Low Prevalence Of Amyloid Positivity In Healthy Elderly Participants Of A Methodology Study Evaluating Remote Tablet-based Cognitive Learning

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Background and Objectives

Accumulation of amyloid in the brain is both a biomarker and a risk factor for progression toward development of AD cognitive symptoms. It is hypothesized that amyloid carriers, compared to non-carriers, may have higher cognitive vulnerability and reduced learning associated with cognitive intervention on a divided attention task. This hypothesis is being examined in study A9001489, in which the effect of dual-task intervention on cognitive measures is examined in amyloid carriers versus amyloid non-carriers.

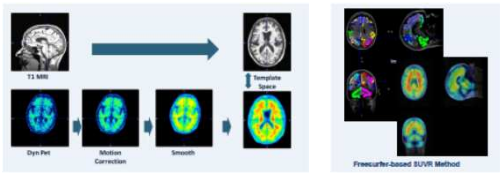
PET amyloid assessments can be assessed visually or quantitatively, each having their own challenges. Qualitative reads by experienced readers can be performed *via* tracer vendor qualitative reading guidelines. However, features such as high non-specific binding, image noise, and extensive cortical thinning could result in readings inconsistent with quantitative results, especially near quantitative cutpoint values. For this reason the A9001489 study used a hybrid visual/quantitative reading method designed to increase concordance of visual and quantitative methods.

Here are presented the results of the PET amyloid reads of the population screened for the study (N=199).

Methods

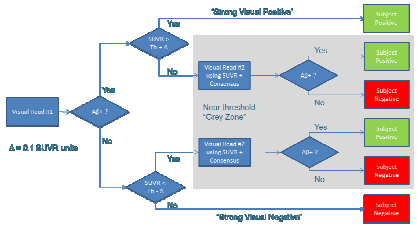
A9001489 is a randomized, double-blind, sponsor-open, parallel-group, placebo-controlled trial with repeated self-administration of the EVO dual-task assessment (Akili Interactive Labs) in healthy elderly subjects. A total of 97 subjects were randomized in the study, at a ratio of no greater than 3:2 in each of the two amyloid groups (non-carrier: carrier). Following both qualitative and quantitative centralized amyloid status determination, the SUVR distribution for the 60-80 age group was examined.

Imaging data were obtained in the process of screening 199 asymptomatic elderly participants at four imaging centers in the US at sites equipped with GE and Siemens PET/CT scanners.

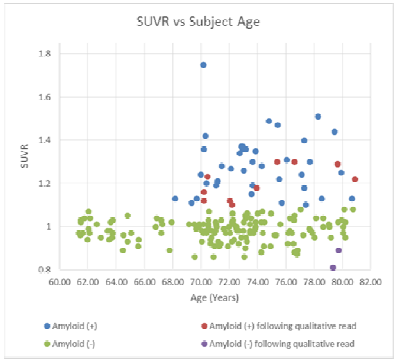


All imaging sites were qualified using Hoffman phantom scans prior to subject imaging to ensure adequate image quality and to provide calibration data for uniform spatial resolution imaging. PET data from subjects were acquired as a 4x5min dynamic acquisition starting approximately 50 minutes after injection of 10 +/- 1 mCi of [18F]Florbetapir (Amyvid). Data were motion-corrected, summed, uniformly smoothed, and resliced to match T1-MRI data before visual assessment. A composite standard uptake value ratio (SUVR) score was also obtained for each subject using a whole cerebellar reference region and the Freesurfer method described previously (Landau et al., 2012).

Final amyloid status for each subject was determined *via* a hybrid visual/quantitative SUVR decision tree. Briefly, for each subject, reader #1 obtained a visual read without SUVR information. If the SUVR was within 0.1 SUVR units of the 1.1 cutpoint, or if the SUVR was in disagreement with the visual read, then a second reader was used to obtain a final consensus read using the SUVR. This decision tree was implemented to reduce errors in amyloid status designation due to either human error or abnormal tracer uptake in reference regions.



Results



In the hybrid visual / SUVR decision tree, 40.7% of all cases went to consensus read. The discordance between SUVR and the first visual read was 10.6%. After SUVR-assisted consensus, discordance between quantitative and visual assessment was 4.0%. Of those cases that went to a consensus using a 2nd visual read supplemented by SUVR, 2 cases changed from positive to negative and 13 cases changed from negative to positive.

Mean age	**72**
Mean SUVR	**1.05**
Stdv SUVR	**0.15**
% SUVR positive	**25.6**
% Visual positive 1st read	**17.1**
% Positive after hybrid read	**22.6**
Initial SUVR/Visual discordance	**10.6**
Post-hybrid read SUVR/Visual discordance	**4.0**
% of subjects in "grey zone"	**36.2**
% of subjects with consensus reads	**40.7**
# Changed + to - via hybrid	**2**
# Changed - to + via hybrid	**13**
# Changed w no initial discordance	**1**

The analysis of the screening data revealed a lower rate of amyloid carrier status than initially expected, challenging the feasibility of study completion. In order to adjust for this lower prevalence, the age range of the study population was amended to 70-80 years of age to minimize screen failure due to negative amyloid PET scan. This change dramatically increased the screen rate of amyloid positive subjects.

	Amyloid (+) rate	Age	Mean SUVR
Pre-amendment	7.27%	67.5	1.02
Post-amendment	27.78%	74.1	1.07

Conclusions

Though a gold standard of amyloid burden was not available, results indicate that a hybrid qualitative visual / quantitative method can be used to obtain greater concordance between quantitative and visual results. Clinical studies using only visual or only SUVR information for eligibility decisions must understand the implications of potential differences between the visual and quantitative methodologies.

Lower than expected amyloid prevalence was observed in this healthy elderly population. This observation required adjustment of study timelines and supports the need for careful consideration of age dependence when planning a preclinical or early AD study. These results also reinforce the importance of developing screening tools to ensure that appropriate subjects are included in early Alzheimer disease studies.

Reference:
Landau SM, Mintun M, Joshi A, et al. *Amyloid deposition, hypometabolism, and longitudinal cognitive decline. Ann Neurol. 2012;72:578–586.*