Neuropsychology of Frontotemporal Dementia and Primary Progressive Aphasia

Beth Borosh, Nancy Johnson

ABSTRACT
Neuropsychology of Frontotemporal Dementia and Primary Progressive Aphasia
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 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 and different patterns of temporal atrophy compared to AD. PPA patients typically show focal atrophy of the left hemisphere frontal, temporal, insular and parietal components of the language network. 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. Reduced metabolism in frontotemporal regions as well as basal ganglia and/or parietal lobes in FTD has been shown with PET imaging. 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. 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, 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. 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) developed as a brief screening test for dementia, has been used frequently in epidemiologic studies as a screening for cognitive impairment and is often considered a “gold standard” against which to examine validity of novel disease severity instruments. It has been shown to be relatively stable in non-demented elderly (ages 70 – 88), even over a 5-year period. 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
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, and other studies have demonstrated the usefulness of tasks of attention and executive function in assisting the early differential diagnosis of FTD and AD. However, there have been studies that did not find consistent differences on attention/executive measures when patients with FTD and AD were directly compared. Thompson et al 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, others have not shown this difference, possibly due to the type of memory testing used. Wicklund et al 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 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, and no specific clinical findings have been found to predict the underlying neuropathology.

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, and may often precede the decline in cognition. 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) and Frontal Behavioral Inventory (FBI) 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. 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.

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. 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. The FBI is also useful in tracking progression of behavioral symptoms in FTD over time.

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 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), and response inhibition (i.e., Stroop Color Word Test) have been found to be sensitive to frontal lobe dysfunction, 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. 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. Other measures of attention and working memory include the Digit Span subtest from the Wechsler Adult Intelligence Scale-3rd Edition (WAIS-III) and the Trail Making Test.

Memory tests with repeated learning trials, followed by recognition, such as the California Verbal Learning Test-II (CVLT-II), 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) 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, 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 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. 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. Primary progressive aphasia is distinct from states of pure progressive dysarthria or phonological disintegration where the articulation rather than usage of words becomes disrupted.

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, the clinical symptoms in PPA are quite variable and most do not conform to the traditional anatomical patterns based on stroke subjects.

Gorno-Tempini et al 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 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. 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) or the Western Aphasia Battery (WAB) 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, the Object and Action Naming Test and the Verb and Sentence Test. The Pyramids and Palm Trees Test 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 compared performance of patients with PPA, AD, FTD, and age-matched controls on the 10 item modified version of the Visual Verbal Test, 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 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**

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. The diagnosis of FTD (N=39) was made based on criteria outlined by the consensus statement on frontotemporal lobar degeneration. A diagnosis of PPA (N=43) was made on the basis of Mesulam’s criteria.

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

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

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


