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L E T T E R to the Editor,

Research criteria for the diagnosis of Alzheimer's disease: genetic risk factors, blood biomarkers and olfactory dysfunction

Dear Editor,

We note with interest the recently proposed new diagnostic framework published in *Lancet Neurology* entitled "Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria" by Dubois *et al.* (2007).

We are generally positively disposed towards this framework, especially with regard to its emphasis (in the context of the extant scientific literature) on the delineation of sensitive and specific biomarkers for the diagnosis of Alzheimer's disease (AD). As Norman Foster (2007) observes in his commentary piece in *Lancet Neurology*, "the NINCDS-ADRDA criteria are showing their age and risk losing their relevance" in the context of recent scientific evidence. However, there is a relative paucity of information provided by Dubois *et al.* (2007) in their article pertaining to (a) genetic risk factors and blood biomarkers for AD, and (b) the role of olfactory dysfunction as a potential predictor of AD.

With respect to (a), there is now accumulating evidence in support of APOE $\varepsilon 4$ carriers (who represent half of all AD cases) being characterized by a different etiology from non- $\varepsilon 4$ carriers (Snowden *et al.*, 2007). An APOE $\varepsilon 4$ gene-dosage effect is also present in AD, in which the risk increases from 20% when no $\varepsilon 4$ alleles are present, to 90% when two copies are present. Therefore, the associations of the $\varepsilon 4$ allele with AD should perhaps also be taken into consideration together with other factors when formulating novel diagnostic criteria for AD. Moreover, there has been a recent suggestion that other genetic considerations are also relevant: several studies have reported an association ofAD with polymorphic markers in SORL1 (e.g. Rogaeva *et al.*, 2007). In addition, given their high penetrance and causal relationships, genetic mutations associated with early onset AD (located on chromosomes 1, 14, and 21) should perhaps be considered separately when assessing individuals where there is a strong family history of AD (St George-Hyslop, 1998).

Blood biomarkers must also be considered given recent findings by Ray and colleagues (2007). These authors found that certain plasma proteins which have cell signaling functions can be used to classify AD and controls with up to 90% accuracy. The authors also suggest that analysis of these proteins from patients with mild cognitive impairment (MCI; i.e. pre-symptomatic AD) can be used to identify patients who are at risk of progressing further and developing AD. This article and other findings indicating that plasma levels of β amyloid are associated with increased risk of AD suggest that blood markers (perhaps together with genetic and cerebrospinal fluid markers) should be investigated as potential diagnostic biomarkers for AD.

Furthermore, while Dubois *et al.* have suggested that sensory deficits should be considered as relevant exclusion criteria for AD, we would like to challenge this proposal, specifically with respect to (b), the role of olfactory dysfunction as a potential predictor of AD (Burns, 2000). In general terms, AD is characterized by an advancing wave of cortical atrophy that moves from limbic and temporal cortices into higher-order association and ultimately primary sensory motor areas. However, there is an exception to this general framework. Specifically, there is increasing evidence that the sensory olfactory cortex is implicated early in the progression of AD (Mesholam *et al.,* 1998). Evidence for the involvement of the olfactory system is

threefold: (i) smell dysfunction has been noted in AD patients, APOE $\varepsilon 4$ carriers and family members of AD patients; (ii) MCI patients and healthy subjects showing cognitive decline indicative of early stage AD manifest olfactory problems; and (iii) there is post-mortem evidence of neurofibrillary tangles and β-amyloid plaques located in the olfactory system of early AD patients. Given the burgeoning literature regarding the involvement of the olfactory system in very early stage/prodromal/preclinical AD (see: Hawkes, 2006; Wilson *et al.,* 2007), we propose that serious consideration should be given to the proposal that olfactory dysfunction should also be incorporated into a revised framework for the reliable diagnosis of AD.

In addition, specific diagnostic criteria pertaining to the potentially important dichotomy between familial (early onset) versus sporadic (late onset) AD – and the possible relevance of age at the time of diagnosis – are not clearly addressed by Dubois *et al.*

A further comment concerns the characterization of the precursor state to full-blown AD. While the authors question the use of the term "mild cognitive impairment" because of its potential ambiguity, we believe that the use of the terms "preclinical" and "prodromal" is not clearly operationalized by Dubois *et al.* The use of these terms in the manner proposed by the authors could therefore contribute towards further confusion, rather than clarifying the stages preceding AD.

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