SCIENTIFIC COMMENTARY

Biomarkers for Alzheimer’s disease: ready for the next step

As potential disease-modifying treatments for Alzheimer’s disease advance into phase II and III human trials, it is apparent that biomarker development will be needed for several reasons. The most relevant of these include the ability to detect treatment response sensitively, to improve understanding of the effect of drugs that target disease mechanisms, and to identify Alzheimer’s disease in its pre-clinical stage. We have reviewed several recent papers published in *Brain*, which address biomarker development in Alzheimer’s disease, and use their findings to suggest further research.

Some of these studies are early results from the Alzheimer’s Disease Neuroimaging Initiative (ADNI), a large multi-centre trial of biomarker modalities in patients with Alzheimer’s disease, mild cognitive impairment (MCI) and cognitively healthy older controls with an emphasis on standardized imaging techniques across centres. Nestor *et al.* (2008) measured ventricular volume changes over time and found that MCI subjects had a faster rate of ventricular enlargement than controls, and that Alzheimer’s disease subjects had an even faster rate. Most importantly, among participants with MCI, the rate of ventricular enlargement was higher in those who progressed to Alzheimer’s disease than in those who did not. The authors estimate that using ventricular enlargement as a surrogate marker of treatment outcome could improve the power of a treatment trial significantly versus standard cognitive outcomes. Desikan *et al.* (2009) developed methods of automated MRI analysis of regional brain volumes with the goal of identifying differences between patients with MCI and healthy controls. Entorhinal and supramarginal gyrus cortical thickness and hippocampal volumes afforded the best discrimination between these two groups. The automated analysis tools were impressively reliable and yielded replicable results in two different cohorts and with many different MRI scanners. Querbes *et al.* (2009) developed a rapid automated method for measuring cortical thickness and found that these changes were good predictors of an alteration in diagnosis from normal to MCI, or from MCI to overt Alzheimer’s disease up to 24 months prior to that change. Their method is particularly attractive as it is relatively simple and builds on a reasonably robust literature on cortical thickness assessed by manual methods. Interestingly enough, more educated subjects had a thinner cortex than those who had the same level of cognitive performance, supporting the notion that they have greater cognitive reserve. Davatzikos *et al.* (2009) identified a characteristic spatial pattern of atrophy across brain regions in Alzheimer’s disease patients in the ADNI cohort. In a separate cohort (Baltimore Longitudinal Study of Aging), they found that although this pattern increased over time in healthy older persons, the change was accelerated in individuals with MCI. Whitwell *et al.* (2007) examined similar hypotheses, reporting a characteristic pattern of regional brain atrophy during the 3 years prior to the diagnosis of incident Alzheimer’s disease, starting in medial temporal lobes and spreading in posterior and anterior directions through the brain, in a temporospatial pattern similar to the spread of neurofibrillary tangles, by the time of diagnosis. These findings increase our confidence that regional brain volume loss parallels known pathological processes in Alzheimer’s disease.

Other recently published papers in *Brain* have examined the association between brain amyloid load and clinical measures or other biomarkers, which may be increasingly important now that putative amyloid-lowering agents are undergoing human trials. Jack *et al.* (2008) found the areas of concordance and discordance between the β-amyloid marker Pittsburgh compound B (11C-PIB) uptake and grey matter volume loss in Alzheimer’s disease, confirming pathological findings that plaque deposition and neuronal loss proceed at different rates in different regions of the Alzheimer’s disease brain. Grey matter volume loss correlated more strongly with cognitive deficits than PIB uptake. The authors propose that PIB uptake occurs early in Alzheimer’s disease and does not track disease severity closely at later stages. Two other recent *Brain* publications support this model. Pike *et al.* (2007) report that 11C-PIB uptake is robustly associated with poorer episodic recall in MCI and normal controls, but not in Alzheimer’s disease. This constitutes the first published report of an association between amyloid load and cognition. Mormino *et al.* (2008) report that 11C-PIB uptake, hippocampal volume loss and deficits in episodic recall are associated in MCI and control subjects, whereas in multivariate models, hippocampal volume loss is more strongly associated with memory loss than...


$^{11}$C-PIB uptake. They propose a model in which amyloid deposition precedes hippocampal volume loss, which is then followed by memory loss. An alternative marker of brain amyloid, ‘β-site amyloid precursor protein-cleaving enzyme 1’ (BACE1), is the major β-secretase of the brain that catalyses the first step in the synthesis of amyloid-β 1–42 ($\beta\beta_{1-42}$). Ewers et al. (2008) reported that ApoE4 allelotype is associated with elevated BACE1 activity in both Alzheimer’s disease and MCI, complementing their earlier finding that BACE1 activity (not BACE1 protein levels) in cerebral spinal fluid is increased in MCI and Alzheimer’s disease, relative to controls. Cerebral spinal fluid BACE1 enzymatic activity is likely to reflect the rate of $\beta\beta_{1-42}$ synthesis rather than the current load and it may have an advantage over other biomarkers since $\beta\beta_{1-42}$ has very rapid brain turnover (Bateman et al., 2006). This biomarker will be crucial for determining whether BACE1 inhibitors affect their intended target. Additionally, the new findings of Ewers and colleagues (2008) shed light on the still-enigmatic mechanisms by which ApoE4 increases incident risk of Alzheimer’s disease.

Another paper recently published in Brain capitalized on the increasing availability of $[18F]$-fluorodeoxyglucose (FDG) positron emission tomography (PET) imaging of glucose metabolism for clinical use and the accumulating evidence for its reliability and validity as a predictor of progression in Alzheimer’s disease (Mosconi et al., 2007, 2008). Fouquet et al. (2009) assessed longitudinal changes in FDG regional brain uptake in MCI, reporting that conversion to Alzheimer’s disease was associated with a faster decline of FDG uptake in two medial brain regions (left anterior cingulate and subgenual region) that have been implicated in early Alzheimer’s disease.

Taken together, these recent publications demonstrate the potential for new biomarkers of Alzheimer’s disease staging within a variety of modalities including imaging and cerebral spinal fluid studies. However, our enthusiasm for these novel biomarkers must be tempered with caution. First, the MRI analyses presented are complex. It is widely agreed that manual methods for measuring regional brain volumes will need to be replaced by automated methods and major improvements have been made in this area in recent years. The automated MRI methodologies are, however, highly sophisticated, sometimes effectively requiring access to a supercomputer (Desikan et al., 2009), very advanced data analysis (Davatzikos et al., 2009) or sophisticated manual pre-processing prior to automated analysis (Nestor et al., 2008; Querbes et al., 2009). Future studies should be directed at validating simpler, more efficient methods for clinical use. Another challenge is that the longitudinal studies reported an association between changes in biomarkers (as opposed to a single assessment) and prognosis (Nestor et al., 2008; Querbes et al., 2009). A measure requiring only one MRI scan, instead of two spaced 6–24 months apart, would be far preferable for translation to clinical work.

Secondly, it is not clear what the optimal method will be for quantifying brain amyloid load. $^{11}$C-PIB-PET has been most widely studied and validated but the short half-life of $^{11}$C renders it a boutique investigative tool, limited to major research centres. A major industry and academic effort is being made to develop $^{18}$F agents for PET amyloid (Cai et al., 2004; Zhang et al., 2007; Zheng, et al., 2008). FDG-PET is already widely available and validated but does not measure a specific disease mechanism or treatment target. Given the expense of PET, clinicians are likely to turn to cerebral spinal fluid biomarkers that may be equally sensitive and specific for predicting cognitive decline in older adults at lower cost, although requiring the invasiveness of lumbar puncture (Fagan et al., 2006, 2007). Cerebral spinal fluid BACE1 activity may become a useful addition to this profile but remains to be fully validated. Future studies must determine which biomarkers independently predict pathological diagnosis or narrow the treatment options.

Thirdly, there is an urgent need for less invasive and potentially less costly peripheral blood-based markers. Potential markers include the $\beta\beta_{1-40}/\beta\beta_{1-42}$ ratio (Hansson et al., 2008; Schupf et al., 2008), signalling moieties such as sphingomyelin and ceramides (Mielke et al., 2008) and mediators of neuroinflammation including pro-inflammatory cytokines (Rosenberg, 2005; Kaplin et al., 2008). Unfortunately, to date the sensitivity, specificity and validity of these markers is suboptimal and it is not yet clear to what extent peripheral blood mechanisms reflect CNS mechanisms.

Fourthly—and most importantly—much of the effort cited before involves assessing the sensitivity and specificity of biomarkers to distinguish diagnostic groups. These are merely preliminary efforts for the more important issue of using biomarkers to predict who will develop Alzheimer’s disease. Logically, this effort starts with a high-risk group (amnestic MCI) and proceeds backwards into studies of cognitively healthy persons. To this end, three of the aforementioned papers (Whitwell et al., 2007; Nestor et al., 2008; Fouquet et al., 2009) must be applauded for addressing risk factors for MCI progression to clinical Alzheimer’s disease. However, future studies must confirm the pathological diagnoses. When the right combination of biomarkers has high sensitivity, specificity and availability for identifying cognitively healthy persons at-risk for developing Alzheimer’s disease or cognitive decline, we will be able to develop truly preventive strategies—the ‘holy grail’ of intervention. We are ready for this next step.

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