropsychological tests will assist in demonstrating the integrity of non-verbal domains in PPA. While brief, screening measures, such as the MMSE may be useful in differentiating AD from non-demented elderly subjects, they are not as useful in detecting non-AD dementias, or in differentiating between dementia syndromes. A comprehensive test battery that emphasizes executive functions in FTD and language functions in PPA is likely to be more effective in early differential diagnosis of these dementia syndromes.

Table 1. Neuropsychological characteristics of early FTD, PPA and AD

Cognitive Domain	AD	FTD	PPA
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Executive functions	Intact	Impaired	Non-verbal intact
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Naming	Mildly reduced	Intact	Semantic impaired
Verbal fluency	Intact	Reduced	Logopenic impaired
Complex comprehension	Intact	Intact	Agrammatic impaired
Visuospatial	Impaired	Impaired due to executive functions	Intact
Memory			
Orientation	Impaired	Intact	Intact
Verbal	Severely impaired	Impaired encoding intact retention	Impaired, due to language deficits
Visual	Severely impaired	Impaired encoding intact retention	Intact
Behavior	Intact or mildly reduced	Severely impaired	Intact
Mood	Risk of depression	Generally intact	Risk of depression
Insight	Intact or mildly reduced	Severely impaired	Intact
Activities of Daily Living	Mildly reduced	Judgment, decision making impaired	Intact

Table 1 provides a summary of typical impairments in FTD, PPA, and AD in each of the major cognitive domains. It is important to remember that there is a great deal of heterogeneity in symptoms between individual patients, and therefore the presence of any single impairment should not be considered pathognomonic, but rather be considered in the context of the overall neuropsychological evaluation results.

REFERENCES

1. Neary, D, Snowden, JS, Gustafson, L, Passant, U, Stuss, D, Black, S, Freedman, M, Kertesz, A, Robert, PH, Albert, M, Boone, K, Miller, BL, Cummings, J, and Benson, DF, *Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria [see comments]*. Neurology, 1998.**51**(6): p.1546-54.
2. Mann, DM, South, PW, Snowden, JS, and Neary, D, *Dementia of frontal lobe type: neuropathology and immunohistochemistry*. J Neurol Neurosurg Psychiatry, 1993.**56**(6): p. 605-14.
3. Frisoni, GB, Pizzolato, G, Geroldi, C, Rossato, A, Bianchetti, A, and Trabucchi, M, *Dementia of the frontal type: neuropsychological and [99Tc]-HM-PAO SPET features*. Journal of Geriatric Psychiatry & Neurology, 1995.**8**(1): p. 42-8.
4. Rahman, S, Sahakian, BJ, Hodges, JR, Rogers, RD, and Robbins, TW, *Specific cognitive deficits in mild frontal variant frontotemporal dementia*. Brain, 1999.**122**(Pt 8): p.1469-93.
5. Mesulam, MM, *Slowly progressive aphasia without generalized dementia*. Ann Neurol, 1982.**11**(6): p.592-8.
6. Mesulam, M-M, *Primary Progressive Aphasia- A Language-Based Dementia*. New England Journal of Medicine, 2003.**349**(16): p.1535-1542.
7. Corey-Bloom, J, Thal, LJ, Galasko, D, Folstein, M, Drachman, D, Raskind, M, and Lanska, DJ, *Diagnosis and evaluation of dementia*. Neurology, 1995.**45**(2): p.211-8.
8. Frisoni, GB, Beltramello, A, Geroldi, C, Weiss, C, Bianchetti, A, and Trabucchi, M, *Brain atrophy in frontotemporal dementia*. J Neurol Neurosurg Psychiatry, 1996.**61**(2): p.157-65.
9. Frisoni, GB, Laakso, MP, Beltramello, A, Geroldi, C, Bianchetti, A, Soininen, H, and Trabucchi, M, *Hippocampal and entorhinal cortex atrophy in frontotemporal dementia and Alzheimer's disease*. Neurology, 1999.**52**(1): p.91-100.
10. Mesulam, MM and Weintraub, S, *Spectrum of primary progressive aphasia*. Baillieres Clin Neurol, 1992.**1**(3): p.583-609.
11. Rosen, HJ, Kramer, JH, Gorno-Tempini, ML, Schuff, N, Weiner, M, and Miller, BL, *Patterns of cerebral atrophy in primary progressive aphasia*. Am J Geriatr Psychiatry, 2002.**10**(1): p.89-97.
12. Talbot, PR, Lloyd, JJ, Snowden, JS, Neary, D, and Testa, HJ, *A clinical role for 99mTc-HMPAO SPECT in the investigation of dementia?* J Neurol Neurosurg Psychiatry, 1998. **64**(3): p.306-13.
13. Pickut, BA, Saerens, J, Marien, P, Borggreve, F, Goeman, J, Vandevivere, J, Vervaet, A, Dierckx, R, and de Deyn, PP, *Discriminative use of SPECT in frontal lobe-type dementia versus (senile) dementia of the Alzheimer's type*. Journal of Nuclear Medicine, 1997.**38**(6): p.929-34.
14. Ishii, K, *Clinical application of positron emission tomography for diagnosis of dementia*. Ann Nucl Med, 2002.**16**(8): p.515-25.
15. Abe, K, Ukita, H, and Yanagihara, T, *Imaging in primary progressive aphasia.* Neuroradiology, 1997.**39**(8): p.556-9.
16. Rosen, HJ, Gorno-Tempini, ML, Goldman, WP, Perry, RJ, Schuff, N, Weiner, M, Feiwell, R, Kramer, JH, and Miller, BL, *Patterns of brain atrophy in frontotemporal dementia and semantic dementia*. Neurology, 2002.**58**(2): p.198-208.

17. Cruts, M, Gijselinck, I, van der Zee, J, Engelborghs, S, Wils, H, Pirici, D, Rademakers, R, Vandenberghe, R, Dermaut, B, Martin, JJ, van Duijn, C, Peeters, K, Sciot, R, Santens, P, De Pooter, T, Mattheijssens, M, Van den Broeck, M, Cuijt, I, Vennekens, K, De Deyn, PP, Kumar-Singh, S, and Van Broeckhoven, C, *Null mutations in progranulin cause ubiquitin-positive frontotemporal dementia linked to chromosome 17q21.* Nature, 2006.**442**(7105): p.920-4.
18. Baker, M, Mackenzie, IR, Pickering-Brown, SM, Gass, J, Rademakers, R, Lindholm, C, Snowden, J, Adamson, J, Sadovnick, AD, Rollinson, S, Cannon, A, Dwosh, E, Neary, D, Melquist, S, Richardson, A, Dickson, D, Berger, Z, Eriksen, J, Robinson, T, Zehr, C, Dickey, CA, Crook, R, McGowan, E, Mann, D, Boeve, B, Feldman, H, and Hutton, M, *Mutations in progranulin cause tau-negative frontotemporal dementia linked to chromosome 17.* Nature, 2006.**442**(7105): p.916-9.
19. Wicklund, A and S, W, *Neuropsychological Features of Common Dementia Syndromes.* Turk Noroloji Dergisi, 2005.**11**(6): p.566-588.
20. Tombaugh, TN and McIntyre, NJ, *The mini-mental state examination: a comprehensive review [see comments]*. Journal of the American Geriatrics Society, 1992.**40**(9): p.922-35.
21. Ganguli, M, Rodriguez, E, Mulsant, B, Richards, S, Pandav, R, Bilt, J, Dodge, H, Stoehr, G, Saxton, J, Morycz, R, Rubin, R, Farkas, B, and DeKosky, S, *Detection and management of cognitive impairment in primary care: The Steel Valley Seniors Survey*. Journal of the American Geriatrics Society, 2004.**52**(10): p.1668-75.
22. Nishiwaki, Y, Breeze, E, Smeeth, L, Bulpitt, C, Peters, R, and Fletcher, A, *Validity of the Clock-Drawing Test as a screening tool for cognitive impairment in the elderly*. American Journal of Epidemiology, 2004.**160**(8): p.797-807.
23. Slachevsky, A, Villalpando, J, Sarazin, M, Hahn-Barma, V, Pillon, B, and Dubois, B, *Frontal assessment battery and differential diagnosis of frontotemporal dementia and Alzheimer disease.* Arch Neurol, 2004.**61**(7): p.1104-7.
24. Starr, JM, Deary, IJ, Inch, S, Cross, S, and MacLennan, WJ, *Age-associated cognitive decline in healthy old people*. Age & Ageing, 1997.**26**: p.295-300.
25. Jacqmin-Gadda, H, Fabrigoule, C, Commenges, D, and Dartigues, JF, *A 5-year longitudinal study of the Mini-Mental State Examination in normal aging.* American Journal of Epidemiology, 1997.**145**: p.498-506.
26. Small, BJ, Viitanen, M, and Backman, L, *Mini-Mental State Examination item scores as predictors of Alzheimer's disease: incidence data from the Kungsholmen Project, Stockholm.* Journals of Gerontology. Series A, Biological Sciences & Medical Sciences, 1997.**52**: p.299-304.
27. Visser, PJ, Verhey, FR, Ponds, RW, Cruts, M, Van Broeckhoven, CL, and Jolles, J, *Course of objective memory impairment in non-demented subjects attending a memory clinic and predictors of outcome.* Int J Geriatr Psychiatry, 2000.**15**(4): p.363-372.
28. Doody, R, Massman, P, and Dunn, J, *A method for estimating progression rates in Alzheimer disease.* Arch Neurol, 2001.**58**(3): p.449-54.
29. Gregory, CA, Serra-Mestres, J, and Hodges, JR, *Early diagnosis of the frontal variant of frontotemporal dementia: how sensitive are standard neuroimaging and neuropsychologic tests?* Neuropsychiatry Neuropsychol Behav Neurol, 1999.**12**(2): p.128-35.
30. Bier, JC, Ventura, M, Donckels, V, Van Eyll, E, Claes, T, Slama, H, Fery, P, Vokaer, M, and Pandolfo, M, *Is the Addenbrooke's cognitive examination effective to detect frontotemporal dementia?* J Neurol, 2004.**251**(4): p.428-31.

31. Mathuranath, PS, Nestor, PJ, Berrios, GE, Rakowicz, W, and Hodges, JR, *A brief cognitive test battery to differentiate Alzheimer's disease and frontotemporal dementia.[see comment]*. Neurology, 2000.**55**(11): p.1613-20.
32. Greene, JD, Baddeley, AD, and Hodges, JR, *Analysis of the episodic memory deficit in early Alzheimer's disease: evidence from the doors and people test.* Neuropsychologia, 1996.**34**(6): p.537-51.
33. Welsh, KA, Butters, N, Hughes, JP, Mohs, RC, and Heyman, A, *Detection and staging of dementia in Alzheimer's disease. Use of the neuropsychological measures developed for the Consortium to Establish a Registry for Alzheimer's Disease.* Archives of Neurology, 1992. **49**: p.448-52.
34. Hodges, JR, Patterson, K, Ward, R, Garrard, P, Bak, T, Perry, R, and Gregory, C, *The differentiation of semantic dementia and frontal lobe dementia (temporal and frontal variants of frontotemporal dementia) from early Alzheimer's disease: a comparative neuropsychological study.* Neuropsychology, 1999.**13**(1): p.31-40.
35. Perry, RJ and Hodges, JR, *Differentiating frontal and temporal variant frontotemporal dementia from Alzheimer's disease.* Neurology, 2000.**54**(12): p.2277-84.
36. Kramer, JH, Jurik, J, Sha, SJ, Rankin, KP, Rosen, HJ, Johnson, JK, and Miller, BL, *Distinctive neuropsychological patterns in frontotemporal dementia, semantic dementia, and Alzheimer disease.* Cogn Behav Neurol, 2003.**16**(4): p.211-8.
37. Walker, AJ, Meares, S, Sachdev, PS, and Brodaty, H, *The differentiation of mild frontotemporal dementia from Alzheimer's disease and healthy aging by neuropsychological tests.* Int Psychogeriatr, 2005.**17**(1): p.57-68.
38. Lindau, M, Almkvist, O, Kushi, J, Boone, K, Johansson, SE, Wahlund, LO, Cummings, JL, and Miller, BL, *First symptoms--frontotemporal dementia versus Alzheimer's disease.* Dement Geriatr Cogn Disord, 2000.**11**(5): p.286-93.
39. Kertesz, A, Davidson, W, McCabe, P, and Munoz, D, *Behavioral quantitation is more sensitive than cognitive testing in frontotemporal dementia.* Alzheimer Dis Assoc Disord, 2003.**17**: p.223-229.
40. Grossman, M, *Frontotemporal dementia: a review.* J Int Neuropsychol Soc, 2002.**8**(4): p. 566-83.
41. Thompson, JC, Stopford, CL, Snowden, JS, and Neary, D, *Qualitative neuropsychological performance characteristics in frontotemporal dementia and Alzheimer's disease.* J Neurol Neurosurg Psychiatry, 2005.**76**(7): p.920-7.
42. Diehl, J, Monsch, AU, Aebi, C, Wagenpfeil, S, Krapp, S, Grimmer, T, Seeley, W, Forstl, H, and Kurz, A, *Frontotemporal dementia, semantic dementia, and Alzheimer's disease: the contribution of standard neuropsychological tests to differential diagnosis.* J Geriatr Psychiatry Neurol, 2005.**18**(1): p.39-44.
43. Wicklund, AH, Johnson, N, Rademaker, A, Weitner, BB, and Weintraub, S, *Word list versus story memory in Alzheimer disease and frontotemporal dementia.* Alzheimer Disease & Associated Disorders, 2006.**20**(2): p.86-92.
44. Rascovsky, K, Salmon, DP, Ho, GJ, Galasko, D, Peavy, GM, Hansen, LA, and Thal, LJ, *Cognitive profiles differ in autopsy-confirmed frontotemporal dementia and AD.* Neurology, 2002.**58**(12): p.1801-8.
45. Galton, C, Patterson, K, Xuereb, J, and Hodges, JR, *Atypical and typical presentations of Alzheimer's disease: a clinical, neuropsychological, neuroimaging and pathological study of 13 cases.* Brain, 2000.**123**: p.484-498.

46. Turner, RS, Kenyon, LC, Trojanowski, JQ, Gonatas, N, and Grossman, M, *Clinical, neuroimaging, and pathologic features of progressive nonfluent aphasia.* Annals of Neurology, 1996.**39**(2): p.166-73.
47. Westbury, C and Bud, D, *Primary progressive aphasia: a review of 112 cases.* Brain and Language, 1997.**60**: p.381-406.
48. Kertesz, A, Hudson, L, Mackenzie, I, and Munoz, D, *The pathology and nosology of primary progressive aphasia*. Neurology, 1994.**44**(2065-2072).
49. Schwarz, M, De Bleser, R, Poeck, K, and Weis, J, *A case of primary progressive aphasia: A 14-year follow-up study with neuropathological findings.* Brain, 1998.**121**: p.115-126.
50. Miller, BL, Ikonte, C, Ponton, M, Levy, M, Boone, K, Darby, A, Berman, N, Mena, I, and Cummings, JL, *A study of the Lund-Manchester research criteria for frontotemporal dementia: clinical and single-photon emission CT correlations.* Neurology, 1997.**48**(4): p. 937-42.
51. Cummings, JL, *The Neuropsychiatric Inventory: assessing psychopathology in dementia patients*. Neurology, 1997.**48**(5 Suppl 6): p.S10-6.
52. Kertesz, A, Davidson, W, and Fox, H, *Frontal behavioral inventory: diagnostic criteria for frontal lobe dementia*. Can J Neurol Sci, 1997.**24**(1): p.29-36.
53. Liu, W, Miller, BL, Kramer, JH, Rankin, K, Wyss-Coray, C, Gearhart, R, Phengrasamy, L, Weiner, M, and Rosen, HJ, *Behavioral disorders in the frontal and temporal variants of frontotemporal dementia*. Neurology, 2004.**62**(5): p.742-8.
54. Srikanth, S, Nagaraja, AV, and Ratnavalli, E, *Neuropsychiatric symptoms in dementia-frequency, relationship to dementia severity and comparison in Alzheimer's disease, vascular dementia and frontotemporal dementia.* J Neurol Sci, 2005.**236**(1-2): p. 43-8.
55. Chow, TW, Miller, BL, Boone, K, Mishkin, F, and Cummings, JL, *Frontotemporal dementia classification and neuropsychiatry.* Neurologist, 2002.**8**(4): p.263-9.
56. Kertesz, A, Nadkarni, N, Davidson, W, and Thomas, AW, *The Frontal Behavioral Inventory in the differential diagnosis of frontotemporal dementia*. J Int Neuropsychol Soc, 2000.**6**(4): p.460-8.
57. Marczinski, CA, Davidson, W, and Kertesz, A, *A longitudinal study of behavior in frontotemporal dementia and primary progressive aphasia*. Cognitive & Behavioral Neurology, 2004.**17**(4): p.185-90.
58. Heaton, RK, Chelune, GJ, Talley, JL, Kay, GG, and Curtis, C, *Wisconsin Card Sorting Test (WCST) Manual Revised and Expanded*. 1993, Odessa, Florida: Psychological Assessment Resources.
59. Golden, CJ, *Identification of brain disorders by the Stroop Color and Word Test.* Journal of Clinical Psychology, 1976.**32**(3): p.654-8.
60. Drewe, EA, *Go No-go learning after frontal lobe lesions in humans*. Cortex, 1975.**11**: p.8-16.
61. Perri, R, Koch, G, Carlesimo, GA, Serra, L, Fadda, L, Pasqualetti, P, Pettenati, C, and Caltagirone, C, *Alzheimer's disease and frontal variant of frontotemporal dementia-- a very brief battery for cognitive and behavioural distinction.* J Neurol, 2005.**252**(10): p.1238-44.
62. Wechsler, D, *Wechsler Adult Intelligence Scale-Third Edition*. 1997, San Antonio, Texas: The Psychological Corporation.
63. Reitan, R and Wolfson, D, *The Halstead-Reitan Neuropsychological Test Battery*. 1985, Tucson: Neuropsychology Press.

64. Delis, D, Kramer, J, Kaplan, E, and Ober, B, *The California Verbal Learning Test*. 1987, San Antonio: The Psychological Corporation.
65. Kaplan, E, Goodglass, H, and Weintraub, S, *The Boston Naming Test*. 1983, Philadelphia: Lea and Febiger.
66. Kertesz, A, *Western Aphasia Battery (WAB)*. 1982, San Antonio, Texas: The Psychological Corporation.
67. Meyers, J and Meyers, K, *Rey Complex Figure Test and Recognition Trial*. 1995, San Antonio: The Psychological Corporation.
68. Broussolle, E, Bakchine, S, Tommasi, M, Laurent, B, Bazin, B, Cinotti, L, Cohen, L, and Chazot, G, *Slowly progressive anarthria with late anterior opercular syndrome: a variant form of frontal cortical atrophy syndromes.* J Neurol Sci, 1996.**144**(1-2): p.44-58.
69. George, A and Mathuranath, PS, *Primary progressive aphasia: a comparative study of progressive nonfluent aphasia and semantic dementia.* Neurology India, 2005.**53**(2): p. 162-5; discussion 165-6.
70. Clark, DG, Charuvastra, A, Miller, BL, Shapira, JS, and Mendez, MF, *Fluent versus nonfluent primary progressive aphasia: a comparison of clinical and functional neuroimaging features*. Brain & Language, 2005.**94**(1): p.54-60.
71. Thompson, CK, Ballard, KJ, Tait, ME, Weintraub, S, and Mesulam, M-M, *Patterns of language decline in non-fluent primary progressive aphasia.* Aphasiology, 1997.**11**(4/5): p. 297-321.
72. Gorno-Tempini, M, Dronkers, N, Rankin, K, Ogar, J, La Phengrasamy, B, BRosen, H, Johnson, J, Weiner, M, and Miller, B, *Cognition and Anatomy in Three Variants of Primary Progressive Aphasia.* Annals of Neurology, 2004.**55**: p.335-346.
73. Joshi, A, Roy, EA, Black, SE, and Barbour, K, *Patterns of limb apraxia in primary progressive aphasia.* Brain & Cognition, 2003.**53**(2): p.403-7.
74. Goodglass, H and Kaplan, EF, *The Boston Diagnostic Aphasia Examination*. 1983, Philadelphia: Lea and Febiger.
75. Druks, J and Shallice, T, *Selective preservation of naming from description and the "restricted preverbal message"*. Brain & Language, 2000.**72**(2): p.100-28.
76. Bastiaanse, R, Hugen, J, Kos, M, and van Zonneveld, R, *Lexical, morphological, and syntactic aspects of verb production in agrammatic aphasics.* Brain & Language, 2002. **80**(2): p.142-59.
77. Howard, D and Patterson, K, *Pyramids and Palm Trees: A Test of Symantic Access From Pictures and Words*. 1992, Bury St. Edmonds, Suffolk, UK: Thames Valley Test Company.
78. Wicklund, AH, Johnson, N, and Weintraub, S, *Preservation of reasoning in primary progressive aphasia: further differentiation from Alzheimer's disease and the behavioral presentation of frontotemporal dementia.* Journal of Clinical & Experimental Neuropsychology, 2004.**26**(3): p.347-55.
79. Feldman, MJ and Drasgow, J, *The Visual-Verbal Test.* Vol. Los Angeles. 1959, Los Angeles: Western Psychological Services.
80. Benedict, RHB, Schretlen, D, Groninger, L, Dobraski, M, and Shpritz, B, *Revision of the Brief Visuospatial Memory Test: Studies of normal performance, reliability and validity.* Psychological Assessment, 1996.**8**: p.145-153.
81. McKhann, G, Drachman, D, Folstein, M, Katzman, R, Price, D, and Stadlan, E, *Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group* under the*

auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology, 1984.**34**: p.939-944.