



PIVOTAL TOPIC: Update on Neurodegenerative Diseases

This issue of the *Bulletin* presents important clinical and research developments in the three most commonly encountered geriatric neurodegenerative diseases: Alzheimer's disease, Frontotemporal dementia, and Parkinson's disease. Clinical Neuropsychology has historically impacted the standards of diagnosis and management of these conditions. As medical science progresses with identifying biomarkers and genotypes associated with each disorder, our field must continue to demonstrate our value in the characterization and treatment of these patients, especially when considering that the prevalence of these diseases is projected to increase considerably over the next several decades. Here, expert neuropsychologists highlight current diagnostic and classification issues, including unprecedented advances and continued diagnostic challenges. We hope that this issue serves to inform readers and stimulate discussion on these topics.

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New Diagnostic Criteria for Alzheimer's Disease: Advances and Conundrums

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Alzheimer's disease (AD) is a major health care menace, affecting over 5.3 million Americans currently and an estimated 13.5 million Americans by mid-century (Brookmeyer, Johnson, Ziegler-Graham, & Arrighi, 2007). The medical impact of the disease is over 148 billion dollars annually and is projected to escalate as more individuals become affected. The personal impact in terms of caregiver burden, as well as patient quality of life, is incalculable. Identification of disease-modifying therapies is an urgent public health priority. Equally critical is the ability to reliably diagnose the disease early in its course, even before symptoms are manifest. Early diagnosis is critical to advance clinical prevention trials and optimize chances of therapeutic success in such a relentless neurodegenerative condition. **Major scientific advances over the last two decades place these objectives within reach.**

Advances in Diagnosis

It is clear that reliable diagnosis of AD, before the dementia is fully expressed, is already achievable through consideration of established patterns of neuropsychological impairment (Dubois et al., 2007; Mayeux et al., 2011), supported by the inclusion of highly specific neuroimaging and cerebrospinal fluid biomarkers of AD. These biomarkers appear to be related to the underlying pathophysiology of the disease and are temporally linked to the emergence of clinical symptoms (DeMeyer et al., 2010; Jack et al., 2010).

Building on these observations, three work groups comprised of current thought leaders in the field of AD were assembled in the last two years to review the disorder's diagnostic criteria (McKhann et al., 1984). The goals were to determine their continuing utility and to make recommendations for revisions. Recommendations aimed to incorporate new evidence-based knowledge on the pathophysiology of the disease and enhancing reliable early diagnosis. Guidelines were introduced in draft form in July, 2010 at the annual International Conference on Alzheimer's Disease (ICAD). After the broader clinical and scientific community vetted the recommendations, the finalized recommendations were recently published in the online issue of the journal, *Alzheimer's & Dementia* (Albert et al., 2011; Jack et al., 2011; McKhann et al., 2011; Sperling et al., 2011).

The new guidelines differ from the previous diagnostic criteria in two key ways. First, they incorporate biomarkers of the underlying disease state. Specifically, they include biomarkers that are closely linked to the pathological criteria of AD: the β amyloid ($A\beta$) protein accumulation in plaques and the tau deposition in neurofibrillary tangles. Second, the new criteria formalize three



distinct stages in the disease progression: a silent, *preclinical disease stage*; an early symptomatic, *pre-dementia stage* of Mild Cognitive Impairment due to Alzheimer’s disease; and a fully expressed, *dementia stage* of the illness.

Biomarkers fall into two broad classes which vary in their disease specificity. The markers most closely linked to the AD diagnosis are those of Aβ accumulation. These markers include abnormal amyloid PET imaging and low CSF Aβ₄₂ concentrations. A second group of AD biomarkers is related to neuronal injury occurring in the disease and include elevated levels of CSF tau (total tau and phosphorylated tau), hypometabolism in the temporoparietal cortex as visualized on fluoro-deoxyglucose positron emission tomography (FDG-PET) imaging, and brain atrophy on magnetic resonance imaging (MRI) within the medial, basal, and lateral temporal lobes as well as in the medial and lateral parietal cortices. This second group of biomarkers is less specific to AD and can be seen in a variety of other neurodegenerative conditions.

Importantly, with the new criteria, biomarker information is used in the diagnostic process at all three stages of the disease (preclinical, pre-dementia, and dementia), but their role and relative importance differ at each phase (see Table 1).

TABLE 1: DIAGNOSTIC TESTS AT EACH CLINICAL STAGE OF AD

Stage of Clinical Syndrome	Aβ biomarkers		Neurodegeneration Markers			Clinical Tests	
	Aβ imaging	CSF Aβ	CSF Tau	FDG-PET	Volumetric MRI	Neuro-psych	Informant interviews
Preclinical (asymptomatic)	X	X				X	
Predementia (MCI of AD)	X	X	X	X	X	X	X
Dementia	(X)	(X)	(X)	(X)	(X)	X	X

TABLE 1 legend: x= part of criteria (x)= helpful to increase certainty of diagnosis but not recommended for routine diagnostic purposes at this time.

In preclinical AD, when the illness is silent, the evidence for disease is almost entirely based on AD biomarkers, although the individual may have subjective complaints and subtle changes evidenced on neuropsychological evaluation.

By the pre-dementia phase, when early symptoms are present, neuropsychological testing and informant interviews are critical for establishing the syndromic profile. Objective evidence of impairment in one or more cognitive domains is required. Episodic memory impairment typically characterizes the pre-dementia stage of AD, but this is not always the case, and the new criteria recognize this clinical heterogeneity. The guidelines also require presence of a complaint, commonly mild functional impairment for complex tasks, which is either voiced by the patient or an informant



and defensible diagnostic inferences regarding the likely etiology for the observed cognitive disorder.

In situations where significant functional impairment is already present, the diagnosis of the dementing disorder at this point is based nearly entirely on clinical methods involving neurological examination, laboratory studies (routine blood chemistries, MRI imaging), and either neurobehavioral examination or more detailed neuropsychological testing, depending on the situation. Straightforward and obvious dementia conforming to the typical clinical picture of AD dementia may not benefit from detailed neuropsychological testing. Neuropsychological evaluation



can be most useful in instances where the presentation is unusual, medically complex, or where a baseline is needed to monitor change over time in response to treatment. The neuropsychological examination also provides an objective accounting of the individual's current cognitive strengths and deficits that may differ from family and patient report. This information can be crucial for education and intervention with the individual and the family. Biomarkers at this dementia stage of the AD process are not a typical part of the routine diagnostic evaluation, nor are they recommended by the new guidelines. Rather, the criteria note their utility in increasing certainty in diagnostically ambiguous settings.

The clinical utility of these new criteria remains to be fully tested. They appear particularly promising for advancing reliability in the early diagnosis of ambiguous symptoms of AD. The guidelines also provide a much-needed tool for researchers working to develop treatments. Employing the same rigorous criteria for early disease across laboratories will facilitate data comparisons, which will likely permit more rapid discoveries and the development of treatments aimed at delaying onset and progression of very early pre-dementia Alzheimer's disease.

Clinical conundrums

The promise these criteria hold for treatment advancement is high. ***But herein we have a clinical conundrum: we don't have a treatment that can prevent the disease from occurring or progressing once underway.*** Consequently, we are in a position of diagnosing preclinical AD while patients are still quite functional, but we are not yet able to offer treatments capable of reversing the condition or preventing decline. Extreme care must therefore be exercised when introducing these new criteria into clinical practice. The use of novel terms, such as pre-dementia AD or preclinical AD, carries the potential for psychological harm and may also have financial implications for patients, as insurance companies and workers' compensation programs may change policies related to their awareness of an underlying disease that has yet to express. Until treatments are available to cure AD and prevent its occurrence, the criteria will be most useful for advancing research; however, in some instances, providing a diagnosis in the absence of available treatment may mitigate distress in patients and family members by providing a better understanding of what they face. In the clinical arena, neuropsychologists are also uniquely positioned to use these criteria to advance patient care by identifying high-risk subgroups in need of further diagnostic evaluation. Whether due to AD pathology or another etiology, medical evaluation to reduce and eliminate comorbidities that may be interfering with cognition is critical. Depression and anxiety are common in early symptomatic AD, but they also occur in other disorders. Treatment of these disorders may result in a higher level of function. Additionally, management of individual risk factors for dementia, including high blood



pressure, obesity, elevated cholesterol, diabetes, and stroke may also lead to better brain health and maintenance of function over longer periods of time. Finally, neuropsychologists can work with pre-dementia patients to develop strategies for ensuring optimal functional independence. Careful evaluation of the patient's ability to manage medications and organize other complex daily decisions may permit an important dialogue with the affected individual, providing for anticipation of future functional difficulties and preemptive troubleshooting. This conversation also becomes an opportunity to discuss future needs and care options, which takes into account the patient's preferences and includes the patient as his/her own advocate.

The new criteria carry promise of revolutionizing the field, improving clinical care, and facilitating prevention and treatment options for AD. As neuropsychologists, we have specialized knowledge to contribute to the detection of subtle cognitive changes early in the disease process. Our role does not end with diagnosis. By applying our expertise toward the development of effective coping strategies and management models, the field of clinical neuropsychology can greatly assist in enhancing and extending patient autonomy in the face of a very devastating and protracted disease.

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Update on Frontotemporal Dementia

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Introduction

Our understanding of the Frontotemporal dementias (FTD) has increased exponentially in the last 12 years. A quick search on PubMed reflects the rapid rate at which research in this field is growing. Using the search term "Frontotemporal Dementia" retrieves 409 citations between 1991-2000, but increases to 2384 citations between 2001-2010. This proliferation of research has led to new insights into genetic contributions, the pathological bases of these diseases, and refinement in our understanding of the clinical phenotypes associated with FTD. The purpose of this article is to provide both an overview of FTD with a specific focus on behavioral variant FTD (bvFTD) and the new International Diagnostic Criteria, which have recently been developed and validated for bvFTD.

Overview of FTD

Initially thought to be rare, we now know that FTD is equally as common as Alzheimer's disease (AD) in individuals under the age of 65 (Ratnavalli, Brayne, Dawson, & Hodges, 2002). Onset is gradual and insidious, with mean age of onset occurring in the sixth decade (Bird et al., 2003; Johnson et al., 2005), though onset may range considerably from the third to the ninth decade (Johnson et al., 2005; Ratnavalli et al., 2002).

Clinically, FTD is expressed as three main variants (Neary et al., 1998). Behavioral variant FTD (bvFTD) is characterized by profound and early changes in personality and behavior (Neary et al., 1998; International bvFTD Criteria Consortium, in submission). The other two variants are characterized by progressive aphasia (PPA). The semantic variant (svPPA) is associated with loss of word knowledge (e.g., semantic structure of language), while the non-fluent variant (nfPPA) is characterized by early disturbances in motor speech output and loss of syntax (e.g., grammatical structure of language) (Gorno-Tempini et al., 2011; Neary et al., 1998). BvFTD is the most common phenotype and accounts for approximately 70% of the clinical expression of FTD cases, while semantic variant and non-fluent variant account for approximately 15% and 10% of cases, respectively (Pickering-Brown, 2007).

As with all neurodegenerative conditions, FTD is associated with the accumulation of abnormally folded proteins. The two most common proteins associated with bvFTD are tau and TDP-43 (Cairns et al., 2007; Mackenzie et al., 2010), with a handful of additional proteins accounting for a very small proportion of FTD cases (Mackenzie et al., 2010). Under normal conditions, both tau and TDP-43 play an important role in neuronal cell structure and function (Ballatore, Lee, & Trojanowski, 2007; Chen-Plotkin, Lee, & Trojanowski, 2010). However, under pathologic conditions, these proteins



aggregate and accumulate in neurons and glia causing neuronal death and atrophy (Cairns et al., 2007; Mackenzie et al., 2010). Interestingly, it is now known that diseases such as progressive supranuclear palsy, corticobasal degeneration and amyotrophic lateral sclerosis have similar underlying neuropathology, and often present with the clinical features of FTD (Josephs et al., 2006; Lillo & Hodges, 2009; Lomen-Hoerth, Anderson, & Miller, 2002; Tolnay & Probst, 2003).

Efforts to develop specific, disease-modifying therapies for FTD are advancing rapidly, focusing on these major proteins. Accurate assessment of the efficacy of these medications depends upon our ability to ensure pathologically homogenous samples in trials. Currently, autopsy is the only definitive way to know an individual's pathology. As such, a major focus of research in the last few years has been to elucidate important relationships between clinical phenotype and pathology. For example, we now know that svPPA is almost exclusively associated with TDP-43 pathology (Rohrer et al., 2010), whereas bvFTD is more pathologically heterogeneous.

Behavioral variant FTD

In the earliest stages of bvFTD, neurodegeneration begins primarily in paralimbic structures such as the anterior cingulate cortex, frontoinsula region, dorsal anterior insula, and lateral orbitofrontal cortex (Broe et al., 2003; Seeley et al., 2008). These structures have been widely implicated in human social function and awareness of the self (Adolphs, 2009). As the disease progresses, neurodegeneration occurs in widespread areas of the frontal and anterior temporal lobes (Perry et al., 2006; Rosen et al., 2002).

At least 30-40% of all cases of bvFTD appear to be genetic in nature (Sikkink, Rollinson, & Pickering-Brown, 2007), with rates of an autosomal dominant pattern of inheritance ranging from 10-30% (Goldman et al., 2005; Seelaar et al., 2008). The vast majority of familial cases result from single gene mutations on two independent, but extremely close locations on chromosome 17 ("MAPT" and "PGRN") (Gass et al., 2006; Hutton et al., 1998; See, LaMarre, Lee, & Miller, 2010).

New Diagnostic Criteria for bvFTD

While diagnosis of bvFTD is most frequently made using the criteria set forth in 1998 (Neary et al., 1998), advancements in the field have led to greater refinement in our knowledge about bvFTD's clinical expression. Recently, an international team of specialists in the field of FTD developed new diagnostic criteria that incorporate these advances.

According to the new criteria, to be considered for a diagnosis of bvFTD a patient must demonstrate progressive deterioration of behavior and/or cognition by observation or history (by an informant). Upon this criterion being met, a diagnosis of *Possible* bvFTD may be given to a patient if they meet at least three of the six following criteria:

1. early behavioral disinhibition
2. early apathy/inertia
3. early loss of sympathy or empathy
4. early perseverative, stereotyped or compulsive behaviors
5. hyperorality or dietary changes
6. neuropsychological profile suggesting deficits on tasks of executive function with *relative* sparing of memory and visuospatial function



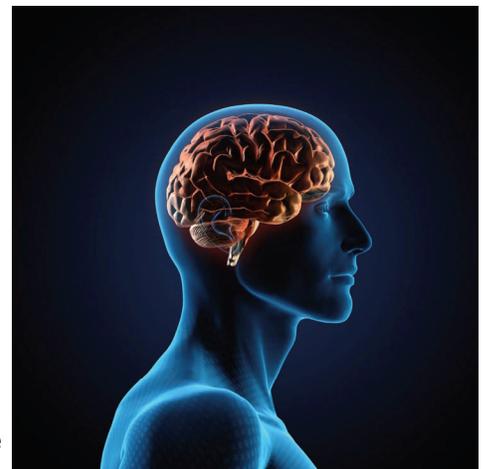
The diagnosis of *Probable* bvFTD represents the clinician's next level in diagnostic certainty, whereby not only are criteria met for diagnosis of *Possible* bvFTD, but the patient also exhibits significant functional decline *and* shows evidence of frontal and/or temporal atrophy, or hypometabolism on structural MRI/ CT, or PET, respectively (International bvFTD Criteria Consortium, in submission).

The core symptoms of the new International criteria are better operationalized with examples of each symptom given. For example, early disinhibition can include socially inappropriate behavior and loss of manners or decorum. Loss of sympathy or empathy may include diminished response to other's needs or feelings and declines in social interrelatedness and warmth. Hyperorality or dietary changes can be altered food preferences (especially sweets) or binge eating and increased consumption of alcohol or cigarettes. Patients may perform well on cognitive testing earlier in the disease, even on executive tasks like Trails and Stroop, although they often do poorly on verbal fluency and exhibit more rule violation errors (Carey et al., 2008; Possin et al., 2009). While bvFTD patients sometimes perform poorly on memory testing, they typically show good preservation of information over delays and do not exhibit significant memory impairment in daily living. Sensitivity of the new criteria has been demonstrated via retrospective chart review of pathologically-confirmed cases in a multi-site study (Rascovsky et al., 2010).

What Role Can Neuropsychology Play?

BvFTD is fundamentally a syndrome of disordered social, emotional, and behavioral conduct. While cognitive deficits can occur, they represent only one of six possible symptoms which may or may not be present. This does not mean, however, that neuropsychologists can not play an important role in the diagnosis and management of the disease.

With regards to differential diagnosis, neuropsychologists' expertise in cognition, behavior, and emotion allows for accurate assessment and clinical interpretation of the six core symptoms of bvFTD. In addition to a skilled and pointed informant interview, informant measures, such as the Neuropsychiatric Inventory (NPI; Cummings, 1997) and Interpersonal Reactivity Index (IRI; Davis, 1983), may also assist in assessment and diagnosis. Efforts to characterize a neuropsychological profile specific to bvFTD have not been successful (for a review, please see Wittenberg et al., 2008 (Wittenberg et al., 2008). As such, *relative test score patterns* between domains appear to be most informative to differential diagnosis (e.g., relative sparing of episodic memory and visuospatial function). Although significant differences between bvFTD and AD on "traditional" tasks of executive function like the Stroop task have been difficult to document (Johns et al., 2009; Nedjam, Devouche, & Dalla Barba, 2004; Heflin et al., in press), quantifying performance errors, particularly rule violations, may have greater diagnostic specificity (Carey et al., 2008; Kramer et al., 2003).





Importantly, neuropsychologists have been actively developing new measures of social behavior that will help capture symptoms germane to bvFTD. For example, Rankin et al. have developed an observer checklist (Social Behavior Observer Checklist 2; Poorzand et al., 2010) for behaviors specific to bvFTD that takes only a few minutes to complete, and is helpful in the differential diagnosis of bvFTD versus AD. They have also developed a simple 22-item yes/no patient questionnaire to determine the degree to which patients understand and can accurately identify implicit, but widely accepted social boundaries in the dominant U.S. culture (Social Norms Questionnaire) (Pishori et al., 2009).

Finally, our knowledge about intervention can be put to good use by providing families with education about their loved one's condition, providing suggestions for managing difficult behaviors, and providing caregivers and family members coping skills to deal with their situation.

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NAN BULLETIN: VOLUME 26 No. 1 - *Neurodegenerative Diseases*

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Understanding Parkinson's Disease: The Need for an Integrated Approach with Neuropsychology Front and Center

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Introduction

For years Parkinson's disease (PD), the "shaking palsy", was primarily considered a motor condition. A diagnosis encompassed two or three hallmark features (e.g., bradykinesia, rigidity, and tremor). Changes in motor functions are used to track progression of PD, and they are scrutinized in relation to levodopa responsiveness. Over time there has been increased emphasis on the identification, study, and treatment of non-motor aspects of PD (e.g., autonomic regulation, sleep irregularities, psychiatric and cognitive problems) in order to understand the disease and to fully appreciate its functional ramifications. This broader view has stimulated integrated approaches to research and treatment. Numerous investigations have provided insights regarding the pathological substrates and genetic underpinnings of PD. New diagnostic classification systems have emerged and these have been validated with data from neuroimaging and autopsy studies. Innovative approaches to treatment include alternative therapies (e.g., chair yoga, choral groups, dance, etc.), pharmacotherapy, brain stimulation and gene therapy. Neuropsychology has assumed a central role in these advances, as cognitive findings provide a metric needed to establish subtypes of PD, progression of disease, and treatment efficacy.

Genetic studies

Knowledge about the genetic contributions to PD comes from studies of familial and sporadic disease, as well as from genome-wide association studies (Morley & Hurtig, 2011). Approximately 15% of individuals with PD have a positive family history. In a small minority of familial cases, genetic risk factors have been identified related to mutations in α -synuclein (*SNCA*), leucine-rich repeat kinase-2 (*LRRK2*), *PRKN*, PTEN-induced kinase-1 (*PINK1*), and *DJ-1*. Among the familial cases, *SNCA* and *LRRK2* result in an autosomal dominant inheritance pattern, whereas *PRKN* and *PINK1* adhere to an autosomal recessive pattern. Other studies have shown that the risk of sporadic PD increases in the context of glucocerebrosidase (*GBA*) as well as *LRRK2* mutations. Although genetic studies are promising, they do not explain the vast majority of sporadic PD cases that are thought to result from a complex interplay of genetic and environmental factors.

Pathology

Neuropathological studies have shown that PD is associated with a loss of dopamine neurons in the region of the ventrolateral nigra and increased α -synuclein aggregates (i.e., Lewy bodies) in brainstem, entorhinal, and cortical brain regions. Attempts to provide criteria for evolution of PD-related pathology have focused on the anatomical distribution and load of α -synuclein pathology. Braak and colleagues (2003) proposed a 6-tiered staging system whereby pathology proceeded in a caudo-rostral direction beginning in the medulla and pontine tegmentum, proceeding to the



substantia nigra and basal forebrain, and finally involving the neocortex. Initial extrapyramidal symptoms stem from α -synuclein in the brainstem, while later cognitive decline reflects neocortical involvement (Braak et al., 2006). The apparent logic of this schema is appealing, though the relationship between α -synuclein burden and clinical presentation is not straightforward. Patients with idiopathic disease and a young onset may adhere to the Braak system, while others show a high Lewy body count in diffuse brain areas early in the disease (Halliday et al. 2008). Additionally, there are individuals with widespread α -synuclein who are neither demented, nor do they demonstrate extrapyramidal symptoms (Parkkinen et al., 2008).

Clinical Phenotypes

PD results in a broad array of motor and non-motor problems that emerge at different times and affect people of different age groups. Recently there have been attempts to develop a nosology of PD using age of onset, rate of progression, and symptom profile as the framework for identification of distinct subgroups, with the ultimate goal of developing more effective treatment. It is expected that earlier interventions will be more useful in delaying neuronal degeneration; hence, many initiatives focus on pre-symptomatic patients. Some non-motor symptoms antedate motor problems by decades. For example, constipation and anxiety may present 20 years prior to motor symptoms, and decreased olfaction and REM sleep behavior disorder are known risk factors for PD (Savica et al., 2010). Neuroimaging that probes dopamine transporter (DAT) systems is useful in the identification of pre-symptomatic PD (Morley & Hurtig, 2011), and neuropsychological studies have emphasized cognitive deficits in pre-symptomatic patients (Troster, 2011). Specifically, individuals identified as “at risk” for PD (on the basis of olfactory and DAT abnormalities) may have processing speed and executive deficits (Hawkins et al, 2010). A higher rate of childhood ADHD has been found in patients with Lewy bodies versus Alzheimer’s disease, suggesting that a cognitive predisposition may predate a diagnosis of PD by decades in some patients (Golimstock et al., 2011).

PD classification systems focus on the nature, extent, and temporal course of motor and non-motor deficits. Early in the course of cognitive decline, patients are described with Mild Cognitive Impairment (MCI) using criteria similar to those in studies of Alzheimer’s disease (Molano, et al., 2010; Troster, 2011). By definition, MCI refers to impairment in one or more domains of cognition with preservation of daily activities. Beyond MCI, patients with more advanced cognitive problems fall into one of two groups: 1) Those with pre-existing cognitive problems at the time of PD diagnosis, who are seen as having dementia with Lewy bodies (DLB); 2) Those with motor deficits predating cognitive decline who are seen as having Parkinson’s disease with dementia (PDD). Similarities between these diagnoses in neuropsychological dysfunction and problems with α -synuclein metabolism raise questions about the validity of distinct diagnoses (Troster, 2007). Nevertheless, consensus criteria have been published for the diagnosis of DLB (McKeith et al, 2005) and PDD (Dubois et al., 2007).

Optimal assessment and diagnosis must consider both motor and non-motor symptoms within the context of relevant demographic variables. For example, patients who develop PD later in life and exhibit abnormal gait typically demonstrate greater cognitive deficits in comparison to young onset



PD patients who present with tremor alone (Janovic, 1990). Other investigators have proposed algorithms for the prediction of dementia risk on the basis of age of onset (>72) and neuropsychological performance (Williams-Gray et al., 2009). These observations offer some evidence of different subtypes of PD, and they suggest that subtyping requires integrated observations across several disciplines. Halliday and colleagues (2008, 2010) described three clinical phenotypes that differ with regard to age of symptom onset, nature of symptom presentation, and pathological substrates. Group one included patients with idiopathic PD, young age of onset, lengthy disease duration and dementia late in the course of illness. These individuals exhibited Lewy bodies in the brainstem and later in the limbic system consistent with the Braak and Braak staging system. A second phenotype included individuals presenting as akinetic, rigid, and demented early in the course of illness. These individuals were identified as having DLB and they were prone to rapid deterioration with severe neocortical α -synuclein deposition and plaque formation. A third phenotype, PDD patients, were older (>70) and they presented with dementia early in the course with a fast rate of decline. This group also exhibited high loads of α -synuclein and plaque formation.

Interventions

By far the most common intervention for PD involves dopamine replacement therapy (e.g., levodopa/Carbidopa), dopamine agonists (e.g., Pramipexole, Ropinerole, etc.) and other medications that extend the lifespan of levodopa (e.g., Selegiline, Rasagiline). These agents provide symptom relief, but offer no neuroprotective or disease-modifying benefits (Morley & Hurtig, 2011). Pharmacotherapy can be challenging in PD because polytherapy is often necessary to mitigate symptoms, and dopaminergic therapy can be associated with disabling side effects (e.g., dyskinesias, hallucinations, on/off fluctuations, daytime sleepiness).

Ablative surgery for treatment of PD (e.g., pallidotomy and thalamotomy) dates back many years. These approaches fell out of favor following the introduction of levodopa, and though there was a resurgence of interest in the 1990s, they were later eclipsed by deep brain stimulation (DBS) surgery, which offered an effective and reversible alternative. DBS involves implanting electrodes in the subthalamic nucleus (STN), globus pallidus pars interna (GPi) or the ventral intermediate nucleus of the thalamus (Vim). High frequency stimulation is provided through a pulse generator implanted in the chest wall. Symptom improvement results from steady electrical pulses, which override abnormal electrical discharges. DBS is primarily useful for patients with tremor predominant PD and it is not effective for axial problems (e.g., postural instability). There is consensus that optimal DBS outcomes depend on careful patient selection (Bornstein et al., 2011). Best results are seen in individuals who have advanced PD, who respond to levodopa therapy (e.g., a reduction of 30% on the UPDRS motor scale), and who do not have psychiatric problems or dementia. The ideal site for DBS stimulation was examined in a recent study (Follett et al., 2010). Three hundred PD patients were randomized to three groups (STN/DBS, GPi/DBS or best medical therapy) and they were followed for six months. Both DBS groups demonstrated significant motor improvement and overall quality of life. The STN group was on a lower dose of PD medicine in the wake of surgery but they were slightly more depressed and had lower cognitive scores than did the GPi group. Both DBS groups had increased falls. Other studies have shown that depression and impulsive behaviors may emerge in the wake of DBS surgery. Some investigators have found



diminished verbal fluency and processing speed in the post operative phase.

Gene therapy has also been explored for treatment of PD symptoms. In a recent double blind study, investigators used a viral vector (AAV2) to insert a gene for glutamic acid decarboxylase (GAD) into the STN (LeWitt et al., 2011). The goal was to increase GABA activity to reduce output from the STN. Preliminary findings revealed improved motor functions but the persistence of this effect remains to be seen.



Role of the neuropsychologist on the movement disorders team

Neuropsychology has assumed a key role in research and the clinical management of PD. Investigations focusing on the interplay between motor and non-motor aspects of PD highlight the complex ways that PD unfolds over time in relation to age, genetics, pathology and in response to surgical and non-surgical interventions. Carefully designed studies have yielded cognitive phenotypes critical for the development of effective treatment.

In the clinic, the neuropsychologist is often the “point person” to affirm a diagnosis of dementia relevant to MCI, PDD, DLB or a different condition. Clinicians differ with regard to preferences for test selection, but all should have a clear grasp of the neurocognitive profiles and clinical features unique to these conditions. Individuals with PD-related MCI should, by definition, have deficits in one or more areas of cognition in the context of preserved activities of daily living (ADL’s). Individuals with PDD have significant cognitive deficits

in one or more domains with impaired ADL’s. Their motor problems precede dementia and often these individuals have axial motor issues. Individuals with DLB often have marked visuospatial deficits as well as problems with memory and word finding. These patients often present with visual hallucinations, fluctuations in their cognitive status, and REM sleep behavior disorders (Ferman & Boeve, 2007; Troster, 2008). Serial cognitive assessments are often needed to measure disease progression and treatment outcome, such as before and after DBS surgery. The initial evaluation establishes a baseline and provides the team with needed information regarding whether an individual is an appropriate surgical candidate. Some DBS patients experience mild verbal fluency and processing speed problems in the wake of surgery. Serial assessment should take into account practice effects, test reliability and variability in PD (Troster, 2007). All evaluations should take into account normal variability in cognitive test performance (Shretlen et al., 2003).

Pragmatically oriented neuropsychological evaluations elucidate functional strengths and weaknesses relevant to management of daily activities, work, finances, and decision making, with an eye towards balancing needs for independence and safety. The end goal for research and clinical endeavors is the development of interventions to promote an optimal quality of life for the individual with PD.



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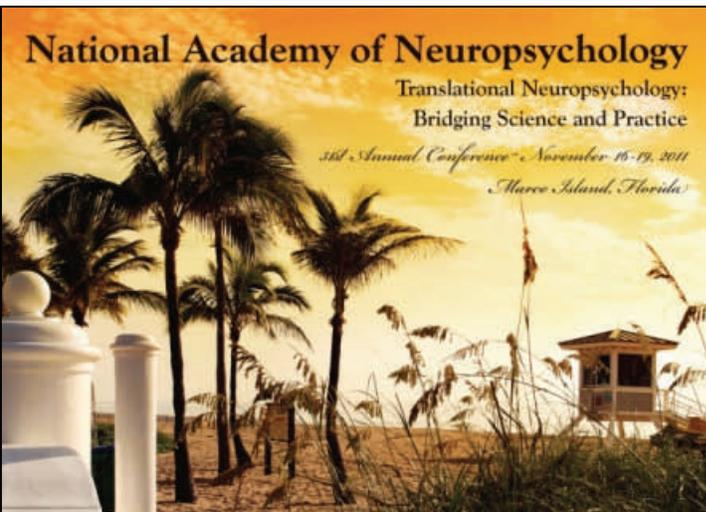
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