Quantitative thresholding of [^{18}F]Florbetapir brain uptake using Thal phases of Aβ deposition relate to clinical stages of disease

N. Seneca*, C. Burger, I. Florea

PMOD Technologies LLC, Zürich, Switzerland

INTRODUCTION

In vivo imaging of Aβ deposition in brain using positron emission tomography (PET) has allowed extrapolation of neuropathological assessments in living brain. The primary focus in the evaluation of PET radioligands selective for Aβ deposits has been defining optimal reference region(s), qualitative and quantitative image analyses, comparison of different PET radioligands, improving image analysis approaches and measuring the accumulation of Aβ deposits throughout different stages of disease. In addition, the majority of PET studies have used a cortical composite region of interest to measure Aβ deposits in brain which includes only frontal, temporal, parietal cortices; as well as cingulate regions and precuneus. However, the cortical composite brain regions do not take into account additional recommended brain regions used during neuropathological assessments as well as the brain regions associated with the thal phases of Aβ deposition. Both the neuropathological assessments recommended by NIA-AA as well as the thal phases of Aβ deposition consist of multiple brain regions in order to measure the spread of pathology throughout the brain. Extrapolating these findings to an *in vivo* measure would potentially have added value compared to the typical cortical composite, which measures brain uptake primarily in cortical brain regions using PET.

OBJECTIVES

The purpose of this study was to measure the brain uptake of [^{18}F]Florbetapir using PET in patients and aged controls in brain regions associated with neuropathological thal phases of Aβ deposition. We compared the brain uptake of PET [^{18}F]Florbetapir across thal phases associated brain regions and between different disease states. In addition, we investigated whether measuring the brain uptake of [^{18}F]Florbetapir across various brain regions associated with thal phases aides in classifying groups of subjects between aged controls and patients with Alzheimer's disease (AD).

MATERIALS AND METHODS

Alzheimer's Disease Neuroimaging Initiative (ADNI)

Data used in the preparation of this article were obtained from the ADNI database (adni.loni.usc.edu).

Patient selection

A total of 675 subjects were downloaded from the ADNI GO/-2 databases and were included in this study. Subjects were clinically diagnosed as per ADNI inclusion criteria and changes in diagnosis were noted for subjects who had converted or reverted in disease state during participation in ADNI. Only baseline imaging data was consider for the analysis (Table 1).

Subjects	*n*	Age	Gender		APO ε4 status			MMSE	CDR-SB	ADAS-Cog 11	ADAS-Cog 13
			M	F	0	1	2	(30 to 0)	(0 to 18)	(0 to 70)	(0 to 85)
Control	136	72 ± 5.0	63	73	102	33	1	29.1 ± 1.1	0.0 ± 0.1	5.6 ± 3.0	8.7 ± 4.5
MCI 'reverter'	49	67 ± 7.3	14	35	23	26	0	29.1 ± 1.0	1.1 ± 0.9	6.3 ± 3.1	9.3 ± 4.4
MCI 'stable'	277	71 ± 6.7	153	124	159	92	26	28.3 ± 1.6	1.2 ± 0.7	8.1 ± 3.4	13.1 ± 5.4
MCI 'converter'	92	72 ± 6.7	53	39	25	50	17	27.3 ± 1.7	2.2 ± 0.9	13.0 ± 5.0	21.0 ± 6.9
Alzheimer's Disease	121	73 ± 7.1	70	51	37	56	28	23.2 ± 2.1	4.5 ± 1.6	20.6 ± 7.0	30.9 ± 8.4

Table 1. Clinical characteristics of subjects included in the study. Values represent either a total value for each group (e.g., *n*, gender and APO ε4 status) or mean ± SD for each group of subjects.

Modified Hammers atlas template organized into brain regions associated with thal phases of Aβ deposition

A modified Hammers template regions of interest were grouped to match the brain regions associated with the five thal phases of Aβ deposition and named 'Thal ROI' (Figure 1).

Image analysis

Pre-processed [^{18}F]Florbetapir PET and the corresponding MRI baseline scans were downloaded from the ADNI GO/-2 databases on and after September 30th 2016. The imaging data were analyzed using the maximum probability atlas (MPA) 'PET only' workflow as implemented in the PNEURO module of the PMOD 3.9 software. Briefly, the thal phase regions of interest atlas template were used for brain segmentation. Disease specific amyloid PET templates used as reference in the normalization step were configured according to the groups of subjects being analyzed. The atlas templates were transformed to the subject space and intersected with standard gray and white matter probability maps already converted to the subject space. The brain uptake of [^{18}F]Florbetapir was analyzed with and without partial volume correction. The region-based voxel-wise partial volume correction methodology was applied at the end of the MPA analysis. Finally, white-matter was chosen as the reference region when calculating SUVr values for each of the Thal ROIs.

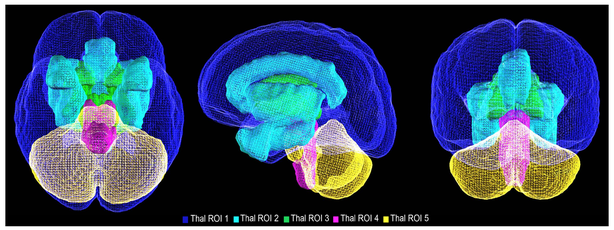

Figure 1. Graphical representation of the grouped modified Hammers template brain regions organized to match the brain regions associated with Thal phases of Aβ-deposition.

Statistical analysis

The differences in the clinical characteristics between groups were assessed using a one way ANOVA with post hoc Tukey tests. A linear mixed effect model was used for the analysis of the effects of the partial volume correction, as well as the groups of subjects and the associated thal brain regions were defined as experimental variables, while the global variation between individuals was absorbed by a random variable. The probability values for the thal regions difference between groups were corrected for multiple comparisons using the Holm correction.
A conditional inference tree in R was used to classify the imaging data measurements into an outcome category (i.e., terminal nodes) represented by the groups of subjects. Each terminal node provides an average value per associated thal brain region and per group or grouping of subjects. Thresholds were calculated from the SUVr values of [^{18}F]Florbetapir for all subjects using the conditional inference tree classifications. The regression-based approach classifies subjects into different phases and derives an SUVr threshold for each thal brain region.

RESULTS

Clinical characteristics of subjects included in the study

The results from one-way ANOVA with Tukey correction for multiple comparisons showed differences between some groups of subjects in relation to differences in years of age. Patients with AD and subjects with MCI who 'converted' had more than one allele of APO ε4 compared to other groups ($p < 0.001$). Subject with MCI who were 'stable' compared to those who had reverted had a lower level of statistical significance in regards to APO ε4 status ($p < 0.01$). Scores in four clinical and neuropsychological assessments (e.g., MMSE, CDR-SB and ADAS-Cog 11/-13) were significantly worse in patients with AD and MCI 'converters' compared to the other groups of subjects ($p < 0.001$).

Patients with AD and MCI 'converters' had statistically higher brain uptake in brain regions associated with thal phases one to three compared to aged controls and MCI 'reverters'

There were highly significant differences between the thal ROIs ($p < 2.2e^{-16}$), and groups of subjects ($p < 2.2e^{-16}$) (Figure 2). Particularly, the highest SUVr value is present in patients with AD followed in decreasing order by the values in MCI 'converters', 'reverters' and 'stable' and lowest SUVr value in the control group. With proper correction for multiple comparisons by the Holm procedure significant results were mainly obtained in thal ROI one, two and three (Table 2).

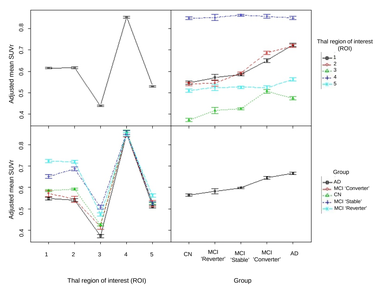

Figure 2. Graphical results of a linear mixed effects model between thal phases and subjects and their interaction.

Contrast	Pr(>Chisq)
Alzheimer's Disease - Control - Thal ROI 2	2.36E-64
Alzheimer's Disease - Control - Thal ROI 1	2.69E-62
Alzheimer's Disease - MCI 'stable' - Thal ROI 1	1.50E-50
Alzheimer's Disease - MCI 'stable' - Thal ROI 2	2.61E-43
MCI 'converter' - Control - Thal ROI 2	1.85E-36
MCI 'converter' - Control - Thal ROI 3	3.06E-31
Alzheimer's Disease - MCI 'reverter' - Thal ROI 2	2.93E-26
Alzheimer's Disease - Control - Thal ROI 3	8.68E-21
Alzheimer's Disease - MCI 'reverter' - Thal ROI 1	8.96E-20
MCI 'converter' - MCI 'stable' - Thal ROI 2	2.19E-19
MCI 'converter' - Control - Thal ROI 1	2.53E-18
MCI 'converter' - MCI 'reverter' - Thal ROI 2	4.35E-16
MCI 'converter' - MCI 'stable' - Thal ROI 3	8.16E-15
MCI 'converter' - MCI 'stable' - Thal ROI 1	3.18E-09
Alzheimer's Disease - MCI 'converter' - Thal ROI 1	9.20E-09
Control - MCI 'stable' - Thal ROI 3	8.99E-08
Control - MCI 'stable' - Thal ROI 2	1.87E-07
Alzheimer's Disease - MCI 'stable' - Thal ROI 3	1.78E-06
MCI 'converter' - MCI 'reverter' - Thal ROI 3	1.89E-06
Alzheimer's Disease - Control - Thal ROI 5	1.37E-05
MCI 'converter' - MCI 'reverter' - Thal ROI 1	5.49E-05
Control - MCI 'stable' - Thal ROI 1	4.53E-04
Alzheimer's Disease - MCI 'stable' - Thal ROI 5	1.22E-03
Alzheimer's Disease - MCI 'reverter' - Thal ROI 3	1.07E-02
Alzheimer's Disease - MCI 'converter' - Thal ROI 5	2.22E-02
MCI 'stable' - MCI 'reverter' - Thal ROI 2	3.86E-02

Table 2. Pairwise contrast between group of subjects and thal phases. Thal phases one, two and three have a stronger effect between groups than other thal phases.

Thal ROIs thresholds identified with the conditional inference tree allowed classification of 95% and 91% of patients with AD and subjects with MCI 'converters', respectively.

Brain regions associated with Thal phase five discriminated more than 40% of patients with AD which is in contrast to aged controls and MCI 'reverters'. Thal phase four brain regions did not discriminate any groups of subjects (Figures 3 and 4) and most likely reflected non-specific binding. Thal phases three to one provided additional differentiation between the groups of subjects. For example, the classification percentages increased in patients with AD and MCI 'converters' on average between the two groups of subjects ~75, 89 and 93% when subsequently applying the thresholds for Thal ROI three, two and one (Figure 4). Whereas, no further discrimination was found when applying Thal phases three to one in aged controls, MCI 'stable' and 'reverters'. Finally, twenty three percent of the initial 675 subjects remained unclassified by the ctree who did not reach any of the thal ROI thresholds. Of the 23 % subjects remaining unclassified, only 4 % were patients with AD and only 5% of the MCI 'converters' groups of subjects.

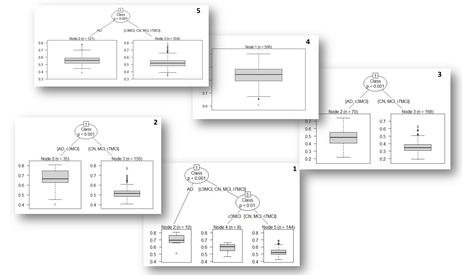

Figure 3. Terminal nodes from c-tree used to classify the groups of subjects.

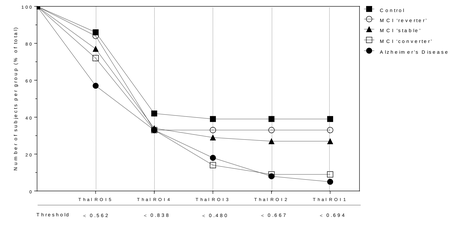

Figure 4. Results from conditional inference tree classifying the number of subjects per group (% of total) by using thresholds from brain uptake of [^{18}F]Florbetapir in patients with AD.

CONCLUSIONS

- ❑ Greater than 90% of all patients with AD and MCI 'converters' could be assigned using Thal phases one to five quantitative thresholds.
- ❑ Patients with AD and MCI 'converters' had higher brain uptake in brain regions associated with Thal phases one to three compared to aged controls and MCI 'reverters'.
- ❑ These results indicate a gradual increase of amyloid signal, which only in part corresponds to the neuropathological binary classification of Aβ deposition in brain. Brain regions associated with Thal phases one to three and in part Thal phase five provided differentiation between groups of subjects.

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* Current affiliation Novartis Institutes for Biomedical Research (NIBR), Division of Translational Medicine, BioMarker Development, Clinical and Translational Imaging, Basel, Switzerland.