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Amyloid biomarkers: pushing the limits of early detection

This scientific commentary refers to 'Cerebrospinal fluid analysis detects cerebral amyloid-β accumulation earlier than positron emission tomography', by Palmqvist *et al.* (doi:10.1093/brain/aww015).

One of the major advances in Alzheimer's disease clinical research over the past two decades has been the development and validation of biomarkers for amyloid plaques and neurofibrillary tangles, the core neuropathological lesions that define the disease. Amyloid plaque deposition can be detected *in vivo* based on reductions in CSF levels of the amyloid-beta 1-42 amino acid polypeptide (amyloid-$\beta_{1\text{-}42}$), or by PET imaging with radiotracers that bind selectively to the fibrillar aggregates of amyloid-β that form plaques (Blennow *et al.*, 2015). Collectively, amyloid-β biomarkers provide strong evidence for a prolonged 'preclinical' or 'asymptomatic at-risk' stage of Alzheimer's disease, in which amyloid pathology is present *in situ* decades prior to the onset of clinical dementia (Sperling *et al.*, 2011). Even in the absence of overt cognitive deficits, normal individuals who have positive amyloid-β biomarkers show accelerated neurodegeneration and declining performance on neuropsychological tests compared to their amyloid-β-negative counterparts, and are at increased risk for developing incident cognitive impairment (Jagust, 2016). These observations have shifted the landscape of Alzheimer's disease clinical research towards preclinical, biomarker-based detection of amyloid, and the implementation of early therapeutic interventions aimed at lowering amyloid and thus delaying or ultimately preventing the onset of clinical dementia (Sperling *et al.*, 2011). In this issue of *Brain*, Palmqvist and colleagues provide compelling evidence that CSF amyloid-$\beta_{1\text{-}42}$ may be more sensitive than amyloid PET to the early stages of amyloid deposition (Palmqvist *et al.*, 2016), a finding that has important ramifications for our understanding of preclinical Alzheimer's disease and for the design of prevention trials.

Though they measure very different elements of amyloid biology, CSF amyloid-$\beta_{1\text{-}42}$ and amyloid PET consistently show high correlation across different populations and studies, and strong (85–95%) agreement in classifying subjects as amyloid-β-positive or negative (Blennow *et al.*, 2015). However, several lines of evidence suggest that CSF amyloid-$\beta_{1\text{-}42}$ may be more sensitive than amyloid PET to the early stages of amyloid deposition. First, when amyloid-β biomarkers disagree, it is more common for CSF to be positive and PET to be negative than vice versa (Blennow *et al.*, 2015). Second, isolated CSF-positivity is more frequent in cognitively normal subjects (21%) than in patients with clinical dementia (6%) (Mattsson *et al.*, 2015), suggesting that CSF detection in the absence of PET signal may be indicative of a relatively low amyloid burden. Third, a rare autopsy in a patient with both biomarkers collected antemortem revealed that early stages of amyloid accumulation were detected by low CSF amyloid-$\beta_{1\text{-}42}$ but not by amyloid PET shortly prior to death (Cairns *et al.*, 2009).

In the present study, Palmqvist and colleagues add to this primarily cross-sectional body of evidence by comparing longitudinal changes in the amyloid PET tracer ^{18}F-florbetapir (as a measure of amyloid accumulation) to baseline CSF amyloid-$\beta_{1\text{-}42}$ and amyloid PET status in 437 non-demented subjects enrolled in the Alzheimer's Disease Neuroimaging Initiative (Palmqvist *et al.*, 2016). All subjects had at least one follow-up amyloid PET scan an average of 2.1 years after the baseline study. Subjects were stratified as positive or negative for each amyloid-β biomarker at baseline based on well-validated thresholds. After eliminating borderline cases that fell within 5% of either threshold, 26 of 354 remaining subjects (7.3%) were classified as CSF+/PET−, while no subjects were classified as CSF−/PET+ for amyloid-β. Increases in florbetapir binding in the CSF+/PET− were equivalent to those measured in the baseline CSF+/PET+ group, and three times higher than those measured in the CSF−/PET− group, consistent with the hypothesis that the CSF+/PET− biomarker profile is capturing subjects who are in early stages of meaningful amyloid accumulation. Conversely, while the CSF+/PET+ group showed significant longitudinal decline in memory performance and hippocampal atrophy, the CSF+/PET− group remained stable on these measures, suggesting that this biomarker profile is capturing an earlier stage in the disease cascade.

The findings presented by Palmqvist *et al.* offer some of the most persuasive evidence to date that isolated CSF amyloid-β positivity is linked to biologically meaningful amyloid deposition. A particularly innovative aspect of the study is the use of increasing florbetapir retention as an endophenotype for amyloid accumulation even in subjects who at baseline are below the threshold of PET detection, an approach that requires further investigation. In a variety of ancillary analyses, the investigators demonstrate that their results are robust to different approaches to PET quantification and threshold definition. However, the authors also acknowledge a number of inherent limitations in their dataset. Most importantly, the number of

Glossary

Amyloid-β: The sequential cleavage of the amyloid precursor protein, a neuronal transmembrane protein, by β-secretase and γ-secretase generates 40–42 amino acid polypeptides known as amyloid-β_{40} and amyloid-β_{42}. Amyloid-β_{42} tends to aggregate into extracellular fibrillar deposits with a beta pleated sheet structure known as amyloid plaques, a core feature of Alzheimer's disease neuropathology. Amyloid-β_{40} aggregates can form in blood vessel walls causing cerebral amyloid angiopathy.

Biomarker: A biological marker is an objectively measured indicator of a biological or pathogenic process. The term may refer to anything from vital signs (blood pressure and heart rate) to laboratory tests and imaging studies.

Preclinical Alzheimer's disease: A state in which an individual shows evidence of amyloid-β deposition in the brain based on CSF or PET measures but has no cognitive impairment. Current research suggests this preclinical state may last two decades or longer. As not all individuals with amyloid-β deposition will develop clinical symptoms, some have argued that this should be defined as an 'asymptomatic at-risk' state rather than as preclinical disease.

Radiotracer: A small molecule labelled with a radioactive isotope that is injected intravenously to image biological processes, e.g. with PET or single-photon emission computed tomography. ^{18}F-florbetapir, labelled with fluorine-18, is one of a number of amyloid-β radiotracers that bind specifically to amyloid plaques deposited in the brain.

subjects who fell in the CSF+/PET− group was relatively small ($n = 26$), and inferences drawn from this sample should thus be considered preliminary. Second, rates of florbetapir change were estimated using only two time points. PET is an inherently noisy technique, and the rates of florbetapir change observed in the CSF+/PET− and CSF+/PET+ groups (~1.2%/year) are within the range of florbetapir's test/retest variability (~2.5%) (Joshi *et al.*, 2012). Furthermore, rates of amyloid accumulation are thought to be non-linear across the Alzheimer's disease continuum (Villemagne *et al.*, 2013), such that estimates of change based on three or more time points would be expected to be more reliable. Finally, the available data still provide only indirect evidence for increased sensitivity of CSF. Ultimate proof that CSF amyloid-β_{42} detects amyloid accumulation prior to amyloid PET will require: (i) more autopsies in subjects who show this biomarker profile proximate to death; or (ii) evidence that CSF+/PET− individuals 'convert' to CSF+/PET+ status with longer follow-up.

Notwithstanding these caveats, the findings of Palmqvist *et al.* challenge a number of current assumptions underlying the implementation of amyloid-β biomarkers in research and clinical trials.

The 2011 National Institute of Aging-Alzheimer's Association diagnostic criteria allow CSF amyloid-β_{42} and amyloid PET to be used interchangeably to establish amyloid-β status (Sperling *et al.*, 2011), an approach that will need to be reconsidered in future iterations of the criteria, particularly in the preclinical state. The criteria proposed by the International Working Group require both low CSF amyloid-β_{42} and elevated total or phosphorylated tau to establish an 'asymptomatic at-risk' state for Alzheimer's disease (Dubois *et al.*, 2014), which would yield lower sensitivity for early amyloid pathology. An important finding from the present study is that 84 of 437 pre-dementia subjects (19.2%) had biomarker results that fell within 5% of the established thresholds. While the findings of the present study were not altered by the inclusion or exclusion of these borderline cases from the analysis, it is concerning that a significant proportion of subjects fell into an equivocal biomarker range, and this may pose challenges when dichotomous thresholds are applied in clinical practice or research.

While there is broad consensus in the field that testing of amyloid biomarkers in cognitively normal individuals is not recommended outside the context of a research study (Sperling *et al.*, 2011), a provocative question raised by the Palmqvist study is how early would one want to detect amyloid when considering enrolment criteria for Alzheimer's disease prevention trials? The preclinical stage of the disease may last up to two decades when onset is defined by conversion to amyloid PET positivity (Villemagne *et al.*, 2013). Based on the average baseline and longitudinal florbetapir uptake observed in the CSF+/PET− group in the present study, an additional 10 years could pass between CSF amyloid-β positivity and conversion to amyloid PET positivity, yielding a potential 30-year window between biomarker detection and dementia. If an effective amyloid lowering agent were available, should it be offered to the average patient in the CSF+/PET− group in the Palmqvist study, who is 74 years old, cognitively normal, and predicted to be 20–30 years away from onset of cognitive impairment? Preventive treatment for such a remote outcome would have to be strongly justified in terms of safety at the individual level and resource utilization at the societal level. Furthermore, measuring the efficacy of therapy in such individuals in a placebo-controlled trial would be challenging with current tools, as no significant changes in cognitive performance or MRI atrophy were observed in this group over 2 years of follow-up in the absence of an intervention.

Ultimately, the findings of Palmqvist and colleagues highlight how far we have come since the days when amyloid plaques could only be detected by a pathologist's microscope. While many questions remain about how to optimally deploy our growing armamentarium of Alzheimer's disease biomarkers to improve patient care, the transformative impact these biomarkers have had on research cannot be overstated. Hand-in-hand with molecular genetics

and *in vitro* disease models, biomarkers are yielding important insights into the *in vivo* dynamics of Alzheimer's disease in humans, and are revolutionizing the design of clinical trials (Andrieu *et al.*, 2015). It is only a matter of time before these advances transform the therapeutic landscape, and offer hope to the tens of millions of people suffering from this devastating disease.

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Conflict of interest

Dr Rabinovici receives research support from Avid Radiopharmaceuticals, and has received speaking honoraria from GE Healthcare, Piramal Imaging and Medscape.

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Time in the orbitofrontal cortex

This scientific commentary refers to 'The neural dynamics of reward value and risk coding in the human orbitofrontal cortex' by Li *et al.* (doi: 10.1093/brain/awv409).

The ability to dynamically process complex reward-related signals is integral to adaptive human behaviour. For example, the human brain must rapidly synthesize information about reward value, probability and associated risk in order to successfully make decisions leading to positive outcomes. Further, complex neural processes may rely on activity spanning multiple timescales (Kringelbach *et al.*, 2015), which is likely to be critically important for understanding the neural computations associated with reward signals. Reward-related computations are widely considered to involve the orbitofrontal cortex (OFC), a brain region comprising a heterogeneous set of interacting areas or subregions. While numerous studies have made progress in characterizing the diverse functions of the OFC, these studies have primarily used spatial evidence from neuroimaging and neuropsychology (Kringelbach, 2005), and thus are limited in their ability to describe the dynamic properties of reward signals in the OFC. As a result, the spatiotemporal dynamics of reward-related processing in the human brain have largely remained elusive.

In the current issue of *Brain*, Li *et al.* (2016) circumvent this methodological constraint by measuring activity in the OFC using intracranial EEG in six patients with drug-refractory partial epilepsy. This technique offers a unique opportunity to directly record local field potentials (LFPs) from implanted depth electrodes, thereby affording superior temporal and spatial resolution in comparison to most other human neuroimaging methods. Using a probabilistic reward-learning task, the authors observed time-dependent differences in OFC responses