The implications of amyloid-β pathology: only time will tell

This scientific commentary refers to ‘Characterizing brain tau and cognitive decline along the amyloid timeline in Alzheimer’s disease’ by Cody et al. (https://doi.org/10.1093/brain/awae116).

The current conceptualization of Alzheimer’s disease is strongly driven by the amyloid cascade hypothesis,¹ which has provided the leading framework for investigating and understanding Alzheimer’s disease pathophysiology. This hypothesis was first introduced in 1991 and has been modified several times, but the basic premise is that the deposition of amyloid-β in the brain initiates a cascade of downstream events, which includes the aggregation of hyperphosphorylated tau in the neocortex, synaptic dysfunction, neuronal loss and cognitive impairment. Thus, the deposition of amyloid-β is a crucial step in the pathophysiology of Alzheimer’s disease. However, amyloid-β deposition can occur decades prior to the onset of cognitive symptoms, and the age at which amyloid-β starts to accumulate is highly variable among individuals. This complicates the in vivo investigation of the entire amyloid-β trajectory and its associated downstream events. In this issue of Brain, Cody and colleagues estimate the age at which amyloid-β became abnormal for each participant in their cohort, thereby reconstructing amyloid-β pathology levels into a participant-specific temporal domain (i.e. years of being amyloid-β positive).² They then use this measure of “amyloid duration” to better understand the associations between amyloid-β, tau accumulation and cognitive decline.

Understanding the temporal relationships between amyloid-β and tau is of great importance for numerous reasons. First, while many preclinical and clinical studies have demonstrated that amyloid-β and tau are key elements in the pathophysiology of Alzheimer’s disease and are closely associated with each other, precisely how amyloid-β and tau are mechanistically (and causally) connected to one another remains unclear.³ Gaining a better understanding of when amyloid-β and tau change in time, may help reveal why they change –
and how changes in one affect the other. Second, recently published phase 3 results testing monoclonal antibodies against amyloid-β pathology suggest that the odds of a beneficial clinical outcome are enhanced when such treatments are applied in the pre-tau-PET-positivity stage. Thus, gaining participant-specific estimates for years of being amyloid-β positive (and subsequently, years until tau-positivity) may delineate the optimal time window for intervention, potentially tailored towards the individual level. Third, given that the magnitude and spread of tau pathology is closely associated with cognitive decline, understanding the temporal relationship between the onset of amyloid-β deposition and subsequent tau accumulation holds highly relevant prognostic information for patients and their caregivers.

However, as Alzheimer’s disease pathology progresses gradually over the course of decades, prolonged longitudinal PET studies starting in early midlife would be required to fully characterize the temporal and spatial trajectories of amyloid-β and tau. Since this is not a viable option, it is essential to explore alternative modelling approaches. Several methods for reconstructing levels of amyloid-β pathology into estimates of age at amyloid-β onset have recently been proposed. These methods make use of the assumption that amyloid-β biomarkers progress along the same sigmoid-shaped curve for all individuals – in line with the hypothetical common biomarker curves initially proposed by Jack et al. In the current study, Cody and colleagues defined age of amyloid-β onset using their previously established sampled iterative local approximation (SILA) algorithm. The SILA algorithm is trained on longitudinal amyloid-β PET data, and first establishes the relationship between amyloid-β burden and mean amyloid-β rate of change by discrete sampling of the amyloid-β burden versus chronological age curve (Figure 1A). Next, it uses Euler’s iterative method to numerically integrate the amyloid-β burden versus amyloid-β rate of change data to generate a non-parametric amyloid-β burden versus time curve. Here, the time axis reflects the number of years of being amyloid-β positive, with zero time corresponding to their threshold for amyloid-β positivity (in this case, a global $^{[11}C$PiB distribution volume ratio [DVR] of 1.16 [equivalent to ~17.1 Centiloids]). For each participant, the authors then estimated the duration of amyloid-β positivity at time of tau-PET imaging by subtracting the SILA-estimated age of amyloid-β onset from the age at tau-PET.

The study includes a large, well-characterized sample of 601 participants from Wisconsin-based cohorts who all completed dynamic $^{[11}C$PiB PET (measuring amyloid-β), static $^{[18}F$MK6240 PET (measuring tau), T1-weighted MRI and neuropsychological testing. Of
note, the cohort consisted predominantly of cognitively unimpaired individuals (89%), with an additional 8% with mild cognitive impairment and 3% with dementia. Among individuals who were amyloid-positive, the estimated age of amyloid-β onset ranged markedly from 38.4 to 80.2 years of age. Cody and colleagues further observed that the magnitude and spread of tau increased with increasing amyloid-β duration. On average, the onset of tau pathology in the earliest tau-region (i.e. Braak stage I, comprising the [trans]entorhinal cortex) occurred ~6.2 years after amyloid-β onset. For tau in later Braak stages, the average time from amyloid-β onset to tau onset was found to be ~10.5 years for Braak stage III (including amygdala, parahippocampal gyrus and fusiform gyrus), ~11.4 years for Braak stage IV (including inferior and middle temporal cortex and the posterior cingulate), ~19.2 years for Braak stage V (including large parts of the parietal, occipital and frontal cortices) and >25 years for Braak stage VI (including the pre- and post-central gyrus and the cuneus) (Figure 1B).

Previous tau-PET studies have suggested that the inferior temporal gyrus (i.e. Braak stage IV) may be the crucial gateway through which tau spreads from the medial temporal lobe towards the neocortex, and that this spreading of tau is closely associated with cognitive impairment. For clinical trial designs, the estimates provided by Cody et al. suggest that the period within the initial decade after amyloid-β onset – before tau has reached the inferior temporal gyrus as detectable by PET – is pivotal for interventions targeting the amyloid-β pathway and/or tau biology. It is important to note, however, that this time window of the first decade might be an overestimation, considering that the propagation of non-aggregated tau species likely precedes the propagation of aggregated tau-species detectable by PET. Cody et al. additionally observed significant linear and non-linear interactions between amyloid-β duration and tau in association with retrospective cognitive decline in individuals who were cognitively unimpaired at baseline. Specifically, those with an amyloid-β duration of >10 years and higher tau load showed the most pronounced (retrospective) cognitive decline, and this was especially noticeable in individuals aged >70 years. These results emphasize that amyloid-β and tau act synergistically and that their co-occurrence is required for cognition to decline over time. Moreover, by modelling cognitive decline in relation to aging rather than follow-up time, the results suggest that the impact of tau pathology on cognitive decline may increase as individuals age. This observation may be explained by greater resilience at younger ages (e.g., through more efficient neuronal repair mechanisms) and/or the cumulative burden of co-pathologies (e.g.,
TDP-43, α-synuclein, vascular lesions) with advancing age that can contribute substantially to cognitive decline.

The results of the current study should be interpreted in light of some important caveats. First, the study provides only limited head-to-head comparisons between the SILA-generated amyloid-β duration metric and more commonly used amyloid-PET metrics such as the Centiloid scale. The direct comparisons that are included indicate that the amyloid-β duration metric generated by SILA does not demonstrate superior performance for predicting tau load in the entorhinal or meta-temporal region compared to the actual observed amyloid-β PET DVR values. In a research context, the SILA-generated amyloid-β duration metric offers a notably practical and intuitive output, thus supporting its utilization for certain use cases. For potential future applications (e.g., in clinical trials), it is crucial, however, to clearly demonstrate that this metric holds complementary or superior value. Second, the robustness of this work would be further strengthened by replication in an independent cohort. While this study featured a large and deeply phenotyped cohort, Cody et al. trained their SILA algorithm on a sample consisting predominantly of cognitively unimpaired individuals, in whom amyloid-β ceiling effects are typically not (yet) observed. It is thus unclear to what extent the SILA-modelled amyloid-β versus time curve can be applied to cohorts that consist of more clinically and pathologically advanced cases. Third, the threshold for amyloid-β positivity plays a key role in defining the amyloid-β timeline. The current study implemented a single threshold (reflecting a Centiloid of ~17.1) for amyloid-positivity, while thresholds can vary widely (between 12 and 30 Centiloids) across studies. It is thus unknown how much variability in the SILA-estimated amyloid-β duration metric can occur when adjusting the threshold.

In conclusion, the modelling work conducted by Cody and colleagues suggests that the first decade after amyloid-β onset – before tau has reached the inferior temporal gyrus and before the most pronounced effects on cognition are observed – is a crucial time window for intervention. Key future directions include applying the SILA-obtained curve on external cohorts, as well as more detailed head-to-head comparisons with more commonly used amyloid-PET metrics. Another potential optimization step would be to incorporate factors like APOE ε4 status into the SILA-algorithm, as a 60-year-old APOE ε4 carrier with a low Centiloid score (<10), for example, is probably closer to becoming amyloid-positive than their APOE ε4 non-carrier counterpart.
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References


Figure legend

Figure 1 The amyloid-PET timeline in relation to other Alzheimer’s disease biomarkers.

Panel A shows a graphic representation of the sampled iterative local approximation (SILA) algorithm that is employed in the current study for defining the amyloid-PET timeline. First, by discrete sampling of the amyloid-β burden versus chronological age curve, the algorithm establishes the relationship between amyloid-β burden and mean amyloid-β rate of change. Next, it uses Euler’s iterative method to numerically integrate the amyloid-β burden versus mean amyloid-β rate of change data to generate a non-parametric amyloid-β burden versus time curve. Here, t=0 on the x-axis corresponds to the threshold for amyloid-positivity on the y-axis. Panel B shows the observed tau-PET and cognitive decline findings from Cody and colleagues on the amyloid-PET timeline (in grey). For tau-PET, findings are shown for neurofibrillary tangle (NFT) Braak stage I, III/IV, V and VI, with the width of the grey boxes corresponding to the 95% confidence intervals provided by Cody and colleagues. Other key biofluidic and neuroimaging Alzheimer’s disease biomarkers derived from the literature are plotted along the amyloid-PET timeline (in blue).
A  
Sampled iterative local approximation (SILA) for defining the amyloid-PET timeline

B  
Alzheimer’s disease key pathophysiological events on the amyloid-PET timeline

Figure 1
176x138 mm (DPI)