

- 1 Dubois, B., Feldman, H. H., Jacova, C., Hampel, H., Molinuevo, J. L., Blennow, K. et al. (2014). Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. *Lancet Neurology*, 13, 614-629.
Notes: In the past 8 years, both the International Working Group (IWG) and the US National Institute on Aging-Alzheimer's Association have contributed criteria for the diagnosis of Alzheimer's disease (AD) that better define clinical phenotypes and integrate biomarkers into the diagnostic process, covering the full staging of the disease. This Position Paper considers the strengths and limitations of the IWG research diagnostic criteria and proposes advances to improve the diagnostic framework. On the basis of these refinements, the diagnosis of AD can be simplified, requiring the presence of an appropriate clinical AD phenotype (typical or atypical) and a pathophysiological biomarker consistent with the presence of Alzheimer's pathology. We propose that downstream topographical biomarkers of the disease, such as volumetric MRI and fluorodeoxyglucose PET, might better serve in the measurement and monitoring of the course of disease. This paper also elaborates on the specific diagnostic criteria for atypical forms of AD, for mixed AD, and for the preclinical states of AD
- 2 Bertoux, M., Funkiewiez, A., O'Callaghan, C., Dubois, B., & Hornberger, M. (2013). Sensitivity and specificity of ventromedial prefrontal cortex tests in behavioral variant frontotemporal dementia. *Alzheimers and Dementia*, 9, S84-S94.
Notes: BACKGROUND: Behavioral variant frontotemporal dementia (bvFTD) is characterized by early and substantial ventromedial prefrontal cortex (VMPFC) dysfunction. To date, however, there is no consensus regarding which tests are most sensitive and specific to assess VMPFC dysfunction in this condition. METHODS: In this study we compared the sensitivity and specificity of four common VMPFC specific tests (Mini-SEA, Go/No-Go Subtest of the Frontal Assessment Battery, Reversal-Learning Test, and Iowa Gambling Task) at first clinic presentation in two neurodegenerative cohorts (bvFTD, Alzheimer's disease) and age-matched, healthy controls. RESULTS: We found that the Mini-SEA, evaluating theory of mind and emotion processes, emerged as the most sensitive and specific of the VMPFC tests employed. The Mini-SEA alone successfully distinguished bvFTD and Alzheimer's disease (AD) in >82% of subjects at first presentation. Similarly, the FAB Go/No-Go and Reversal-Learning Tests also showed very good discrimination power, but to a lesser degree. The Iowa Gambling Task, one of the most common measures of VMPFC function, was the least specific of these tests. CONCLUSION: Sensitivity to detect VMPFC dysfunction was high across all test employed, but specificity varied considerably. The Mini-SEA emerged as the most promising of the VMPFC-specific diagnostic tests. Clinicians should take into account the variable specificity of currently available VMPFC tests, which can complement current carer-based questionnaires and clinical evaluation to improve the diagnosis of behavioral dysfunctions due to VMPFC dysfunction
- 3 Cummings, J. L., Dubois, B., Molinuevo, J. L., & Scheltens, P. (2013). International Work Group criteria for the diagnosis of Alzheimer disease. *Medical Clinics of North America*, 97, 363-368.
Notes: Alzheimer-type biomarker changes are identifiable in asymptomatic and mildly symptomatic predementia phases of Alzheimer disease (AD) and AD dementia. The International Work Group (IWG) guidelines for diagnosis identify a unified spectrum of 3 phases. The classic clinical feature that indicates AD is an episodic memory defect of the amnesic type. IWG criteria require biomarker support for the diagnoses of AD at any clinical stage. Pathophysiologic and topographic biomarkers are recognized. These criteria are proposed to allow highly specific diagnosis of AD and assist in identifying patients for clinical trials of AD-related treatments and other types of AD research
- 4 Dubois, B., Gauthier, S., & Cummings, J. (2013). The utility of the new research diagnostic criteria for Alzheimer's disease. *International Psychogeriatrics*, 25, 175-177.

- 5 Teichmann, M., Migliaccio, R., Kas, A., & Dubois, B. (2013). Logopenic progressive aphasia beyond Alzheimer's--an evolution towards dementia with Lewy bodies. *Journal of Neurology, Neurosurgery and Psychiatry*, *84*, 113-114.
- 6 Dubois, B., Tolosa, E., Katzenschlager, R., Emre, M., Lees, A. J., Schumann, G. et al. (2012). Donepezil in Parkinson's disease dementia: A randomized, double-blind efficacy and safety study. *Movement Disorders*, *27*, 1230-1238.
 Notes: Parkinson's disease dementia (PDD) is associated with cholinergic deficits. This report presents an efficacy and safety study of the acetylcholinesterase inhibitor donepezil hydrochloride in PDD. PDD patients (n = 550) were randomized to donepezil (5 or 10 mg) or placebo for 24 weeks. Coprimary end points were the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) and Clinician's Interview-Based Impression of Change plus caregiver input (CIBIC+; global function). Secondary end points measured executive function, attention, activities of daily living (ADLs), and behavioral symptoms. Safety and tolerability were assessed. ADAS-cog mean changes from baseline to week 24 (end point) were not significant for donepezil in the intent-to-treat population by the predefined statistical model (difference from placebo: -1.45, P = .050, for 5 mg; -1.45, P = .076, for 10 mg). Alternative ADAS-cog analysis, removing the treatment-by-country interaction term from the model, revealed significant, dose-dependent benefit with donepezil (difference from placebo: -2.08, P = .002, for 5 mg; -3.31, P < .001, for 10 mg). The 10-mg group, but not the 5-mg group, had significantly better CIBIC+ scores compared with placebo (3.7 vs 3.9, P = .113, for 5 mg; 3.6 vs 3.9, P = .040, for 10 mg). Secondary end points-Mini-Mental State Exam; Delis-Kaplan Executive Function System; Brief Test of Attention, representing cognitive functions particularly relevant to PDD-showed significant benefit for both donepezil doses (P </.007). There were no significant differences in ADLs or behavior. Adverse events were more common with donepezil but mostly mild/moderate in severity. Although the study did not achieve its predefined primary end points, it presents evidence suggesting that donepezil can improve cognition, executive function, and global status in PDD. Tolerability was consistent with the known safety profile of donepezil.
 Universite Pierre et Marie Curie-Paris 6, Centre de Recherche de l'Institut du Cerveau et de la Moelle epiniere (CRICM), UMR-S975; AP-HP, Groupe hospitalier Pitie-Salpetriere, Institut de la Memoire et de la Maladie d'Alzheimer (IMMA); Inserm U 975, Paris, France.
 bruno.dubois@psl.aphp.fr
- 7 Dubois, B., Feldman, H. H., Jacova, C., Cummings, J. L., DeKosky, S. T., Barberger-Gateau, P. et al. (2010). Revising the definition of Alzheimer's disease: a new lexicon. *Lancet Neurology*, *9*, 1118-1127.
 Notes: Alzheimer's disease (AD) is classically defined as a dual clinicopathological entity. The recent advances in use of reliable biomarkers of AD that provide in-vivo evidence of the disease has stimulated the development of new research criteria that reconceptualise the diagnosis around both a specific pattern of cognitive changes and structural/biological evidence of Alzheimer's pathology. This new diagnostic framework has stimulated debate about the definition of AD and related conditions. The potential for drugs to intercede in the pathogenic cascade of the disease adds some urgency to this debate. This paper by the International Working Group for New Research Criteria for the Diagnosis of AD aims to advance the scientific discussion by providing broader diagnostic coverage of the AD clinical spectrum and by proposing a common lexicon as a point of reference for the clinical and research communities. The cornerstone of this lexicon is to consider AD solely as a clinical and symptomatic entity that encompasses both predementia and dementia phases
- 8 Dubois, B., Picard, G., & Sarazin, M. (2009). Early detection of Alzheimer's disease: new diagnostic criteria. *Dialogues.Clin.Neurosci.*, *11*, 135-139.
 Notes: There has been unprecedented growth of scientific knowledge about Alzheimer's disease (AD). The description of distinctive and reliable biomarkers that are now available through structural brain imaging with magnetic resonance imaging, molecular neuroimaging with positron emission tomography, and cerebrospinal fluid analyses, and a better definition

of the clinical profile of amnesic disorders that occur early in the course of the disease, make it possible to identify AD with high accuracy, even in the early stages of the disease. Accordingly, new criteria for the diagnosis have been proposed that capture both the prodromal and the more advanced dementia stages of the disease in the same diagnostic framework

INSERM-UPMC UMRS 975, Federation of Neurology, APHP, Salpêtrière Hospital, University Paris 6, Paris, France. bruno.dubois@psl.aphp.fr

- 9 Dubois, B., Andrade, K., & Levy, R. (2008). Executive dysfunction and neuropsychological testing. In *Handbook of Clinical Neurology, Vol.89*. Ed.by P.J.Vinken & G.W.Bruyn.Amsterdam:Elsevier, (35-52).
- 10 Dubois, B., Pillon, B., & McKeith, I. G. (2007). Parkinson's disease with and without dementia and Lewy body dementia. In B.L.Miller & J. L. Cummings (Eds.), *The human frontal lobes: Functions and disorders* (2 ed., pp. 472-504). New York: Guilford Press.
- 11 Dubois, B., Feldman, H. H., Jacova, C., DeKosky, S. T., Barberger-Gateau, P., Cummings, J. et al. (2007). Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. *Lancet Neurology, 6*, 734-746.
Notes: INSERM U610, Hopital de la Salpêtrière, Paris, France. bruno.dubois@psl.aphp.fr
The NINCDS-ADRDA and the DSM-IV-TR criteria for Alzheimer's disease (AD) are the prevailing diagnostic standards in research; however, they have now fallen behind the unprecedented growth of scientific knowledge. Distinctive and reliable biomarkers of AD are now available through structural MRI, molecular neuroimaging with PET, and cerebrospinal fluid analyses. This progress provides the impetus for our proposal of revised diagnostic criteria for AD. Our framework was developed to capture both the earliest stages, before full-blown dementia, as well as the full spectrum of the illness. These new criteria are centred on a clinical core of early and significant episodic memory impairment. They stipulate that there must also be at least one or more abnormal biomarkers among structural neuroimaging with MRI, molecular neuroimaging with PET, and cerebrospinal fluid analysis of amyloid beta or tau proteins. The timeliness of these criteria is highlighted by the many drugs in development that are directed at changing pathogenesis, particularly at the production and clearance of amyloid beta as well as at the hyperphosphorylation state of tau. Validation studies in existing and prospective cohorts are needed to advance these criteria and optimise their sensitivity, specificity, and accuracy
- 12 Dubois, B. & Pillon, B. (2005). Added value of the neuropsychological evaluation for diagnosis and research of atypical parkinsonian disorders. In I.Litvan (Ed.), *Atypical parkinsonian disorders: Clinical and research aspects* (pp. 185-195). Totowa,NJ: Humana Press.
- 13 Dubois, B. & Albert, M. L. (2004). Amnesic MCI or prodromal Alzheimer's disease? *Lancet Neurology, 3*, 246-248.
Notes: Federation de Neurologie and Inserm E007, Hopital de la Salpêtrière, Paris, France. b.dubois@psl.ap-hop-paris.fr
The concept of mild cognitive impairment (MCI) draws attention to cognitive changes not severe enough to warrant the diagnosis of dementia. As used today, it covers many pathological disorders and characterises a diverse population of patients who attend memory clinics. Our concern is the underlying heterogeneity. We suggest that it will soon be possible (if it is not already) to identify the underlying pathological disorders before the affected patients meet the criteria of dementia, thanks to specific neuropsychological assessments, neuroimaging, and biomarkers. In particular, patients with Alzheimer's disease (AD), the most important subgroup of patients with MCI, can already be identified before appearance of the fully developed clinical dementia syndrome. Accordingly, this paper proposes diagnostic criteria for "prodromal AD"

- 14 Dubois, B., Slachevsky, A., Litvan, I., & Pillon, B. (2000). The FAB: a Frontal Assessment Battery at bedside. *Neurology*, *55*, 1621-1626.
 OBJECTIVE: To devise a short bedside cognitive and behavioral battery to assess frontal lobe functions. METHODS: The designed battery consists of six subtests exploring the following: conceptualization, mental flexibility, motor programming, sensitivity to interference, inhibitory control, and environmental autonomy. It takes approximately 10 minutes to administer. The authors studied 42 normal subjects and 121 patients with various degrees of frontal lobe dysfunction (PD, n = 24; multiple system atrophy, n = 6; corticobasal degeneration, n = 21; progressive supranuclear palsy, n = 47; frontotemporal dementia, n = 23). RESULTS: The Frontal Assessment Battery scores correlated with the Mattis Dementia Rating Scale scores ($\rho = 0.82$, $p < 0.01$) and with the number of criteria ($\rho = 0.77$, $p < 0.01$) and perseverative errors ($\rho = 0.68$, $p < 0.01$) of the Wisconsin Card Sorting Test. These variables accounted for 79% of the variance in a stepwise multiple regression, whereas age or Mini-Mental State Examination scores had no significant influence. There was good interrater reliability ($\kappa = 0.87$, $p < 0.001$), internal consistency (Cronbach's coefficient alpha = 0.78), and discriminant validity (89.1% of cases correctly identified in a discriminant analysis of patients and controls). CONCLUSION: The Frontal Assessment Battery is easy to administer at bedside and is sensitive to frontal lobe dysfunction
- 15 Dubois, B. (2000). 'Prodromal Alzheimer's disease': a more useful concept than mild cognitive impairment? *Current Opinion in Neurology*, *13*, 367-369.
- 16 Dubois, B., Verin, M., Teixeira-Ferreira, C., Sirigu, A., & Pillon, B. (1994). How to study frontal lobe functions in humans. In A.-M.Thierry, J. Glowinski, P. S. Goldman-Rakic, & Y. Christen (Eds.), *Motor and cognitive functions of the prefrontal cortex* (pp. 1-16). Berlin: Springer.
 Notes: (Review of neuropsychological tests used to study frontal lobe deficits, and a study of 10 patients with focal lesions (7 left, 3 right hemisphere) compared with 10 patients with posterior lesions and 24 normal controls. The task was a computer delayed response task with 3 phases: delayed response, delayed alternation, and delayed non-alternation with reversals. Rules changed automatically upon criterion of the previous phase being met, and had to be discovered by deductive reasoning. Frontal lobe patients made errors on delayed response, alternated (surprisingly) spontaneously, and were highly deficient in delayed non-alternation)
- 17 Dubois, B. & Pillon, B. (1992). Biochemical correlates of cognitive changes and dementia in Parkinson's disease. In S.J.Huber & J. L. Cummings (Eds.), *Parkinson's disease: Neurobehavioral aspects* (pp. 178-198). New York: Oxford University Press
- 18 Dubois, B., Boller, F., Pillon, B., & Agid, Y. (1991). Cognitive deficits in Parkinson's disease. In F.Boller & J. Grafman (Eds.), *Handbook of neuropsychology, Vol.5* (pp. 195-240). Amsterdam: Elsevier.
- 19 Dubois, B., Pilon, B., Lhermitte, F., & Agid, Y. (1990). Cholinergic deficiency and frontal dysfunction in Parkinson's disease. *Annals of Neurology*, *28*, 117-121.
 Notes: Inserm U 289 et Clinique de Neurologie et Neuropsychologie, Hopital de la Salpetriere, Paris, France To investigate the influence of central cholinergic deficit on cognitive function in Parkinson's disease (PD), we compared the neuropsychological performance of a group of 20 patients who were treated with anticholinergic drugs (mean daily dose, 10.2 mg) with that of a group of 20 patients who received no anticholinergics. The two groups were matched for all the variables of parkinsonism and levodopa therapy. At the dose used, there was no significant difference between the two groups of patients for intellectual, visuospatial, instrumental, and memory function. In contrast, in the group that received anticholinergics severe impairment was observed on tests believed to assess frontal lobe function. These results suggest that the lesion of the ascending cholinergic neurons, which has been demonstrated post mortem in PD, may play a role in the subcortical behavioral impairment of this disease