Supplementary Methods

Comparison of Pseudo-Temporal Analysis versus Standard T-Test using Simulations

By using apriori knowledge about how amyloid is deposited within the brain, it is hypothetically possible to obtain higher statistical power when comparing two groups with different spatiotemporal deposition patterns. Our proposed method fits this model, in that it assumes that the cortex is relatively free of amyloid deposits at some time point, then accumulates amyloid in a spatially heterogeneous pattern.

To test the improvement in statistical power provided by our method, we compared it to a standard t-test using two simulated groups (N=20) that had a different inflection point, i.e., a different cDVR value at which the simulated region begins accumulating amyloid. First, each group's DVR was randomly sampled from a normal distribution (mean = 1.2, sigma = 0.2) (Figure S1a). Then for each group, a regional cDVR was calculated from the DVRs based on a simulated inflection point (Figure S1b). For simplicity, the baseline signal before the inflection point was set to zero and the rate of amyloid signal increase (slope) was set equal to 2.

For standard t-test analysis, the cDVR values for each group were compared using a two-tailed t-test, and the minimum difference in inflection point values for the two groups to obtain a p-value of < 0.05 was estimated. This analysis was repeated 100 times with different samplings of DVR values.

Similarly, the cDVR values were fitted using the two-piece linear spline as described in the methods section. Then group membership was permuted 5000 times to obtain a distribution of values for inflection and accumulation. The minimum difference in inflection or accumulation to obtain a p-value < 0.05 was determined from these distributions.

Figure S2 shows the minimum inflection point difference between groups in order to detect a significant group difference. When the inflection points for both groups occurred relatively late, there were some DVR distributions that did not reach a p-value < 0.05. Figure S3 shows the percentage of randomly sampled DVR distributions that reached significance for the minimum inflection point value (cDVR) between the two groups.

The spline fitting approach is able to detect much smaller differences in inflection points between two groups, and it was able to detect significant differences even when both inflection point values occurred relatively late in disease progression.

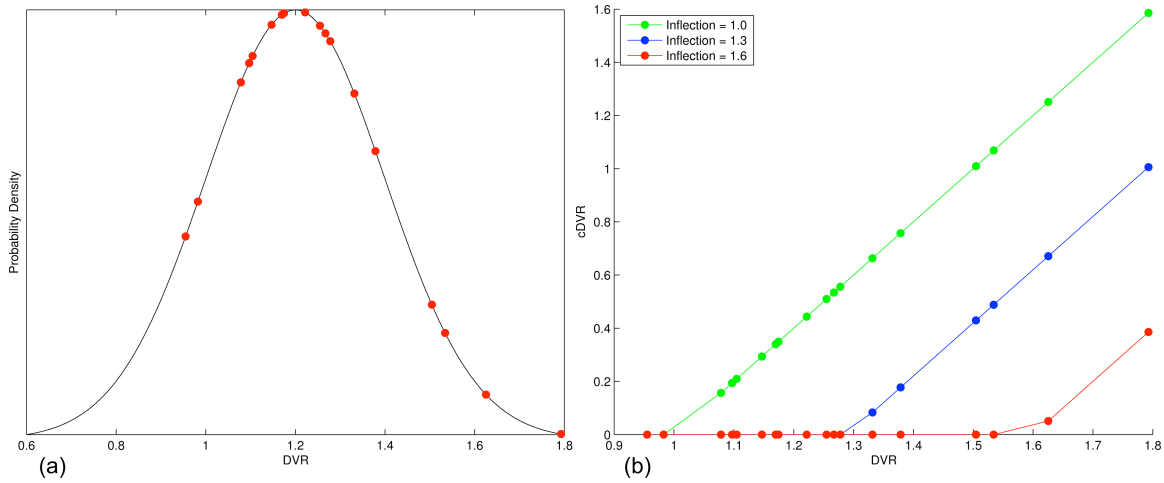

Figure S1. For each simulated group, group DVR values are randomly sampled from a normal distribution, then cDVR values are calculated from the group DVR values using a varying inflection point value. (a) Twenty DVR values (red circles) are sampled from a normal distribution, with mean of 1.2 and sigma of 0.2. (b) These DVR values are used to generate cDVR values, using varying inflection point values.

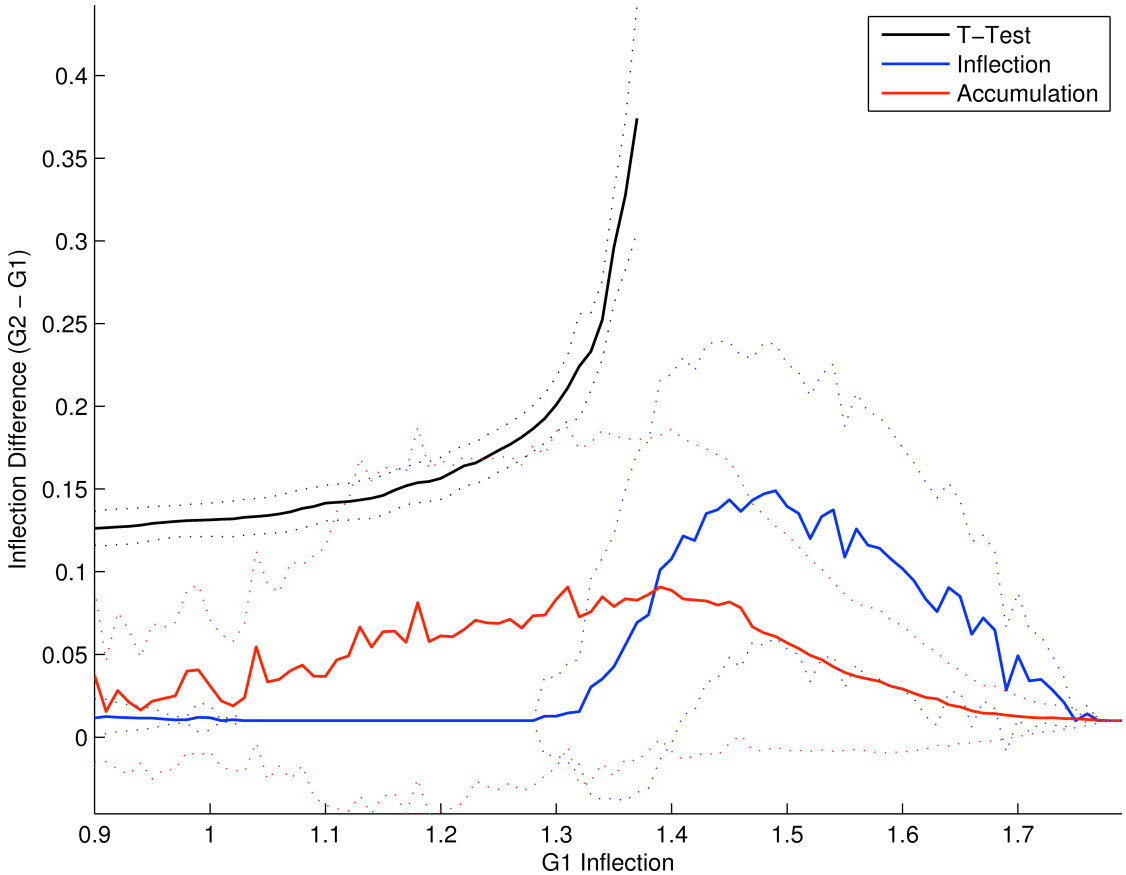

Figure S2. Shown are the average inflection point differences for which a p-value of < 0.05 was reached over 100 random samplings of DVR values, with standard deviation with dotted lines. Compared to the standard t-test, the pseudo-temporal analysis approach is able to detect smaller inflection point differences between groups. As expected, detection decreases when both groups have relatively late inflection points.

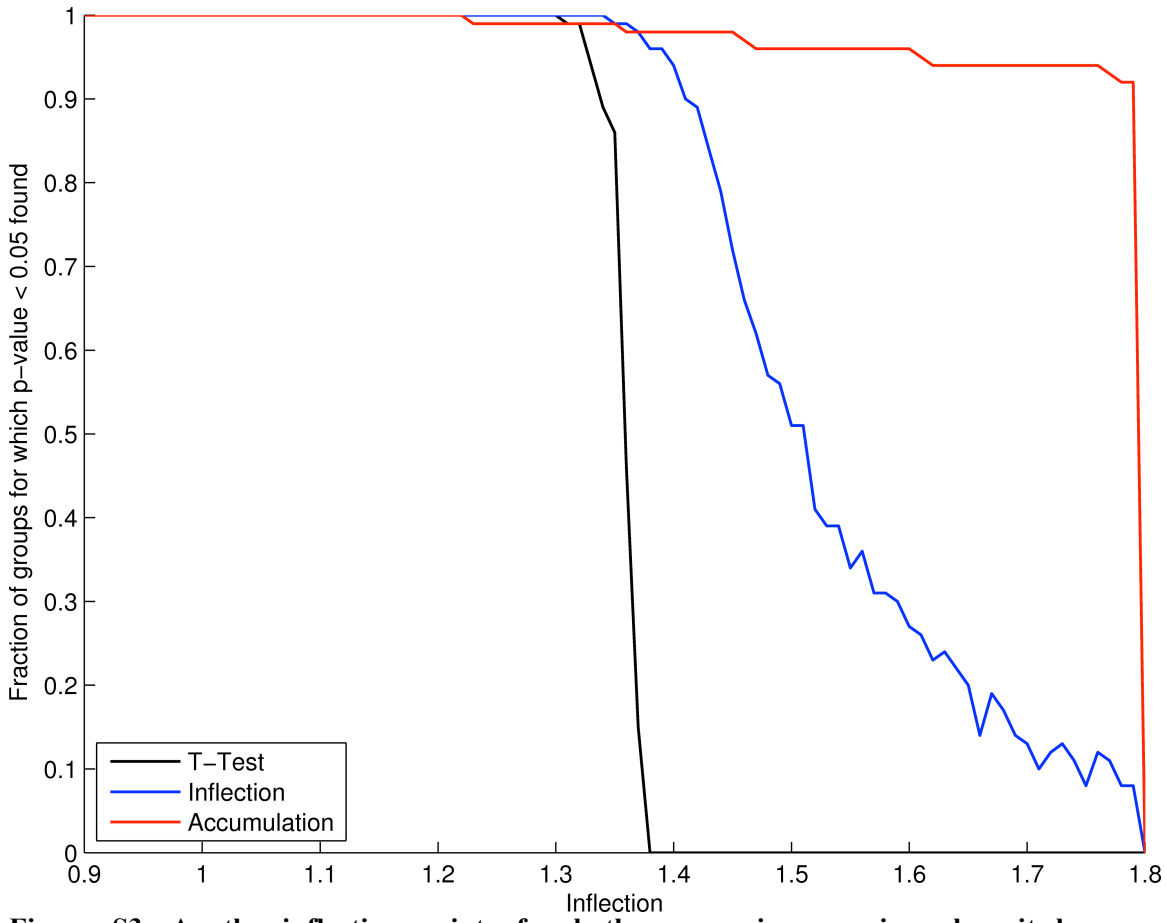

Figure S3. As the inflection points for both groups increase in value, it becomes progressively more difficult to detect significant differences between groups. This is due in part to the large number of subjects that have low cDVR values, which reduces statistical power. The inflection axis value is the minimum inflection value between groups. Despite the small differences between groups, the accumulation metric is still able to detect statistically significant differences in inflection values.

Supplementary Results

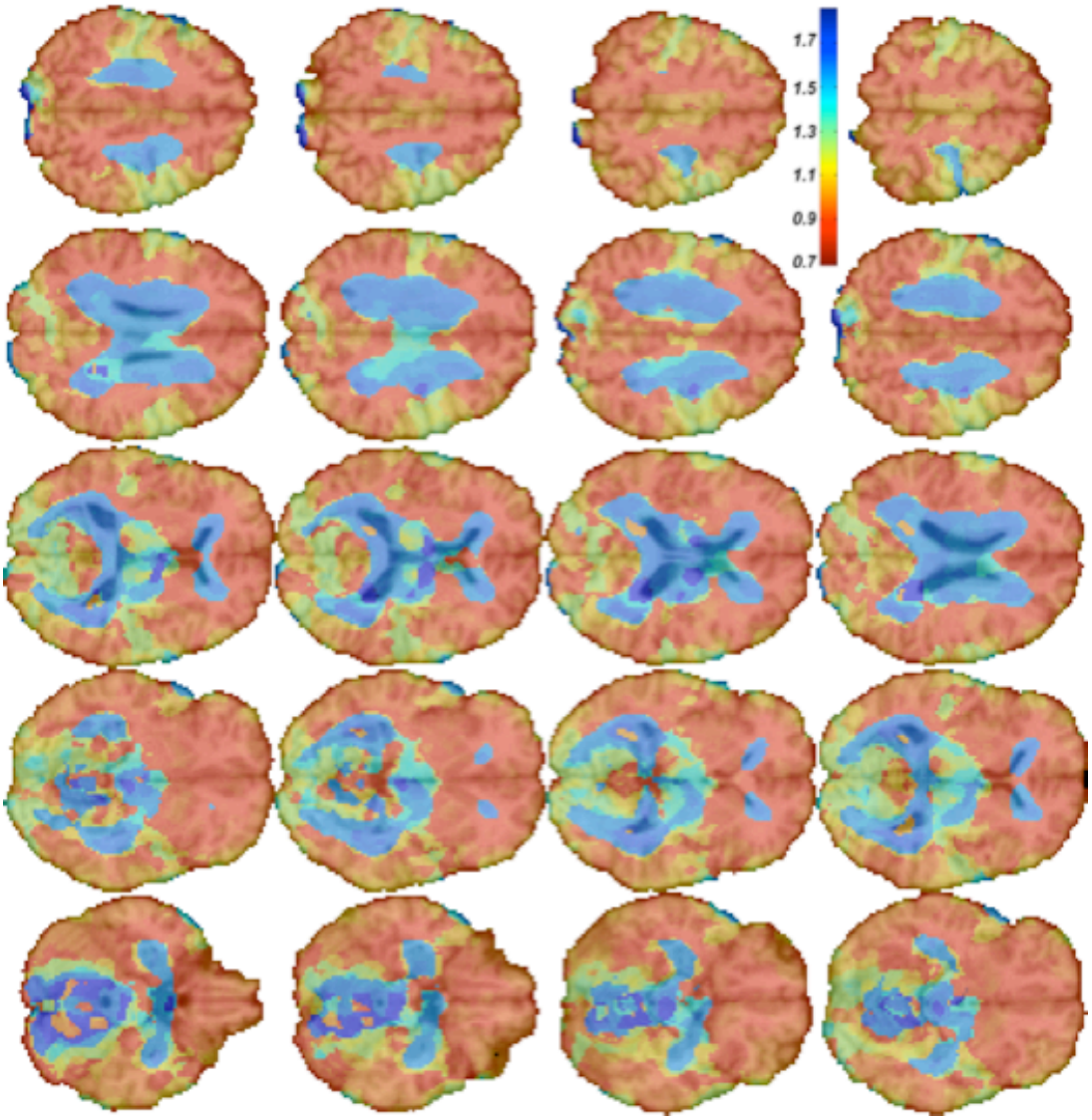

Figure S4. Shown are slice data of the inflection point, or relative sparing. While the sensorimotor and occipital areas are relatively spared, the precuneus, orbitofrontal, and lateral temporal lobes are affected early in disease progression.

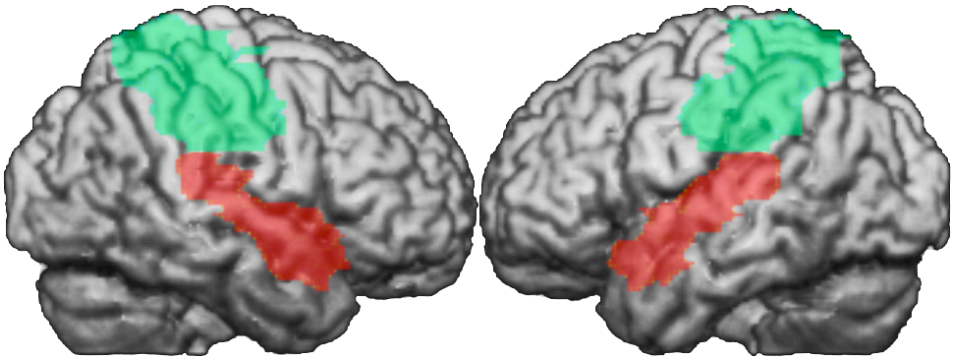

Figure S5. Four ROIs were defined to determine significance between groups. These include the left and right sensorimotor areas (green) and the left and right temporal areas (red).

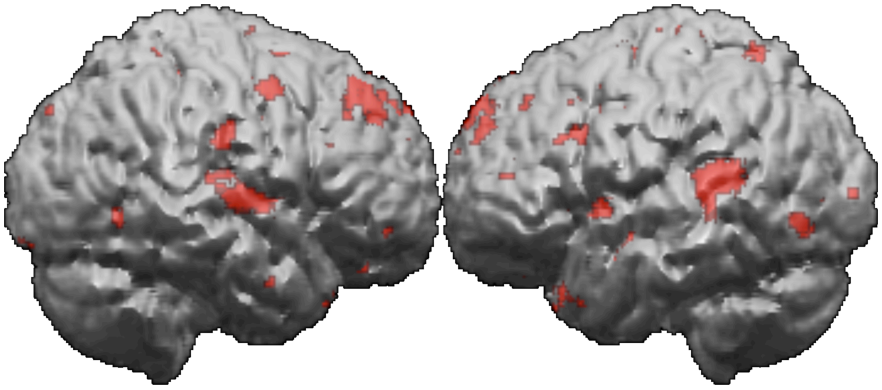

Figure S6. There are significant differences in grey matter atrophy between the cognitively stable and declining groups. Highlighted areas have significant atrophy differences as measured from RAVENS maps, corrected for multiple comparisons using the false discovery rate with a threshold of $q < 0.05$. There is some overlap with the ROIs analyzed in this study.

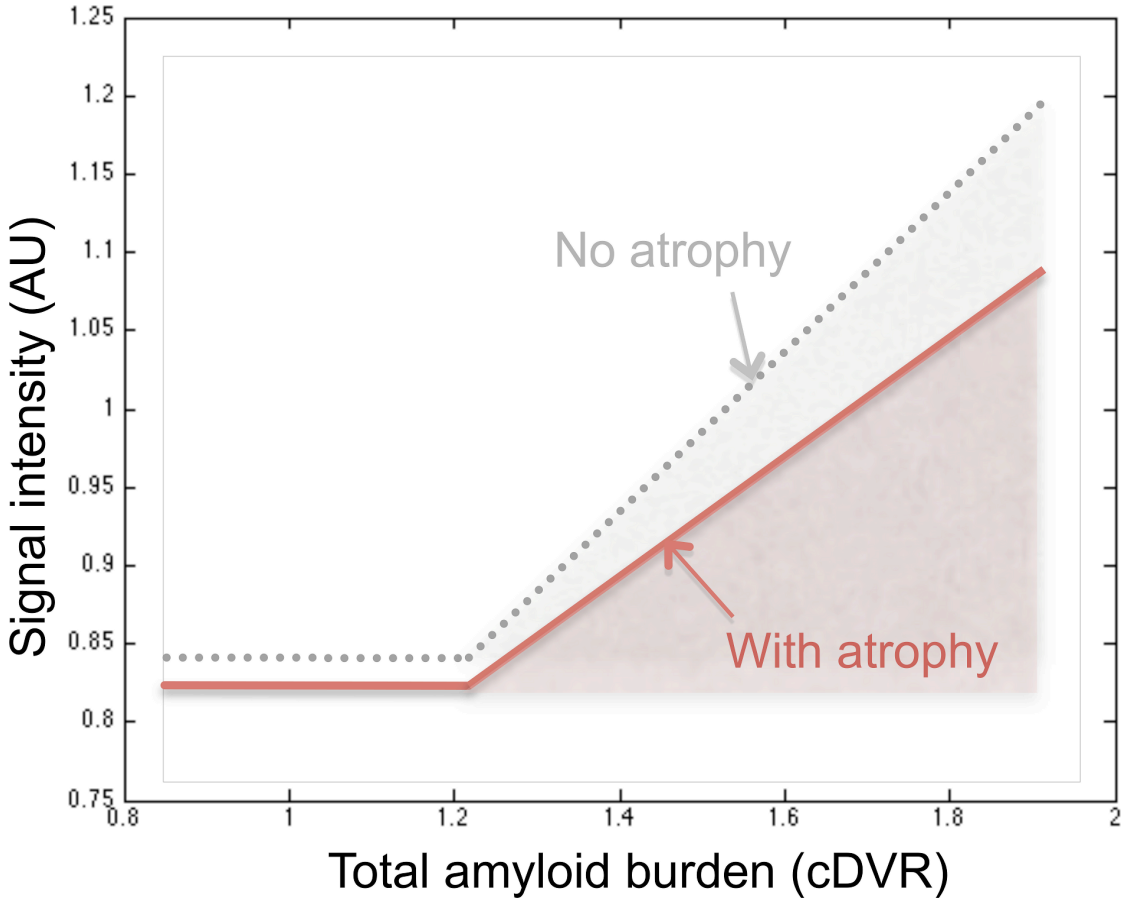

Figure S7. Shown is the theoretical effect of atrophy on the analysis method proposed here. Regions with grey matter atrophy would have lower tissue density after registration to a common template. This lower tissue density would result in a global decrease in PET signal intensity. If atrophy co-varied with total amyloid burden, such that there was more atrophy at higher amyloid burdens, the decrease in signal intensity would decrease. The result would be less apparent accumulation, however our results indicated that the CD group had more accumulation than the CS group. If the total amyloid burden was calculated from template-registered image maps, it may result in an underestimation of the cDVR values; however, the cDVR values were calculated from hand-drawn ROIs on images registered in subject space.