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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 (^{11}C-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 ^{11}C-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 ^{11}C-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 ($A\beta_{1-42}$). 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 $A\beta_{1-42}$ synthesis rather than the current load and it may have an advantage over other biomarkers since $A\beta_{1-42}$ 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 $A\beta_{1-40}/_{1-42}$ 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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References

Bateman RJ, Munsell LY, Morris JC, Swarm R, Yarasheski KE, Holtzman DM. Human amyloid-beta synthesis and clearance rates as measured in cerebrospinal fluid in vivo. Nat Med 2006; 12: 856–61.

Cai L, Chin FT, Pike VW, Toyama H, Liow JS, Zoghbi SS, et al. Synthesis and evaluation of two 18F-labeled 6-iodo-2-(4′-N,N-dimethylamino)

phenylimidazo[1,2-a]pyridine derivatives as prospective radioligands for beta-amyloid in Alzheimer's disease. J Med Chem 2004; 47: 2208–18.

Davatzikos C, Xu f, An Y, Fan Y, Resnick S. Longitudinal progression of Alzheimer's-like patterns of atrophy in normal older adults: the SPARE-AD index. Brain 2009 (in press).

Desikan R, Cabral H, Hess C, Dillon W, Weiner M, Schmansky N, et al. Automated MRI measures identify individuals with mild cognitive impairment and Alzheimer's disease. Brain 2009 (in press).

Ewers M, Zhong Z, Burger K, Wallin A, Blennow K, Teipel SJ, et al. Increased CSF-BACE 1 activity is associated with ApoE-epsilon 4 genotype in subjects with mild cognitive impairment and Alzheimer's disease. Brain 2008; 131: 1252–8.

Fagan AM, Mintun MA, Mach RH, Lee SY, Dence CS, Shah AR, et al. Inverse relation between in vivo amyloid imaging load and cerebrospinal fluid Abeta42 in humans. Ann Neurol 2006; 59: 512–19.

Fagan AM, Roe CM, Xiong C, Mintun MA, Morris JC, Holtzman DM. Cerebrospinal fluid tau/beta-amyloid(42) ratio as a prediction of cognitive decline in nondemented older adults. Arch Neurol 2007; 64: 343–9.

Fouquet M, Desgranges B, Landeau B, Duchesnay E, Mezenge F, Viader F, et al. Longitudinal brain metabolic changes from amnestic mild cognitive impairment to Alzheimer's disease. Brain 2009 (in press).

Hansson O, Zetterberg H, Vanmechelen E, Vanderstichele H, Andreasson U, Londos E, et al. Evaluation of plasma abeta(40) and abeta(42) as predictors of conversion to Alzheimer's disease in patients with mild cognitive impairment. Neurobiol Aging 2008.

Jack CR Jr, Lowe VJ, Senjem ML, Weigand SD, Kemp BJ, Shiung MM, et al. 11C PiB and structural MRI provide complementary information in imaging of Alzheimer's disease and amnestic mild cognitive impairment. Brain 2008; 131: 665–80.

Kaplin AM, Carroll KAL, Cheng J, Allie R, Lyketsos CG, Calabresi P, et al. IL6 release by LPS-stimulated peripheral blood mononuclear cells as a potential biomarker in Alzheimer disease. Int Psychogeriatr 2009; 21: 413–4.

Mielke MM, Bandaru VV, Haughey NJ, Rabins PV, Lyketsos CG, Carlson MC. Serum sphingomyelins and ceramides are early predictors of memory impairment. Neurobiol Aging 2008.

Mormino EC, Kluth JT, Madison CM, Rabinovici GD, Baker SL, Miller BL, et al. Episodic memory loss is related to hippocampal-mediated {beta}-amyloid deposition in elderly subjects. Brain 2009; 132: 1310–23.

Mosconi L, Tsui WH, Pupi A, De Santi S, Drzezga A, Minoshima S, et al. 18F-FDG PET database of longitudinally confirmed healthy elderly individuals improves detection of mild cognitive impairment and Alzheimer's disease. J Nucl Med 2007; 48: 1129–34.

Mosconi L, Tsui WH, Herholz K, Pupi A, Drzezga A, Lucignani G, et al. Multicenter standardized 18F-FDG PET diagnosis of mild cognitive impairment, Alzheimer's disease, and other dementias. J Nucl Med 2008; 49: 390–8.

Nestor SM, Rupsingh R, Borrie M, Smith M, Accomazzi V, Wells JL, et al. Ventricular enlargement as a possible measure of Alzheimer's disease progression validated using the Alzheimer's disease neuroimaging initiative database. Brain 2008; 131: 2443–54.

Pike KE, Savage G, Villemagne VL, Ng S, Moss SA, Maruff P, et al. Beta-amyloid imaging and memory in non-demented individuals: evidence for preclinical Alzheimer's disease. Brain 2007; 130: 2837–44.

Querbes O, Aubry F, Pariente J, Lotterie JA, Duret V, Puel M, et al. Early individual diagnosis of Alzheimer's disease using cortical thickness: impact of cognitive reserve. Brain 2009 (in press).

Rosenberg PB. Clinical aspects of inflammation in Alzheimer's disease. Int Rev Psychiatry 2005; 17: 503–14.

Schupf N, Tang MX, Fukuyama H, Manly J, Andrews H, Mehta P, et al. Peripheral abeta subspecies as risk biomarkers of Alzheimer's disease. Proc Natl Acad Sci USA 2008; 105: 14052–7.

Whitwell JL, Petersen RC, Negash S, Weigand SD, Kantarci K, Ivnik RJ, et al. Patterns of atrophy differ among specific subtypes of mild cognitive impairment. Arch Neurol 2007; 64: 1130–8.

Zhang W, Kung MP, Oya S, Hou C, Kung HF. 18F-labeled styrylpyridines as PET agents for amyloid plaque imaging. Nucl Med Biol 2007; 34: 89–97.

Zheng MQ, Yin DZ, Zhang L, Lei B, Cheng DF, Cai HC, et al. Biological characters of [18F]O-FEt-PIB in a rat model of Alzheimer's disease using micro-PET imaging. Acta Pharmacol Sin 2008; 29: 548–54.