Early detection of amyloid load using ^{18}F-Florbetaben PET

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Introduction

- Accurate measurement of Aβ deposition is critical in longitudinal interventional therapeutic trials of Aβ-modifying treatments for Alzheimer disease (AD).
- The amount of brain Aβ load is widely assessed in PET imaging by means of the SUV ratio (SUVR) because of its simplicity.
- Pathology-proven ^{18}F-Florbetaben (FBB) SUVR abnormality cutoffs have been developed to discriminate between AD patients with established Aβ pathology and elderly Aβ-negative non-demented controls ($SUVR_{established}$=1.48 (Sabri et al. 2015)).
- However, observational research studies and interventional therapeutic trials focus on the early stages of Aβ deposition. A lower Aβ amount and extent may limit the use of previously developed SUVR cutoffs.

Objective

To develop and validate an FBB SUVR cutoff:

- to detect early Aβ deposition
- to identify those subjects that will likely accumulate Aβ over time
- to be used in the screening of clinical trials with asymptomatic population

Material and methods

Subjects

The samples of participants in this study included:

1) Young healthy controls (YHC). A sample of YHC subjects (n=70, 27.6±5.1 y (mean±SD)) that underwent an FBB PET scan were used to generate an SUVR cutoff for the detection of early Aβ deposition ($SUVR_{early}$). The cutoff was derived as two standard deviations above the mean SUVR in this sample of YHC. The previously reported cutoff for established Aβ pathology ($SUVR_{established}$, Sabri et al. 2015) and the $SUVR_{early}$ allowed defining three regions in the SUVR continuum: Aβ-negative subjects (< $SUVR_{early}$), early Aβ accumulation ("gray zone") ($SUVR_{early}$ < SUVR < $SUVR_{established}$) and established Aβ deposition (SUVR > $SUVR_{established}$).

2) Subjective cognitive decline (SCD) subjects. A sample of subjects with SCD (n=166, 64.9±7.2 y) from the FACEHBI study (Rodríguez-Gómez et al. J Prev Alz Dis. 2017) that underwent two FBB PET scans at baseline and at 2 years were included in this study to validate the SUVR cutoff generated.

3) Mild cognitively impaired subjects. Forty-five participants with MCI (n=45, 72.69 7 ± 6.54 y) (Ong K et al. Alzheimers Res Ther. 2013;5:4) that underwent three FBB PET scans at baseline, at one year and at years were included in this study to validate the SUVR cutoff generated.

Image processing

Image processing was performed using Statistical Parametric Mapping (SPM8; revision 4290) (http://www.fil.ion.ucl.ac.uk/spm/doc/) as described by Klunk et al. (Alzheimers Dement. 2015 Jan;11(1):1-15.e1-4).

Two different ROI approaches were used for the analysis:

1) Standard centiloid (CL) ROIs: ROIs downloaded from the GAAIN website (http://www.gaaing.org) for the cerebral cortex and whole cerebellum (WC) were applied on the normalized PET images. The CL values using the WC as a RR were determined (CL = 153.4 $SUVR_{FBB}$ – 154.9) (Rowe CC et al. Eur J Nucl Med Mol Imaging. 2017 Nov;44(12):2053-2059.

2) Individualized MRI-based ROIs: Baseline MRI images were segmented into cerebral gray and white matter and normalized on the T1 template provided with SPM. ROIs in the cerebral cortex and cerebellar gray matter (CG) were defined as the intersection between the Automated Anatomic Labeling template (Tzourio-Mazoyer N et al. Neuroimage. 2002;15:273–289) and the normalized gray matter segmentation with p > 0.2. The composite SUVR (CSUVR) was calculated as the mean of the SUVRs of the frontal, parietal, lateral temporal, anterior and posterior cingulate and occipital cortex ROIs.

Results

SUVR cutoff generation in YHC

- The mean ± SD of the composite SUVR derived from the YHC sample was 1.16±0.04 (MRI-based ROIs). The resulting cutoff was $SUVR_{early}$=1.25 (**Fig 1, Table 1**).
- With the standard CL ROIs the mean ± SD was 1.02±0.4, and the resulting cutoff was $SUVR_{early}$=1.09, CL_{cutoff}=12 (**Table 1**).
- Three regions in the SUVR continuum were defined as: Aβ-negative subjects (SUVR<1.25), early Aβ accumulation ("gray zone") (1.25-1.48) and established Aβ deposition (SUVR>1.48) (**Fig 1**).

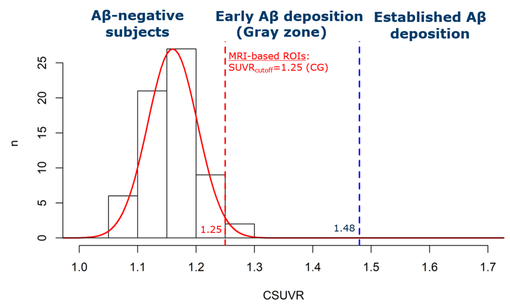

Fig 1. *Histogram of the CSUVRs obtained from the YHC sample A gaussian curve was fitted to the histogram. The cutoff was set at two SD above the mean SUVR. The previously validated SUVR threshold for established Aβ deposition is also represented.*

Region	MRI-based ROIs*	CL*
Composite/Cortex	1.16±0.04 (1.25)	1.02±0.4 (1.09)
Frontal	1.09±0.04 (1.17)	-
Parietal	1.11±0.04 (1.20)	-
Lateral temporal	1.09±0.03 (1.16)	-
Occipital	1.18±0.04 (1.27)	-
Ant. Cingulate	1.21±0.07 (1.34)	-
Post. Cingulate	1.27±0.09 (1.45)	-

* mean±SD (cutoff=mean+2SD)

Table 1. *SUVRs (*mean ± SD) and SUVR cutoffs derived from the sample of YHCs.

SUVR cutoff validation in SCD subjects

- SUVR histograms in a sample of SCD subjects showed a peak coincident with the gaussian function fitted to the sample of YHC (**Fig 2**).
- The histogram showed a tail with higher SUVRs that increased numbers at follow-up (**Fig 2**).
- The SCD subjects with SUVRs in the "gray zone" and "established Aβ deposition" had rates of Aβ accumulation statically different from zero (p<0.001) (1.6±1.8 %/year and 2.3±2.4 %/year, respectively) (**Fig 3**).
- No accumulation statically different from zero was found in Aβ-negative subjects (0.2±1.5 %/year, p=0.08).

Cut-off validation in MCI subjects

- The accumulation rates in the "gray zone" (0.94±1.6 %/year) and for "established Aβ deposition" (1.1±2.1 %/year) were significantly different from zero (**Fig 4**).
- Only those subjects in the upper limit of the gray zone converted to AD after 4-years. None of the Aβ-negative subjects converted to AD after 4-years clinical follow-up (**Fig 4**).

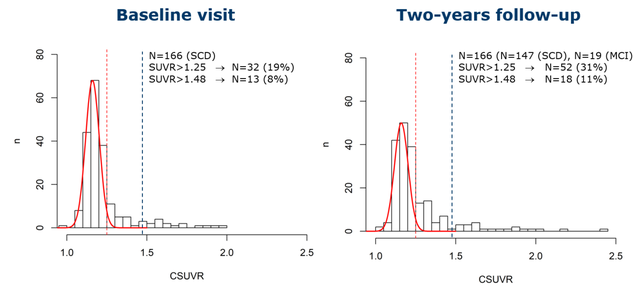

Fig 2*. CSUVR histograms of the SCD participants at baseline (left) and follow-up (right). The gaussian from the YHC sample has been plotted over each histogram (in red), as well as the gray zone (in blue) early detection threshold.*

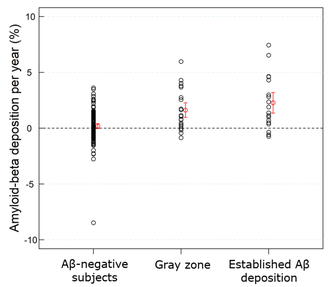

Fig 3*. Rate of Aβ accumulation (and 95% confidence interval) in SCD subjects in three regions in the SUVR continuum: Aβ-negative, gray zone and with established Aβ deposition.*

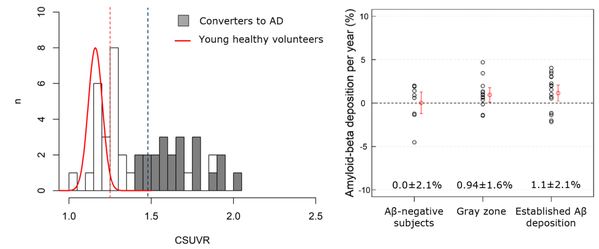

Fig 4. *Histogram of the CSUVR for a sample of MCI subjects. The gaussian function derived from the YHC sample has been plotted over it, as well as the gray zone. Converters to AD after 4-year clinical follow-up are shown in gray (left panel). Rate of Aβ accumulation in MCI subjects (and 95% confidence interval) in three regions in the SUVR continuum: Aβ-negative, gray zone and with established Aβ deposition (right panel).*

Conclusions

An SUVR range from 1.25 to 1.48 is optimal to detect early Aβ deposition and to identify subjects that are likely accumulating Aβ.