# Amyloid deposits in the banks (of the superior temporal sulcus) yield a high return about memory futures

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Guo et al.[1] report a landmark study in this issue of Neurology® that illustrates the continuing importance of amyloidosis in both the conceptual understanding and clinical treatment of Alzheimer disease (AD). Using data from cognitively normal adults enrolled in the Alzheimer's Disease Neuroimaging Initiative (ADNI), they show that a high amyloid burden in the banks of the superior temporal sulcus (BANKSSTS) predicts memory decline over 4 years, even in those who are classified as β-amyloid (Aβ) negative by the ADNI-defined composite score, which represents the aggregation of amyloid combined across regions. In addition to memory, amyloid positivity in the BANKSSTS predicts decline in executive function, although the association is weaker. It is worth noting that the study is a model of state-of-the-art methodology, providing a template for best practices that should be broadly used by researchers to advance the field. We describe the conceptual, clinical, and methodologic strengths (and occasional weaknesses) of the study below.

Conceptually, the study validates and underscores the importance of thinking about amyloidosis as a multifaceted measure rather than as a positive/negative dichotomy. The predictive value of BANKSSTS compared to the ADNI-defined global composite standardized uptake value ratio suggests that the concept of Aβ negativity may need rethinking, or at least refining. We now know that there is a long, slow road from early amyloid deposition to clinical symptomatology that can span a decade or more. On the one hand, given the complexity and many specialized regions of the human brain, it should not be surprising that a single brain subregion yields more information about future decline than a combination of regions. On the other hand, the apparent ability to predict future cognitive function and the potential vulnerability to AD from a single brain structure with an Aβ burden so low that the global composite score has classified participants as negative, is remarkable. Moreover, the study highlights the central role that amyloid imaging plays in predicting the disease process, independent of the controversy of whether amyloidosis is a fundamental causal mechanism of AD.

Clinically, the study is important because it potentially pushes the window of identification of AD risk to a point that is even earlier than the nominally preclinical stage of AD. Moreover, the authors propose a 3-stage classification system for amyloid accumulation that likely provides clinically relevant information about future progression of cognitive decline. Stage 0 defines individuals who are amyloid negative in both BANKSSTS and the ADNI global composite; stage 1 reflects high amyloidosis in BANKSSTS, while the global composite is Aβ−; and stage 2 indicates amyloid positivity in both BANKSSTS and the global composite. Higher stage predicts an accelerated rate of future memory decline. It is possible that clinical norms could be developed from BANKSSTS for a very early classification system of AD risk. Moreover, given that participants in stage 1 show little evidence of neurodegeneration as measured by CSF tau and phosphorylated tau, it is possible that stage 1 represents a reliable early window for intervention.

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Methodologically, the study is a template of best practices for researchers focused on isolating early brain biomarkers that predict future cognitive decline in cognitively normal individuals. The study built on recent work that first showed evidence that memory decline accompanies subthreshold amyloid accumulation,[2] which was followed by evidence that pointed to the posterior cingulate cortex as the region where Aβ burden was most predictive of future memory decline in globally Aβ− adults, even in middle-aged adults.[3] In the present study, the authors increased the number of FreeSurfer-derived regions of interest to 34 and determined that, in fact, BANKSSTS had the highest Aβ burden and was more strongly associated with memory decline than the posterior cingulate cortex, which was second, followed by the precuneus. Another best practice was the use of a large sample size (n = 355), which permitted the authors to have sufficient data for analysis that they were able to split participants into 2 randomly determined subsamples and repeat the primary analysis on each subsample. Each analysis yielded nearly identical findings, thus adding considerable confidence to the reliability of the focus on BANKSSTS. In addition, the association of BANKSSTS amyloid burden with cognitive decline in participants with global Aβ+ was confirmed. Another methodologic strength was the use of multiple measures of memory and executive function to develop reliable constructs of cognitive function, rather than the use of single tasks, and the authors also validated the relationship of BANKSSTS to other biomarkers, including hippocampal volume and tau. The statistical sophistication of the analyses, combined with genuine attempts to disconfirm the critical finding via sensitivity analyses, adds to the caliber of the research. Finally, while the identification of early amyloidosis in the BANKSSTS region is well supported by the ADNI data used in the study, the authors also acknowledge that the findings must be validated outside of the highly selected ADNI study population and that longer follow-up is needed.

## Author contributions

D.C. Park wrote an initial draft, which was expanded and edited by E. Abner.

## Study funding

## Disclosures

## References

1. Guo T, Landau SM, Jagust WJ. Detecting earlier stages of amyloid deposition using PET in cognitively normal elderly adults. Neurology 2020;94:e1512–e1524.
2. Landau SM, Horng A, Jagust WJ. Memory decline accompanies subthreshold amyloid accumulation: for the Alzheimer's Disease Neuroimaging Initiative. Neurology 2018;90:e1452–e1460.
3. Farrell ME, Chen X, Rundle M, Chan MY, Wig GS, Park DC. Regional amyloid accumulation and cognitive decline in initially amyloid-negative adults. Neurology 2018;91:e1809–e1821.

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