INTRODUCTION
In vivo imaging of Aβ deposition in brain using positron emission tomography (PET) has allowed extrapolations of neuropathological assessments in living brain. The primary focus in the evaluation of PET radiotracers selective for Aβ deposition has been defining optimal reference region(s), quantitative and qualitative image analyses, comparison of different PET radiotracers, 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 subject template to calculate uptake of Aβ deposition in brain which includes only frontal, temporal, parietal cortices; as well as disputable results and procedures. Aβ deposition is a complex process where Aβ aggregates 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 AD or MCI. 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. Establishing specific regions, 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 [18F]Florbetapir using PET in patients and aged controls in brain regions associated with neuropathological phases of Aβ deposition. We compared the brain uptake of PET [18F]Florbetapir across brain regions associated with different disease states. In addition, we investigated whether measuring the brain uptake of [18F]Florbetapir across various brain regions associated with thal phases aid 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 (http://adni.loni.usc.edu). Subject 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 considered for the analysis (Table 1).

Table 1: Clinical characteristics of subjects included in the study. Values represent either a total value for each group (e.g., n, g, and gender and APOE c4 status) or mean ± SD for each group of subjects.

| Subjects | n  | Age | Gender | APOE status | MMSE | MCI | ADNI-Go | ADNI-Dog | APOE Inflow | APOE Outflow | APOE Inflow | APOE Outflow |
|----------|----|-----|--------|-------------|------|-----|---------|----------|------------|-------------|------------|-------------|-------------|
| Controls | 72  | 60 | 30 | 1 | 28.1±1.1 | 0.5±0.1 | 5.3±0.3 | 7.8±0.7 | 63.3±9.2 | 65.7±10.5 | 64.2±10.7 | 65.7±10.5 |
| MCI reversion | 49 | 75 | 76 | 10 | 2.8±3.0 | 0.5±0.1 | 5.3±0.3 | 7.8±0.7 | 63.3±9.2 | 65.7±10.5 | 64.2±10.7 | 65.7±10.5 |
| MCI stable | 217 | 71 | 67 | 10 | 2.8±3.0 | 0.5±0.1 | 5.3±0.3 | 7.8±0.7 | 63.3±9.2 | 65.7±10.5 | 64.2±10.7 | 65.7±10.5 |
| MCI convert | 62 | 72 | 65 | 17 | 27.3±7.1 | 0.3±0.2 | 10.0±0.5 | 21.0±0.9 | 63.3±9.2 | 65.7±10.5 | 64.2±10.7 | 65.7±10.5 |

Adjusted mean SUVr Adjusted mean SUVr

Patient selection
A modified Hammers template brain regions were grouped to match the brain regions associated with thal phases of Aβ deposition. 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 APOE ε4 compared to other groups (p < 0.001). Subjects with MCI were ‘stable’ compared to those who had reverted had a lower level of statistical significance in regards to APOE 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).

RESULTS
Clinical characteristics of subjects included in the study
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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 = 2.4e-17) (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 that ROI one, two and three (Table 2).

CONCLUSIONS
Greater than 95% of all patients with AD and MCI ‘converters’ could be assigned using Thal phases one to five quantitatively.

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 provides differentiation between groups of subjects.

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Table 3: Distribution of the number of subjects per group (% of total) by using thresholds from brain uptake of [18F]Florbetapir in patients with AD.

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.

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

Figure 3. Terminal nodes from ctree 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 [18F]Florbetapir in patients with AD.