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Neuropsychological Features of Common Dementia Syndromes / *Sık Görülen Demans Sendromlarında Nöropsikolojik Özellikler*

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ABSTRACT

To date, there is no reliable biological markers for the early detection of the neurodegenerative diseases that cause dementia in the majority of cases over the age of 65. The clinical neuropsychologic evaluation, thus, has taken on an important role in the assessment of individuals with suspected dementia. This paper discusses the role of neuropsychology in the assessment of dementia and reviews the neouropsychological features that characterize the most common forms of neurodegenerative dementia: Alzheimer's disease (AD), the frontotemporal dementias (FTD), dementia with cortical Lewy bodies (LBD) and vascular dementia (VaD). In the current diagnostic criteria, forms of dementia are differentiated based on etiology. However, there is a group of clinical syndromes that could fall under the rubric of dementia, with respect to their impact on daily living, but would not conform to DSM criteria. The assessment of cognitive function through neouropsychological testing has contributed to the characterization and diagnosis of neurodegenerative and vascular dementia. The gold standard in the diagnosis of dementia is the post mortem neuropathologic examination. The role of neuropsychology is to strive to increase the accuracy of the in vivo diagnosis of dementia so that it predicts the neuropathologic findings. Thus, a need exists for more specialized tools to help differentiate types of dementia and to adequately characterize their cognitive and behavioral profiles.

ÖZET

65 yaş üzerindeki olguların çoğunda demansa yol açan nörodejeneratif hastalıkların erken dönemde saptanması için güvenilir biyolojik belirteçler henüz bulunmamaktadır. Dolayısıyla, klinik nöropsikolojik inceleme, demans şüphesi olan bireylerin değerlendirilmesinde önemli bir rol üstlenmiştir. Bu yazıda demansın değerlendirilmesinde nöropsikolojinin rolü tartışılmakta ve en sık rastlanan nörodejeneratif demans tiplerinin karakteristik nöropsikolojik özellikleri gözden geçirilmektedir: Alzheimer hastalığı (AH), frontotemporal demanslar (FTD), kortikal Lewy cisimcikli demans (LBD) ve vasküler demans (VaD). Güncel tanı kriterlerinde, demans formları etyolojisine göre ayırt edilmektedir. Bununla birlikte, günlük yaşam üzerindeki etkilerinden ötürü demans başlığı altında incelenen, fakat DSM kriterlerine uymayan bir grup klinik sendrom bulunmaktadır. Kognitif işlevin nöropsikolojik testlerle değerlendirilmesi, nörodejeneratif ve vasküler demansın özelliklerinin saptanması ve tanısına katkıda bulunmuştur. Demans tanısında altın standart postmortem nöropatolojik incelemedir. Nöropsikolojinin rolü, nöropatolojik bulguları öngörerek in vivo demans tanısının doğruluğunu artırmaya çalışmaktır. Dolayısıyla, demans tiplerini ayırt etmek ve kognitif ve davranışsal profillerini yeterince karakterize etmek için daha özelleşmiş araçlara ihtiyaç duyulmaktadır.

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I. Introduction: Some General Principles and Issues in the Diagnosis of Dementia

The early identification of dementia in older individuals is a pressing public health need worldwide, as the population over the age of 60 rapidly grows. In addition to limiting personal freedom and quality of life, cognitive decline places a burden on caregivers and financially stresses healthcare delivery systems. To date, there are no reliable biological markers for the early detection of the neurodegenerative diseases that cause dementia in the majority of cases over the age of 65. In addition, neurodegenerative dementia is being identified with greater frequency in individuals in their 40's and 50's. The clinical neuropsychological evaluation, thus, has taken on an important role in the assessment of individuals with suspected dementia. This paper discusses the role of neuropsychology in the assessment of dementia and reviews the neuropsychological features that characterize the most common forms of neurodegenerative dementia: Alzheimer's disease (AD), the frontotemporal dementias (FTD), dementia with cortical Lewy bodies (LBD) and vascular dementia (VaD). General principles of assessment and some of the challenges facing dementia nosology and semiology are reviewed in the context of the neuropsychological perspective.

The Definition of Dementia and the Need for Qualification: The Diagnostic and Statistical Manual of Mental Disorders, 3rd ed. (DSM-III) proposed the first set of standardized guidelines for the diagnosis of dementia.[1] The current edition, DSM-IV, states:

"The essential feature of a dementia is the development of multiple cognitive deficits that include memory impairment and at least one of the following cognitive disturbances: aphasia, apraxia, agnosia, or a disturbance in executive functioning. The cognitive deficits must be sufficiently severe to cause impairment in occupational or social functioning and must represent a decline from a previously higher level of functioning." (APA, 1994, p.134)

Further criteria require that the diagnosis should only be made in the absence of delirium. There is also no criterion for the duration of cognitive change, so slowly progressive changes in cognition, as well as short-term changes in mental status (i.e. those etiologically related to medical conditions such as diabetes, and hyperthyroidism, or toxic effects of substances and medications) can constitute criteria for diagnoses of dementia. The presence of a primary disturbance of memory, or amnesia, is also required. In the current diagnostic criteria, forms of dementia are differentiated based on etiology (Table 1).[2]

Table 1. DSM-IV Dementia Diagnoses (American Psychiatric Association, 1994)

Dementia of the Alzheimer's Type
Vascular Dementia
Dementia due to HIV disease
Dementia due to head trauma
Dementia due to Parkinson's disease
Dementia due to Huntington's disease
Dementia due to Pick's disease
Dementia due to Creutzfeldt-Jakob disease
Dementia due to other general medical conditions
Substance-Induced persisting dementia
Dementia due to multiple etiologies
Dementia not otherwise specified

In the years since these criteria were initially conceived, intense research into dementia has revealed a number of facts that challenge the current definition. The most important of these is that there are several forms of dementia in which memory is spared, especially in the earlier stages. This is the case, for example, for frontotemporal dementia (FTD). Secondly, there are forms of dementia in which only one non-memory cognitive domain or function can be impaired for many years prior to the development of more generalized cognitive impairment. The clinical syndrome of primary progressive aphasia (PPA)[3,4] is one such example in which language functions decline in relative isolation from other cognitive and behavioral symptoms, in some instances for many years before other cognitive deficits emerge. In the dementia associated with cortical Lewy body disease, hallucinations and other psychiatric phenomena may mark the onset and

memory loss may be absent for a number of years.[5] Thus, there is a group of clinical syndromes that could fall under the rubric of dementia, with respect to their impact on daily living, but would not conform to DSM criteria. Thus, the current definition of dementia is in need of revision in order to account for these facts. Another point that challenges the DSM-IV criteria for dementia has to do with the lack of clear cut guidelines for features like the nature of symptom onset (i.e. abrupt, subacute, insidious), the number of affected domains (one versus many), and the course of the symptoms (static versus fluctuating versus progressive). Thus, with the DSM-IV definition one can be given a diagnosis of dementia following a single stroke at one point in time that impairs multiple cognitive domains in the absence of further worsening over time. In this instance, dementia refers to multiple cognitive deficits.

In the discussion that follows, the term "dementia" will be restricted by the following definition: the insidious onset and progression of cognitive and/or psychiatric and behavioral symptoms that worsen over time and that interfere with customary activities of daily living.[6] This definition stipulates progression, and allows for a deficit in one cognitive domain to be sufficient for a diagnosis of "dementia", and does not require the presence of amnesia. This definition would encompass degenerative brain diseases and dementia of vascular etiology. In the instance of multiple cognitive deficits following a single acute cerebrovascular insult, perhaps other terms such as "multi-domain, static encephalopathy" would be more appropriate and would differentiate this form of mental impairment from progressive dementia.

Neuropsychological Contributions to the Study and Diagnosis of Dementia: In the late 1970's, when researchers began to study Alzheimer's disease with intensity, the neuropsychological investigation of dementia was not considered fruitful as a tool for understanding brain-behavior relationships. The reason for this attitude was that by the time patients came for study, they were typically in moderate to late stages of disease, a time when deficits were widespread. However, more recently, patients are identified far earlier in the course of their illness when presenting symptoms can be confined to single cognitive or behavioral domain. It has been shown that the nature of the earliest presenting symptoms reflect dysfunction in the neuroanatomical regions that normally support those functions. For example, the amnestic profile of early Alzheimer's disease corresponds to the very early involvement of the hippocampal-entorhinal cortex complex.[7-9] That is, the symptoms reflect the underlying specialization of the neuroanatomical regions affected by early pathological change according to well-established principles of brain-behavior organization.

In contrast to the dependable link between clinical features and the neuroanatomical distribution of pathology, the link between the clinical symptoms and the nature of the neuropathology is not as reliable. However, there are distinct probabilities with which different types of neurodegenerative change can be associated with clinical profiles. Thus, in series of published clinico-pathologic correlations, the plaques and tangles of definite AD are associated with the clinical syndrome of probable AD (i.e., an amnestic dementia with additional cognitive deficits) at least 87% of the time.[10] The clinical profile of progressive comportmental and executive dysfunction, known as frontotemporal dementia, has been linked to the pathological findings of Pick's disease, dementia lacking distinctive histology, motor neuron disease, corticobasalganglionic degeneration, and less frequently to the pathology of Alzheimer's disease.[11-13] In the clinical syndrome of PPA, the probability of AD pathology is significantly reduced (about 30% of cases), while the proportion of non specific neurodegenerative change is most common, along with the pathological findings of Pick's disease, and corticobasalganglionic degeneration.[14-18]

Figure 1 illustrates that the terms used to label various forms of dementia are not all derived from the same root.

Some are derived from clinical symptoms, some from neuroanatomical landmarks, others from tissue diagnosis and, most recently, others derived from

known genetic mutations (not shown in figure). Since in many cases there is no one to one correspondence between the clinical dementia syndrome and its associated neuropathology, the mapping among terms from different levels of classification remains challenging. Since, at present,

Figure 1. Current terminology for dementia syndromes derives from several nosological levels: clinical symptoms, neuroanatomical distribution of pathology, and neuropathologic tissue abnormalities.

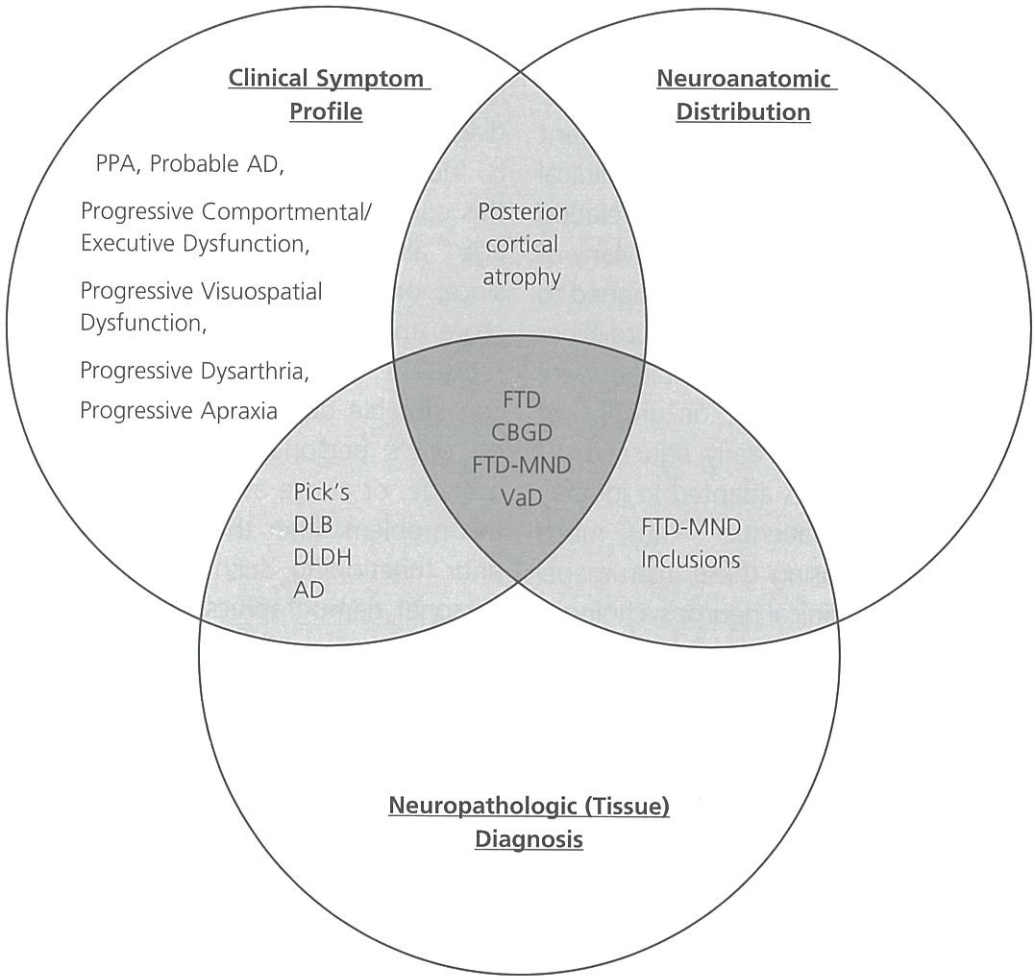

Figure Legends

Figure 1: Each circle represents a level of nosological classification. Terms for the various dementia syndromes are placed within the circles reflecting the nosological level from which the term is derived. A syndrome can be labeled according to its key clinical symptom profile (e.g. primary progressive aphasia), the area of the brain implicated in the disorder (e.g. frontotemporal dementia), or the type of tissue abnormality causing the disease (e.g. cortical Lewy body disease). The overlapping grey regions contain terms that confound levels of classification. For example, posterior cortical atrophy is given as a diagnosis in a clinical setting, but the term is derived from the anatomical region of primary disruption. Corticobasalganglionic degeneration is used as a diagnosis in clinical practice, but also describes a pathological entity as well as anatomic regions affected by the pathology.

PPA=Primary Progressive Aphasia, AD=Alzheimer's disease, FTD=Frontotemporal dementia, CBGD=Corticobasal ganglionic degeneration, FTD-MND=Frontotemporal dementia with motor neuron disease, VaD=Vascular dementia, DLB=Dementia with Lewy Bodies, DLDH=Dementia lacking distinctive histopathology.

the only measurable evidence of dementia rests in the clinical symptoms, until such time as definitive biomarkers are identified, it is suggested that the clinical features guide the labeling of syndromes: progressive amnesia, primary progressive aphasia, progressive visuospatial dysfunction, progressive comportmental/executive dysfunction, primary progressive apraxia, and so on.

II. Principles of Neuropsychological Assessment of Dementia

Use of Tests: Neuropsychological assessment combines standardized testing with expert clinical knowledge of principles of brain-behavior correlation and diseases that can perturb brain function. Many of the tests in current use were not originally designed to detect brain disease. For example, the Stanford-Binet (and later on the Wechsler intelligence scales) were designed to measure "intelligence", or groups of abilities that predicted success in early education.[19] Only later were these instruments adapted to identify "organicity" in brain-injured patients.[20] Thus, much of the clinical interpretation using these instruments relies on the expertise of the clinical neuropsychologist rather than on any intrinsic properties of the tests.

A number of instruments have been designed specifically to detect dementia and to measure the cognitive and behavioral deficits associated with dementia. The Mini Mental State Examination (MMSE),[21] the Dementia Rating Scale (DRS)[22] and the battery of tests developed by the Consortium to Establish a Registry for Alzheimer's Disease (CERAD)[23] are examples of these. However, even using tests specifically designed for dementia does not guarantee accurate diagnosis in the absence of clinical expertise. For example, the aphasic patient will certainly obtain a poor score on verbal memory tests. Whether retentive memory is truly impaired in such a patient requires clinical expertise to further differentiate amnesia from aphasia. Similarly, in a patient with primary visuoperceptual deficits, extra steps are needed to determine if impaired performance on tests that require visual perception are primary deficits or are secondary to the visual perceptual deficit.[247]

One of the obstacles to detecting dementia with standardized instruments is a relative lack of normative data for older individuals. In addition to providing age- and education-appropriate norms, there are growing efforts to collect normative data appropriate for racially and ethnically diverse populations.[25-29] Such norms are critical since dementia may be over-diagnosed in patients with limited reading ability and/or education.[30,31]

Is Test Performance Normal?: The first step in diagnosing dementia is to determine if performance is "normal". However, a fundamental drawback in this concept is that a test score that is "normal for age" already implies that some loss has occurred since, on average, test scores decline with age. A score that is "normal for age", therefore, may represent no change for one individual and a considerable degree of loss for another, depending on one's personal starting point, below average, average, or above average. There is no way to avoid this problem other than to derive some estimate of prior functioning, such as using equations based on personal demographics (Barona IQ estimate[32]) and performance on measures that are "resistant" to the effects of aging, such as single word reading or vocabulary knowledge. Such tests include the National Adult Reading Test (NART)[33,34] Reading subtest of the Wide Range Achievement Test,[35] Wechsler Test of Adult Reading,[36] and Wechsler Adult Intelligence Scale – 3rd edition Vocabulary subtest,[37] all of which can provide some direction for estimating pre-morbid ability. However, these tests have been normed primarily on Westernized nations and cultures, and a paucity of instruments exist to assess pre-morbid IQ in other languages and cultures. In the absence of these measurement tools, especially in non-English speaking populations, historical information about educational attainment and life accomplishments can serve as a qualitative standard for comparison with obtained test scores.

Once the degree of deviation of current performance from some standard of prior performance is determined (i.e., normal, or mildly, moderately, or severely impaired), the neuropsychologist evaluates

the nature of the deficits. The primary clinical deficits should be distinguished from those that are secondary, as in the earlier example of the aphasic patient who fails verbal memory tests despite normal retentive ability. This distinction is critical for differentiating between, for example, primary progressive aphasia and probable Alzheimer's disease. The clinical profile is also essential for making appropriate recommendations for management. Thus, recommendations that are useful in the case of aphasia are not suitable for managing symptoms of amnesia.

Neuropsychological tests are also used as a screening tool for dementia. Screening instruments, such as the MMSE[21] or DRS,[22] can detect a problem but are not capable of differentiating among various forms of dementia. In addition, most screening instruments are insensitive to mild dementia in patients with formerly high levels of intellectual functioning. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) 38 provides an expanded test with a higher level of difficulty than most screening measures, while being easy enough for mild to moderately demented individuals. Studies have shown that this measure can generate distinct profiles of cognitive performance for AD and Huntington's disease, for example.[39]

In individuals with prior capabilities in the superior or above-average range, more detailed and sensitive neuropsychological testing is necessary to detect clinically meaningful change, as they may still perform within the average range. Conversely, in patients experiencing the character changes associated with the behavioral variant of FTD, performance may be normal on all neuropsychological tests. The expertise of the clinician is critical in this instance, to derive the appropriate information from an informant to make an accurate diagnosis.

Test Selection: Unlike a blood test that can be applied universally to detecting a vast majority of diseases in medicine, there is no single test or all-purpose neuropsychological battery that will suffice in the evaluation of dementia. Therefore, some useful principles can be applied to test selection. First, it is important to select instruments that are most relevant for a particular patient. Thus, the CERAD word list may be insensitive to the memory loss in a college professor with incipient dementia, but the California Verbal Learning Test (CVLT),[40] a more difficult task, may reveal a defect in learning or retrieval in such a well-educated individual. The CVLT, in contrast, might penalize an individual not in the labor force with a fourth grade education who, in fact, may have no learning deficits if tested with a simpler measure, such as Three Words-Three Shapes Test[41] or a battery of tests recently designed for illiterate individuals in Brazil (Brief Cognitive Screening Battery).[42] Thus, the clinician needs to have a flexible array of instruments that are appropriate to the patient's demographics. Instruments that avoid floor and ceiling effects are also helpful in tracking progression over time. Another important principle in test selection is to review all cognitive domains (i.e. attention, memory, visuospatial abilities, language, and executive function) so that a profile of primary deficits can be established and primary deficits can be distinguished from secondary impairments on testing.

Neuropsychological assessment has traditionally required many hours to conduct. The time and labor-intensive nature of the procedures is impractical as well as fatiguing for older patients especially as their symptoms progress and as they become increasingly incapable of completing more difficult measures. Therefore, more streamlined methods of assessment are desirable. Table 2 presents recommended dementia screening batteries, questionnaires, and tests of premorbid intellectual functioning that can be used in aging and dementia populations. Table 3 lists neuropsychological test instruments by primary cognitive domain examined by the test, and by level of difficulty. The experienced clinician will tailor the test battery to address the referral question and select appropriate instruments to highlight the presenting symptoms.

Table 2. Test Batteries, Questionnaires, and Premorbid IQ in the Assessment of Dementia

Short Mental State Tests
Mini-Mental State Examination[21]
Blessed Dementia Scale[194]
Brief Dementia Batteries
Mattis Dementia Rating Scale[22]
Alzheimer's Disease Assessment Scale[195]
CERAD Battery[23]
Repeatable Battery for the Assessment of Neuropsychological Status[38]
Assessment of Daily Living Activities
Instrumental Activities of Daily Living[196]
Record of Independent Living[197]
Activities of Daily Living Questionnaire (ADL-Q)[51,185]
Independent Living Scales[184]
Behavioral Symptoms of Dementia
Neuropsychiatric Inventory 89
Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVEAD)[198]
Geriatric Depression Scale[199]
Frontal Behavioral Inventory[90]
Clinical Severity Rating/Stages
Clinical Dementia Rating Scale[90,200]
Global Deterioration Scale[201]
Functional Assessment Staging[202]
Assessment of the Patient with Superior Premorbid Intellectual Capacity
Microcog[203]
Wechsler Adult Intelligence Scale – 3rd edition[37]
Wechsler Memory Scale – 3rd edition[49]
Estimate of Premorbid IQ
National Adult Reading Test[34]
Barona IQ Estimate[32]
Wechsler Test of Adult Reading (WTAR)[36]

III. Neuropsychological Profiles of Clinical Dementia Syndromes

Probable Alzheimer's Disease

The best known clinical-pathological correlation exists for the dementia of Alzheimer's disease which has been linked to multifocal plaque and tangle deposits that appear in the limbic system early in the disease course and then in other cortical areas over time.[8,43] The essential clinical profile is a progressive decline in short term memory with additional cognitive symptoms that can include anomia, visual perceptual disorders, and reduced reasoning and executive functions.[44] There may also be an early decline in motivation, resulting in apathy and social withdrawal, as well as depression.[45]

Memory tests with measures of learning and retention are the most sensitive probes for the cognitive deficits of AD.[46,47] The more commonly used measures include: California Verbal Learning Test (CVLT),[40] Rey Auditory Verbal Learning Test (RVLT),[48] forms of the Wechsler Memory Scale,[49] Free and Cued Selective Reminding Test,[50] and the CERAD word list.[23] Stories and word lists differ in that the latter are frequently repeated over several trials while the former are usually presented only once. Patterns of performance on these different measures can help differentiate between primary amnesia and memory problems secondary to other factors such as attentional deficits and executive dysfunction. For example, the patient who learns 6 of 10 words by the last of four trials but retains all 6 after a delay has a problem in initial encoding but not with retention over time. In contrast, the patient who learns 8 of 10 words but after a delay of 10 minutes recalls only,[2] has a retentive memory problem in the absence of initial learning problems. The latter example is consistent with the pattern of Alzheimer's disease while the former could be seen in a patient with vascular dementia, frontotemporal dementia, severe depression, or in a patient with no dementia but a temporary beclouding of mental state due to hepatic encephalopathy, for example.

In addition to amnesia, other cognitive deficits are apparent in AD. Examining these deficits can be a useful to track and stage the disease progression, as patients may demonstrate a floor effect on tests of memory at a very early stage.[51] For example, language and semantic knowledge have been shown to be impaired early in AD.[52-54] AD patients typically show a reduction in the number of words produced on tests of lexical and category fluency, as well as a

Table 3. Recommended Assessment Instruments by Level of Difficulty

Cognitive Domain	Easy	Moderate	Hard
Attention	Counting 1-20, 20-1 Serial 2's	Months forward/backward Serial 3's Category Fluency Digit Span (WAIS-III) Trail Making Part A	Serial 7's Lexical Fluency (F-A-S)
Memory	Drilled Word Span Procedure Three Words-Three Shapes Test	CERAD Word List Warrington RMT Brief Visuospatial Memory Test – Revised RBANS Story, Word List, and Figure Memory Rivermead Behavioural Memory Test	Logical Memory and Visual Reproduction (WMS-III) Rey Auditory Verbal Learning Test California Verbal Learning Test
Language	BNT, Items 1-20 Category Fluency	BNT items 21-40 Boston Diagnostic Aphasia Examination Western Aphasia Battery	BNT, items 41-60 Lexical Fluency (F-A-S) Pyramids and Palm Trees Test (semantic knowledge)
Constructions	Copy a Clock	Clock Drawing Copy a cube RBANS Figure Copy	Rey Complex Figure Copy Block Design (WAIS-III)
Visuoperception	Judge if pairs of faces, objects, or angles are the same or different	Facial Recognition (1-6) RBANS Line Orientation Visual Shape Cancellation	Facial Recognition (7-13) Judgment of Line Orientation Visual Shape and Object Perception Battery
Executive Functions	Sort geometric forms or objects	Visual Verbal Test** Trail Making Part B Go/No-Go Paradigm	Raven's Standard Progressive Matrices Wisconsin Card Sort Test

* For test references, reader is referred to text explanations, Weintraub, 2000, in Principles of Cognitive and Behavioral Neurology, or original publisher of test materials.
** 10-item abbreviated (Wicklund et al., 2004)

decline in performance on the Boston Naming Test. Over time, these tests have been shown to be the best predictor for tracking disease progression.[51] Within the realm of attention, individuals with AD demonstrate impairments in disengaging and shifting attention, while focused and sustained attention do not become impaired until later on.[55]

Visuospatial, visuoperceptual, and constructional abilities also decline in AD, as measured by tests such as Luria Mental Rotation,[56] WAIS-R Block Design,[57] and the Judgment of Line Orientation.[58,59] However, these deficits have not been shown to be a useful indicator for tracking of disease progression, or in differentiating AD from normal aging.[51] The Clock Drawing Test is one exception, as studies have demonstrated the utility of this test in distinguishing AD from normal aging.[60,61] Performance on tests

sensitive to executive function, particularly cognitive flexibility, reasoning, and problem solving is also impaired in AD. This has been demonstrated with the Wisconsin Card Sort Test,[62] Tower of London,[63] a modification of the Visual Verbal Test,[64] and Ravens Progressive Matrices.[65] In addition, performance on the Trail Making Test is typically slowed in AD,[66,67] and patients demonstrate more errors on Part B suggesting executive dysfunction characterized by an inhibitory deficit.[68] In fact, impairments on Clock Drawing may also reflect executive dysfunction deficits (i.e. difficulty with planning and organization) rather than visual dysfunction.

Differentiating normal aging from AD has been the topic of intense investigation over the past ten years. A group of individuals have been identified as having "Mild Cognitive Impairment – amnestic type" (MCI), a stage intermediary between normal aging and mild AD. Individuals demonstrate focal memory changes without other impairments in cognition, or disruption to their activities of daily living.[69,70] While not all individuals with MCI go on to develop AD, all individuals with AD likely go through a stage of MCI. Detecting changes in cognition in this stage has implications for future research on slowing the progression of the disease process. Tests of memory, such as the WMS Logical Memory and Visual Reproduction subtests, and word list learning tests can differentiate among individuals on the continuum of normal aging, MCI, and early AD.[69,71,72] Recent studies by Chen and colleagues[71,72] showed that a decline on word list delayed recall and Trail Making Parts A and B were the best discriminators of individuals who would go on to develop AD from a sample of individuals with pre-symptomatic AD.

Alzheimer's disease is differentiated from other forms of dementia on the basis of the primary memory impairment that is its hallmark. For example, AD can be distinguished from frontotemporal dementias based on the pattern of explicit memory deficits, and less prominent behavioral and personality changes in early stages.[73-75] Individuals with dementia due to vascular disease typically demonstrate memory impairments secondary to encoding difficulties on neuropsychological tests, without the pattern of rapid forgetting seen in AD.[76] Thus, in a clinical evaluation, the use of neuropsychological test instruments is particularly helpful for differentiating among dementia syndromes.

Dementias Associated with Frontotemporal Degeneration

Frontotemporal degeneration results in a group of disorders in which the clinical phenotypes of FTD are heterogeneous. However, they can be divided into two general classes: those that are characterized by prominent changes in behavior, comportment, and/or executive functions and those that are characterized by a progressive aphasic dementia. The former type has been called frontotemporal dementia (FTD)[77,78] and frontal lobe dementia.[79] The latter type has been called primary progressive aphasia (PPA).[3,4,80] Within the group of PPA, there are several forms of aphasic dementia. Perhaps the most easily identified is a form in which there is agrammatic speech output. This form has also been referred to as progressive nonfluent aphasia.[78] Another form, called logopenic PPA[81,82] is marked by dysfluent speech due to hesitation for word finding and anomia in the absence of agrammatism. A third variety is characterized by significant comprehension deficits for single words in the presence of grammatically correct speech and anomia and a visual agnosia,[78] referred to as semantic dementia. There has been a tendency to use the term "semantic dementia" to refer t o a form of aphasia in which comprehension is affected without a concomitant visual agnosia,[78,83] but care should be taken to differentiate these cases from those with visual agnosia.

The pattern of clinical symptom presentation in FTD can lead to speculation about the neuropathological etiology. However, a one-to-one relationship does not exist between the pathological process and clinical subtypes.[18] Pick's disease, corticobasal degeneration, dementia lacking distinctive histopathology, and

frontotemporal lobar degeneration with motor neuron disease inclusions (FTD-MND type) can be responsible for the clinical picture of the frontotemporal dementias.[12,13] The pathological diagnosis of Alzheimer's disease is less frequent in these cases.[84] Thus, characterizing the pattern of cognitive deficits in vivo is instrumental in accurately diagnosing FTD. The cognitive and behavioral characteristics of the clinical presentation of the phenotypes of FTD, PPA, and SD will be described separately.

Frontotemporal dementia (FTD) [also known as frontotemporal lobar degeneration (FTLD)], (Neary, 1998), dementia of the frontal lobe type,[85] and progressive behavioral/executive dysfunction syndrome:[18] The clinical picture is characterized by an insidious onset and progressive alteration in behavior/comportment, and the onset is typically presenile.[78] Core diagnostic features proposed by Neary and colleagues[78] include inappropriate social interpersonal conduct, emotional blunting, and diminished insight. Suggested supportive features include a decline in personal hygiene, hyperorality, perseverative or stereotypic behavior, and mental rigidity. Patients may also be avolitional or demonstrate disinhibition. Cognition may initially be preserved or only mildly affected. When cognitive deficits arise they typically occur in the domains of attention and executive functioning (i.e. abstract reasoning, planning, and problem solving), with visuospatial abilities typically intact.[78] Retentive memory is also relatively preserved, although impairments on neuropsychological testing can occur, and are usually secondary to prominent attention and executive dysfunction.[86-88] While behavioral changes are prominent and apparent initially, other faculties, such as language, can become impaired over time as the pathology spreads. The characterological and personality changes associated with FTD can be difficult to quantify. A detailed history is necessary to ascertain progression, and cognitive deficits may not be present initially, or may be subtle on standardized neuropsychological instruments. However, qualitative questionnaires, such as the Neuropsychiatric Inventory (NPI) 89 and Frontal Behavioral Inventory,[90] completed by interviewing informants have been shown to be sensitive to detecting behavioral changes in FTD and may be useful in tracking progression over time.[91]

Tests of so-called "frontal lobe function" should be included in a comprehensive battery to assess frontal lobe dementia. However, variability in performance is likely across patients. This is due, in part, to the fact that orbitofrontal, ventromedial, and dorsolateral regions of the frontal lobes support different functions, and any one individual may display unique patterns of atrophy affecting one or more of these regions.[92] However, within the context of this heterogeneity, some tests of executive dysfunction have been shown, with some frequency, to be sensitive to FTD. For example, patients perform worse than non-neurologically impaired individuals on tasks of reasoning and cognitive flexibility such as the Wisconsin Card Sort Test,[93] tests of verbal fluency (letter fluency) and sustained attention, and tasks measuring inhibition of automatic responses (e.g. Stroop Test).[86,94] Another measure of response inhibition, the "go-no-go" paradigm is also sensitive to subtle changes in frontal lobe functions.[95]

Attention and executive dysfunction can influence a patient's pattern of performance on tests not customarily thought of as tests of "frontal lobe function". For example, while visuoperceptual abilities are typically intact in FTD, patients may exhibit impulsivity and difficulty at the level of planning and organization when copying the Rey Complex Figure.[96] This can occur within the context of relative preservation of primary visuoconstructional and visuoperceptual abilities. Language abilities, such as confrontation naming are also typically preserved, at least early in the course of illness.[87,94]

The profile of memory impairment in FTD differs from AD. AD patients are typically differentiated on the basis of profound impairment in episodic memory that is not apparent in FTD.[88,94,97] By contrast, FTD patients may show only mild deficits in episodic

memory and preservation of semantic memory,[94] or the type of memory originally defined by Tulving to describe our knowledge of concepts, facts, objects, and words and their meaning.[98,99] Memory tests with repeated exposures to information followed by recognition, such as the CERAD word list or CVLT, may be useful in examining the contribution of attentional difficulties to memory performance. For example, FTD patients may demonstrate a pattern of decreased encoding, with delayed recall commensurate with the initial amount of information acquired and preserved recognition, suggestive of preservation of primary retentive memory.

In summary, behavioral and comportmental changes are the hallmark of the behavioral variant of FTD and are correlated with prominent atrophy and pathological changes in the frontal lobes. However, a pattern of cognitive deficits including deficits in attention and executive dysfunction may also be apparent during the course of illness. Due to the heterogeneity of symptoms in FTD, the clinical history may be the most valuable source of information for tracking and staging of the illness, and corroborative evidence from an informant should be an instrumental component of a comprehensive neuropsychological examination.

Primary Progressive Aphasia (PPA)(aphasic dementia): PPA is a clinical syndrome characterized by the insidious onset and progressive worsening of language in the absence of deficits in other cognitive domains, at least during the first two years of symptom presentation.[4,80] Anomia constitutes the most common feature in the earliest stages.[4,100-102] Over time, individuals with PPA develop impairment in both production and comprehension of language, and eventually, sometimes after as many as 15 years, the patient may become mute, or only able to emit a few sounds. The onset of PPA typically occurs in the presenium, and men tend to be afflicted more often than women,[101] although the epidemiology of this syndrome is not fully known.

Within at least the first two years of PPA only the aphasia contributes to deficits in activities of daily living. PPA patients have been shown to perform at average levels or beyond on neuropsychological tests of non-verbal memory such as the Benton Visual Retention Test,[103] immediate and delayed recall of the WMS-R Visual Reproduction subtest, and on tests of reasoning and abstraction.[64,81,104-107]

There is no single pattern of language impairment or dissolution in PPA, but patients rarely fit the classical categories of aphasia based on focal strokes.[81,102,108] Many of the cases described in the literature present with a "non-fluent" type of PPA but over time, fluent forms of aphasia can become nonfluent. Gorno-Tempini and colleagues[82] have recently proposed nomenclature to account for the varieties of PPA. One group is characterized by the term "logopenic PPA"[81] and consists of patients who have grammatically intact speech that is nonfluent due to pauses for word-finding, and normal comprehension. A second group, "agrammatic PPA," is characterized by grammatical deficits in speech and comprehension. A third group, "semantic dementia" is characterized by fluent speech and semantic memory deficits.

A comprehensive neuropsychological examination of all cognitive domains in patients with PPA is challenging. Aphasia can confound performance on tests that are verbally mediated, and lead to the erroneous conclusion that other domains of cognition also are affected. A thorough examination of language functioning can lay the foundation for how to structure an appropriate test battery. The Boston Diagnostic Aphasia Examination (BDAE)[109] or Western Aphasia Battery (WAB) 110 are commonly utilized to characterize the type of aphasia and include subtests to assess functions of grammar, naming, comprehension, fluency, repetition, reading, and writing. The WAB also provides a global measure of aphasia severity, the Aphasia Quotient. Supplemental language tests may include the Pyramids and Palm Trees[111] which tests the ability to match pictures on the basis of relatedness, Boston Naming Test,[112] and tests of calculation abilities and praxis.

Eliminating the need for verbal mediation on neuropsychological tests is another strategy for quantifying cognition in PPA. Visual memory tests, such as the Brief Visuospatial Memory Test[113] and Visual Reproduction subtest of the WMS-III,[49] or tests based on recognition paradigms, such as the Recognition Memory Test[114] or Rivermead Behavioural Memory Test[s] assess nonverbal memory while circumventing the language impairment. However, sometimes constructional deficits, which can also be seen in stroke-related aphasia, can interfere with performance in patients with PPA. In that case, informants may need to be questioned about evidence of preserved primary memory from examples of daily life.

Wicklund and colleagues 64 demonstrated preservation of non-verbal reasoning and cognitive flexibility in PPA by using a non-verbal administration of an abbreviated form of the Visual Verbal Test.[116] The Wisconsin Card Sort Test[117] and Raven's Standard Progressive Matrices[118] are alternate tasks of reasoning, problem solving, and cognitive flexibility utilizing non-verbal stimuli. However, the instructions on these tasks may be difficult for patients to comprehend.

PPA can be distinguished from the behavioral variant of FTD and AD on the basis of progressive language impairment and prominent anomia. While language dysfunction such as decreased naming and verbal fluency difficulties have been reported in FTD and AD, they occur in the context of more salient deficits of behavior and memory, respectively.[52,94,119] Differentiating PPA from other dementia syndromes has implications, particularly for treatment as PPA patients can benefit from intervention from a Speech-Language Pathologist who may be able to teach alternate communication strategies.

Semantic Dementia (SD): The original description of semantic dementia is of a clinical syndrome characterized by the gradual and progressive deterioration of word comprehension and knowledge of attributes of objects, with accompanying visual recognition deficits, or agnosia.[83,120,121] SD overlaps with the larger category of PPA in that there are language comprehension deficits. Anomia also presents as the most common neuropsychological deficit in SD. However, phonemic errors in naming are almost never produced in semantic dementia, which is in contrast to patients with a progressive non-fluent aphasia, who produce many.[81,121] On language testing, patients with SD also demonstrate decreased category fluency, loss of verbal and non-verbal semantic knowledge, and surface dyslexia.[83,122] By contrast, phonological aspects of language as well as syntax are typically preserved. Studies have demonstrated that other cognitive domains such as non-verbal memory, visuospatial abilities, non-verbal problem solving, and working memory remain relatively preserve.[83]

A comprehensive assessment of language abilities is necessary in SD to describe the language dysfunction and differentiate SD from other focal dementia syndromes. The aforementioned language instruments such as the BDAE or WAB characterize a broad range of language abilities. Supplemental tests of access to conceptual information, including the Pyramids and Palm Trees Test[111] are also warranted, as are tests of confrontation naming, such as the Boston Naming Test.[112] As in the case of PPA, adjusted administrations of neuropsychological tests, circumventing language dysfunction, are useful for characterizing performance in other cognitive domains.

Semantic Dementia can be differentiated from AD by the absence of primary amnesia. While SD patients may have difficulty on verbal memory tasks, their performance is superior on non-verbal memory tests when compared to AD patients.[94] In addition, attention and executive function have been shown to be preserved in SD helping to differentiate it from FTD[97]

Dementia with Lewy Bodies (DLB)

In 1912, F.H. Lewy described the eosinophilic, intracytoplasmic, neuronal inclusions that bare his name.[123] Typically associated with Parkinson's disease

(PD), Lewy bodies have a predilection for subcortical regions[124] and have more recently been appreciated in a subcortical and cortical distribution.[125,126] By some reports they are found in 15 – 25% of cases of demented elderly individuals, second only to Alzheimer's disease (AD) in terms of post-mortem pathological findings upon brain autopsy.[125,127-129]

There is considerable overlap in the occurrence of cortical Lewy bodies and Alzheimer's pathology.[127] The 1996 consortium to establish guidelines for the clinical and pathologic diagnosis of Lewy body disease suggested the term "Dementia with Lewy Bodies" (DLB) to acknowledge the presence of LB without highlighting other pathologic entities that may occur simultaneously, but without consistency.[5] A clinical diagnosis of DLB includes core features of fluctuations in cognitive function, visual hallucinations, and motor parkinsonism.[5] Supportive features include repeated falls, syncope, transient loss of consciousness, and neuroleptic sensitivity. Progressive cognitive impairment is a hallmark feature, and necessary for the diagnosis. Focal memory impairment, while sufficient, is not necessary given the fluctuating course of illness. Attentional impairments and deficits on tests of executive functions and visuospatial skills are also often present. The onset of DLB typically occurs in the 6th and 7th decade of life, and more men than women are affected.[130]

The fluctuations in mental status associated with DLB can occur within the course of minutes and hours or over days and weeks, and may initially lead to diagnoses of transient ischemic attacks or delirium.[131] Patients are described as "glazed looking" or "switched off."[132] Ferman and colleagues[133] attempted to quantify these fluctuations through informant questionnaires. The characteristics of drowsiness and lethargy, daytime sleepiness, staring into space, and disorganized flow of ideas significantly differentiated DLB from AD patients. Neuropsychological testing can also provide documentation of fluctuating mental status. Mega and colleagues[134] suggested that fluctuations of five or more points on the Mini-Mental State Examination 21 over a six month period is a good indicator of DLB. Psychotic symptoms, such as visual and auditory hallucinations and delusions, are a presenting feature of DLB and occur in over 80% of patients.[135] Depression is also apparent in 20 – 25% of DLB patients.[136] The most common neuropsychological profile in DLB is one of disruption to frontal-subcortical circuitry, due to the cortical and subcortical distribution of the pathology, resulting in deficits on tests of attention, executive function, and psychomotor speed.[128,137-139] Deficits in visuospatial abilities, such as difficulty with Clock Drawing, Block Design, and figure copying, as well as memory dysfunction have also been reported.[128,138-141] Early in the disease course, digit span is also typically impaired.[128,142]

Executive function deficits in DLB are characterized by difficulty with abstraction (WAIS-R similarities), cognitive flexibility (Wisconsin Card Sort Test, Trail Making Test – Part B) and sustained word generation (verbal fluency).[128,138,139] Psychomotor slowing has been demonstrated, on tests of psychomotor speed and fine motor coordination (grooved pegboard).[139] DLB patients also show profound deficits in visuospatial and visuoconstructional abilities, measured by performance on the WISC-R block design and clock drawing test.[138]

Memory impairments have also been demonstrated in DLB. While some studies have shown a pattern of performance on memory testing that resembles AD.[128,141] others have demonstrated that memory is less effected in DLB.[137,143] Hamilton and colleagues[140] conducted an analysis of memory function in patients with an autopsy-confirmed DLB variant of AD versus individuals with AD only, who were matched for dementia severity. On the CVLT, DLB patients showed better retention and recognition memory than individuals with AD, while AD patients showed a pattern of difficulty with delayed retrieval and recognition discriminability. The authors suggested that the differences represented difficulty at the level of retrieval for DLB patients, while the established

pattern of rapid forgetting was evident in the AD patients. The findings are consistent in terms of pathological changes in the respective diseases, with prominent damage to medial temporal lobe structures in AD mediating an amnestic profile, and subcortical disruption in DLB resulting in difficulty with initiation and retrieval.[43,144,145]

Differentiating DLB from other dementia syndromes poses a diagnostic challenge. While a general pattern of neuropsychological deficits has been described, variability is likely the rule rather then the exception when evaluating cases in clinical practice. Thus, a comprehensive battery of tests that examine all cognitive domains is necessary for detecting patterns of deficits and staging of the disease course. The fluctuations in mental status in DLB may resemble those seen in multi-infarct dementia or delirium, while hallucinations are common in other neurodegenerative diseases such as moderate to late AD and Parkinson's disease with dementia.[136,146-149] In addition, consensus in our understanding of this complex disease is complicated by the fact that patients may present to gerontology, psychiatry, or neurology services depending on their symptom presentation. Alterations in mental status, coupled with visual hallucinations, when not accounted for by other central nervous system conditions or medication side effects, strongly suggest a diagnosis of DLB.[130] Thus, documenting the constellation of clinical symptoms as well as the neuropsychological profile of deficits in DLB are the most useful techniques for increasing clinical acumen for a diagnosis.[150]

Vascular Dementia (VaD)

Vascular dementia was initially conceptualized as a cognitive decline resulting from multiple and/or successive cortical infarcts.[151] More recently, it has been appreciated that various forms of vascular disease can result in dementia. For example, subcortical small-vessel ischemic disease, lacunar infarcts, and genetic disorders (CADASIL) have also been associated with progressive cognitive decline[152-]

However, there is confusion associated with diagnosing cognitive impairment from multiple vascular etiologies, and controversy as to whether there are common neuropsychological deficits on testing.

The term vascular cognitive impairment (VCI) has been offered to include cognitive impairment with a cerebrovascular origin without the requisite of memory loss or dementia[156,157] and represents a consensus of criteria from the DSM-IV, ICD-10, and the National Institute for Neurological Disorders and Stroke Association Internationale pour la Recherche et l'Enseignement en Neuroscience (NINDS-AIREN) International Work Group conference.[2,152,158] This conceptualization includes conditions of mixed etiologies (AD + Vascular disease) and mild cognitive impairment associated with cerebrovascular disease. The present review will focus on the neuropsychological profile of vascular cognitive impairment which results in a clinical picture of dementia (vascular dementia; VaD).

The clinical course of VaD is one of acute onset and stepwise progression of cognitive decline.[159] Compared to AD, VaD patients more frequently demonstrate fluctuations in cognition.[152] The patients' history may include transient ischemic attacks, and risk factors of hypertension, diabetes, hyperlipidemia, heart disease, and alcohol and tobacco use.[160] Vascular dementia is typically associated with ischemic cerebral damage and dementia syndromes can result when multiple lesions are present in a cortical and/or subcortical distribution.[161]

Describing a distinct cognitive profile associated with VaD is challenging given the heterogeneity of the population and the diverse use of diagnostic criteria for diagnosis.[162] However, within the context of these limitations, profiles of cognitive impairment in VaD have emerged. The pattern includes difficulties in attention, executive function, and processing speed, resembling the cognitive profile historically described as a "subcortical dementia."[7,162-164] The

neuroanatomical substrate for these deficits is disruption to the frontal-subcortical network of pathways involved in functions such as working memory, attention, word retrieval, reasoning, planning and organization, mood, and motivation, among others.[165-168] In a longitudinal study of 28 patients with VaD, Boyle and colleagues[169] demonstrated that baseline estimates of executive function deficits were predictive of decline in independent activities of daily living at 1-year follow-up. Deficits in memory in VaD have been reported at the level of encoding and retrieval, secondary to inattention, while primary retentive memory is thought to be relatively preserved.[162,168,170] However, these findings have been best established in patients who experience subcortical lesions, or diffuse white matter disease. In the case of vascular dementia related to cortical infarcts, lesion location will ultimately dictate the cognitive deficits, which can also include prominent language or visuospatial impairment, depending on the hemisphere of primary insult, and can vary between individuals.

There is debate over the correlation between white matter changes on neuroimaging and progression of cognitive decline in VaD.[171] Some studies have failed to find a relationship between severity of white matter disease and neuropsychological function[172] while others have observed associations.[173,174] De Groot and colleagues[175] reported that individuals with periventricular white matter lesions showed cognitive decline (measured on the MMSE) at a rate three times faster than healthy elderly individuals. However, the same relationship was not found in individuals with subcortical white matter changes. In a study of 94 patients with lacunar infarcts, Wen and colleagues[176] showed a correlation between severity of white matter changes and executive dysfunction (Mattis Dementia Rating Scale – Initiation/Perseveration subscale), with no relationship to other cognitive domains. A very recent paper suggests that white matter changes are correlated with blood pressure even in healthy individuals, which may constitute a substrate for the cognitive changes associated with these markers[177]

Much of the literature on neuropsychological status in VaD has been conducted by contrasting the pattern of impairment in VaD to that in Alzheimer's disease. Looi and colleagues 178 conducted a review of 27 studies of neuropsychological status in VaD versus AD. When controlled for overall level of cognitive decline, the majority of the studies demonstrated that AD and VaD patients did not differ significantly on tests of language (Boston Naming Test, Controlled Oral Word Association), visual perception (Judgment of Line Orientation, Hooper Visual Organization Test), visual memory (WMS-R Visual Reproduction, Benton Visual Retention test, Famous Faces), conceptual flexibility (WAIS-R similarities and Raven's Progressive Matrices), immediate attention (digit span), and working memory and concentration (Trail Making Test, Symbol Digit Modalities Test, Digit Cancellation Test, Stroop Test, Continuous Performance Test). By contrast, VaD patients showed superior performance to AD patients on tasks of verbal long-term memory (CVLT; VaD > AD in 61% of the studies), while AD patients demonstrated superior performance on tests of executive functioning (Luria D-test battery, Porteus maze, Wisconsin Card Sort Test, Graphical Sequence Test; AD > VaD in 90% of the studies). While these findings represent overall patterns, contrary findings were also reported.

The diagnostic profile associated with vascular dementia continues to evolve. Attentional impairments, executive dysfunction, and psychomotor slowing are the most commonly described features and this profile has been useful for differentiating VaD from other forms of dementia such as Alzheimer's disease. However, limitations in research on VaD persist due to the prominent heterogeneity in the population. As with other forms of dementia, a documented history of onset, progression, and course of symptoms, coupled with neuroimaging, and neuropsychological testing are instrumental components for an accurate clinical diagnosis of VaD.

IV. Summary

The assessment of cognitive function through neuropsychological testing has contributed to the

characterization and diagnosis of neurodegenerative and vascular dementia. The foundation of the neuropsychological approach is the translation of brain-behavior relationships into clinical profiles of cognitive abilities utilizing specialized testing instruments. These tools, coupled with the expertise of the clinician, allow for in vivo assessment and fine clinical distinctions to be made in patients with neurodegenerative and cerebrovascular disease. For example, amnestic forms, behavioral forms, language forms, and visuospatial forms of dementia can be profiled to increase clinical accuracy of diagnosis and inform treatment planning.

However, neuropsychological assessment is not without limitations. The multifactorial nature of the currently available test instruments can limit the interpretation of deficits on testing. For example, lexical and category fluency tests require sustained attention and word generation, and can be impaired in patients with prominent attentional deficits as well as individuals with language dysfunction but no attentional problems. In medicine, routine blood tests can provide outcome measures of normal or abnormal results. In neuropsychology, multiple cognitive domains may influence performance on one test. Thus, abnormal results in neuropsychology require further investigation, utilizing the expertise of the clinician, to ascertain the nature of the abnormality and the level of cognitive dysfunction that influences the test result.

A second limitation, is that neuropsychological tests were largely developed in North American, Caucasian populations. Tests need to be developed that are less culturally biased, and that can be applied across cultures worldwide. In addition, another focus in the field is to create normative data sensitive to cultural factors, and factors such as education and race, on tests that are already established within the neuropsychological community. Beyond cultural effects, normative data must also be expanded to include individuals well over the age of 80 as life expectancy increases. Progress has been made in this realm with newly developed normative data for Caucasian and African American individuals ranging in age from.[20-85-29]

There are also behaviors and cognitive functions for which there are no standardized tests available. Utilization and imitation behaviors,[179] for example, may be observed in patients' everyday activities as reported by their families, or under certain clinical conditions, but do not receive formal evaluation. It is also difficult to quantify areas such as insight, apathy, and social skills other than through a clinical interview, or information from subjective questionnaires.

Finally, there is the issue of the ecological validity of neuropsychological test performance, meaning, can neuropsychological test performance predict and/or translate into functional abilities of individuals with dementia in their everyday activities? For example, the neuropsychological test environment may not be representative of a daily living situation as tests are typically administered in a non-distracting clinical environment. Patients with dementia may perform better than expectation on tests of attention in the distraction-free clinical examination room, but their families may report that they have difficulty attending to information when in a crowded room when many conversations are taking place, or there is background noise. Alternately, patients may perform poorly on neuropsychological tests, but anecdotally their family may describe that they are able to carry out ADL's such as cooking and cleaning, which may reflect the habitual or routinized behavior of the task. Studies have shown that tests of memory, visuospatial abilities, and executive functions are most highly correlated with an individuals' functional status in populations of patients with probable Alzheimer's disease, suspected dementia, or elderly individuals with neuropsychiatric dysfunction.[180-182] Research has also suggested that neuropsychological tests that measure complex cognitive abilities such as problem solving and memory may best predict cognitively demanding ADL's rather than more habitual activities such as the ability to attend to personal hygiene.[183] Thus, a comprehensive

evaluation should utilize cognitive testing in addition to functional measures of ADL's. For example, the Independent Living Scales[184] or an informant-completed questionnaire such as the ADL-Q[185] have been shown to be useful in staging functional capacity. These functional measures coupled with test of cognitive abilities can result in a profile identifying areas of strength and weakness, and may inform recommendations for treatment planning based on both cognitive and functional capacity.

V. Future Directions of Neuropsychology

The gold standard in the diagnosis of dementia is the post mortem neuropathologic examination. The role of neuropsychology is to strive to increase the accuracy of the in vivo diagnosis of dementia so that it predicts the neuropathologic findings. Proper characterization of dementia syndromes has implications for medication management, the development of new pharmacologic agents to target specific pathology, treatment planning, and behavioral interventions.[186]

At the present time, the closest correlation between clinical symptom presentation and pathological diagnosis is that of a progressive amnesia with plaques and tangles in the hippocampal-entorhinal cortical complex. The accurate correlation between clinical characterization and a pathological diagnosis in other forms of dementia remains far less consistent. While there is some level of predictability between the pathology and clinical characterization in other dementia syndromes, as in the case of PPA or FTD, a future direction for neuropsychology is to increase the diagnostic accuracy of our tools utilizing the model of neuropsychological testing in Alzheimer's disease. Many instruments, such as the Clinical Dementia Rating,[187] for example, were developed on the AD population. These instruments are heavily weighted on symptoms of memory loss and therefore behavioral disorders or aphasia are not well captured by them. Thus, a need exists for more specialized tools to help differentiate between different types of dementia and to adequately characterize their cognitive and behavioral profiles.

The search for biomarkers of disease is also integral in the quest for accurate diagnosis of dementia. For example, autosomal dominant genetic mutations on chromosomes 1,14, and 21 have been identified in a small percentage of cases in autopsy confirmed AD.[188,189] The apolipoprotein epsilon 4 allele, linked to chromosome 19 has also been identified as a risk factor for Alzheimer's disease.[190] In FTD, abnormalities have been identified in the tau gene located on chromosome 17.[191,192] Pathologically these cases have been described as Frontotemporal Dementia with Parkinsonism linked to chromosome 17 (FTDP-17) and Frontotemporal Dementia with Motor Neuron Disease (FTD with MND).[193] Knowledge of the genetic contributions to dementia has implications for families, clinical characterization, treatment, and pharmacologic intervention, and is a fundamental future direction in the field of dementia research.

While the quest for biomarkers of neurodegenerative disease may answer the question of etiology, the discovery of biomarkers will not negate the need for neuropsychological assessment in individuals with dementia. Clinical characterization, staging, and disease progression cannot be quantified by a genetic test. Nor can recommendations and directions for psychosocial and behavioral planning and intervention be guided by a blood test. Neuropsychological characterization can quantify patterns of strength and weakness as they relate to employment ability, safety, and competency. Neuropsychological assessment is also useful for delineating the contribution of comorbid, and possibly treatable factors that can affect cognition and behavior such as sleep disruption, depression, and other medical conditions. Finally, neuropsychologists are trained to assess the emotional impact of a diagnosis of dementia on the individual and their family, a role that will be focused on more in the future as the incidence of dementia diagnosis increases, and the field of neuropsychology continues its evolution.

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