INTRODUCTION

Amyloid deposition in the brain is thought to underlie a neurodegenerative cascade, leading to the development of cognitive decline and conversion to AD. In an ongoing phase 1b multi-center clinical trial (221AD103), amyloid PET is used as a screening tool to identify amyloid-positive participants as an enrichment strategy for clinical trials of Alzheimer’s disease (AD).

METHODS

Study Population
The study was conducted in the first 279 patients in a phase 1b clinical trial who fulfilled clinical criteria for either prodromal or mild Alzheimer’s Disease.

Florbetapir PET Imaging
Florbetapir PET data were acquired from 25 US imaging centers using 18 different PET or PET/CT scanner models manufactured by GE, Philips and Siemens. Prior to imaging patients, each center completed a qualification process including on-site training to the imaging protocol and Hoffman phantom data acquisition to provide scanner quality and to provide calibration data for spatial resolution normalization. A 20-minute emission acquisition was acquired starting at 50 minutes after administration of 370 MBq of florbetapir.

Visual Reading
The binary classification methodology followed guidelines described in the Amyvid™ FDA label. Visual reads were based primarily upon PET image data, while the registered MRI and fused PET/MRI data were used to provide supplemental anatomical information.

Scans were independently interpreted by one of two board-certified neuroradiologists trained by the Avid Amyvid™ process.

Readers had the ability to interrogate and review all the data sets including the co-registered MRI/PET data in all three orthogonal orientations.

SUV R Method
Following PET imaging, semi-quantitative values of cortical to whole cerebellar standard uptake value ratios (SUVr) were computed.

Data were defined in native patient space using FreeSurfer, and regional SUVr values for the entire parcellation were computed by normalizing to activity in a reference region.

Averaged SUVr were calculated by averaging normalized activity in the frontal, anterior/posterior cingulate, lateral parietal, and lateral temporal parietal regions used by the ADNI Berkeley PET Core, and referenced to whole brain, white-matter, eroded white-matter, whole cerebellum, cerebellar grey matter, cerebellar white matter, brainstem, thresholded brainstem, and a composite including whole cerebellum, brainstem and eroded white matter (Figure 1).

RESULTS

Study Population
Positive amyloid binding was observed in 61% of study participants, based on visual read.

SUVr Calculations
SUVr were normalized to activity in a reference region.

SUVr were computed.

Data
These results confirm that subregions used in previous ADNI composite SUVr calculations show highly significant differences in amyloid tracer uptake between visually positive and negative prodromal and mild AD subjects.

Figure 1: FreeSurfer Parcellation Composite ROIs and SUV Values

Figure 2: FreeSurfer Parcellation Effect Sizes, Amyloid Positive vs. Negative Participants, Composite Reference Region

Figure 3: SUVr values by diagnostic category (composite reference region, unless otherwise noted)

CONCLUSIONS

These results confirm that subregions used in previous ADNI composite SUVr calculations show highly significant differences in amyloid tracer uptake between visually positive and negative prodromal and mild AD subjects.

Given the weak regional effect sizes seen in some brain areas (notably temporal lobe), these results suggest an optimized selection of FreeSurfer-based regions could improve amyloid positive vs. negative group separation.

Visual reading amyloid binding classification appears most robustly captured through an averaged composite SUVr using a whole-brain reference region. The composite ROI effect appears driven primarily by binding differences in frontal regions, though the choice of reference region is also important.

Genetic as well as diagnostic factors should be considered when enriching an AD population for clinical trials. Specifically, prodromal AD subjects who are APOE e4 non-carriers are by far the most likely group to demonstrate negative amyloid binding patterns.

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