Uncovering the Relationship between Metabolism and β-amyloid in Mild Cognitive Impairment

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Introduction

Recent PET studies have interrogated the relationship between β-amyloid load, glucose metabolism, and apolipoprotein ε4 (APOE ε4) genotype. It has been reported that APOE ε4, and not aggregated fibrillar β-amyloid, contributes to glucose hypometabolism in older, cognitively normal and MCI subjects. The main limitation of these studies is the representation of the overall β-amyloid load by a single measurement taken from the mean SUVR of either the whole cortex or a composite region-of-interest (ROI) from areas expected to show a plausible AD-signature.

Methods

• [18F]florbetapir PET, [18F]FDG PET, and 3D T1-weighted MR images were obtained from 384 ADNI-GO/-2 study MCI subjects (n=201 early MCI; n=183 late MCI).
• PET volumes were registered to a customized MRI template in MNI stereotaxic space via the 3D T1-weighted MR images using Biospective’s fully-automated PIANO™ image processing software.
• We utilized a Singular Value Decomposition (SVD) approach to reveal patterns of the large-scale, cross-correlation structure between FDG and β-amyloid PET data.
• The SVD produced a set of eigenimages and individual subject loading pairs corresponding to both β-amyloid and glucose metabolism.
• For confirmation, we fitted a GLM with β-amyloid subject loadings as a predictor variable, metabolic measurements as response variables, and age, gender, and APOE ε4 status as covariates.

Results

• The first SVD component (Figures 1A, 2A) accounted for 89.7% of the total variability explained by the cross-correlation between the florbetapir and FDG PET images.
• The second (Figures 1B, 2B) and third (Figures 1C, 2C) SVD components accounted for 2% and 1.3% of the total variability, respectively.
• The stronger positive weights in the first β-amyloid eigenimage (Figure 1A) correspond to the middle frontal and posterior cingulate cortices, inferior temporal and fusiform gyri, as well as the paracentral lobule.
• The stronger negative FDG weights appear in the angular and inferior temporal gyr (Figure 2A).
• The GLM fitting revealed that the bilateral angular gyrus and posterior cingulate cortex are regions that show a statistically significant reduction in glucose metabolism associated with the increase of β-amyloid (Figure 3B). This result is not explained by the APOE ε4 effect. In contrast, fewer and smaller significant regions were observed using a whole cortex average of β-amyloid measurements (Figure 3D).
• Interaction with clinical diagnosis (early vs. late MCI) revealed that the observed relationship between glucose metabolism and β-amyloid primarily occurs during the late MCI stage (Figure 4).

Conclusions

Multivariate, cross-correlation analyses can uncover complex brain patterns not found with univariate statistical analysis approaches. These results support the notion that it is the spatially distributed, rather than focal, accumulation of β-amyloid that is associated with metabolic dysfunction. Future work will expand this analysis to identify the pattern of β-amyloid maximally related to metabolic connectivity.

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