**Introduction**

While regional glucose hypometabolism is characteristic of Alzheimer’s disease (AD), this feature has been shown to be primarily associated with the ApoE4 genotype, rather than fibrillar β-amyloid, during the pre-clinical/early stages of the disease process (Jagust & Landau, J. Neurosci., 2012). However, derangements of metabolic connectivity are intimately related to β-amyloid plaque burden. In order to assess the specific alterations in metabolic connectivity in early disease, we have performed a quantitative analysis of correlation patterns derived from [18F]FDG positron emission tomography (PET) images from ADNI MCI subjects with different levels of cortical β-amyloid.

**Methods**

[18F]Florbetapir PET, [18F]FDG PET, and 3D T1-weighted MR images were obtained from ADNI-GO/-2 study subjects classified as having mild cognitive impairment (MCI) (n=200). All PET image volumes were registered to a customized MRI template in MNI stereotaxic space, and standardized uptake value ratio (SUVR) images were generated using Biospective’s fully-automated PIANO™ image processing software. The amyloid burden for each subject was determined from a composite region-of-interest (ROI), consisting of precuneus, posterior cingulate, and medial frontal cortex, and subjects were categorized into Amyloid-Low (AβL) and Amyloid-High (AβH) groups based on a vertexwise discriminant analysis. We generated vertexwise correlation strength (CS) maps, which summarize all correlations associated with each vertex across the entire cerebral cortex (Figure 1). We then decomposed the CS maps into short- and long-range components using a Euclidean distance cut-off of 20 mm (Figure 2). Finally, we further decomposed the CS maps into seed-based correlation maps in order to provide a detailed view of the all metabolic correlations associated with each particular vertex (Figure 3).

**Results**

- An overall reduction in metabolic correlations was observed in the AβH group (Figure 1).
- Decomposition of the overall CS maps into short- and long-range components (Figure 2) revealed: (1) a global reduction in long-range metabolic correlations, and (2) a regional increase (temporal-parietal, medial prefrontal, and occipito-parietal cortical regions) in short-range metabolic correlations in the AβH group relative to the AβL group.
- The seed-based correlation analysis of two illustrative regions are shown in Figure 3. The right inferior temporal gyrus showed a specific pattern of decreased metabolic correlations in the AβH group, particularly in the superior temporal gyrus, pars opercularis, supplementary motor area, orbitofrontal cortex, and fusiform gyrus. In contrast, a local increase in metabolic correlations was observed for the left angular gyrus seed region.

**Conclusions**

We have employed metabolic connectivity analysis to examine disruptions of the cortical correlation architecture as a function of β-amyloid burden. Decomposition of the summary CS maps into short-range, long-range, and individual components revealed aberrant metabolic connectivity patterns in the AβH group. These aberrant metabolic connectivity patterns could be a consequence of variable spatio-temporal patterns of compensatory responses and/or cortical remodeling during the early stages of AD. This quantitative, metabolic connectivity approach may serve as a powerful, non-invasive imaging biomarker for the evaluation of the efficacy of novel amyloid-lowering therapeutic agents.

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