Heterogeneity in neuroanatomical differences in relation to amyloid burden in mild cognitive impairment

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Introduction

Amyloid deposits have long been considered to be related to the initiation of Alzheimer’s disease (AD), but a high amyloid burden alone does not predict the diagnosis of AD. The goal of this work was to determine neuroanatomical differences between subjects with high and low amyloid burden and to investigate how those differ in the diagnostic groups of mild cognitive impairment (MCI) and cognitively normal controls (NL).

Methods

3458 3T T1-weighted magnetic resonance images (MRI) and analyzed florbetapir positron emission tomography data were obtained from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) database for 850 subjects (142 AD, 455 MCI, 263 NL; baseline to 3 years).

Florbetapir analysis was obtained from ADNI. Florbetapir standardized uptake rate (SUVR) at baseline were averaged across the 4 cortical regions (frontal, anterior/posterior cingulate, lateral parietal, lateral temporal) and divided by cerebellar reference region SUVR. A cut-off of 1.11 was used to divide subjects into high and low amyloid groups. MRI scans were processed using the CIVET pipeline for cortical thickness (CT), MAGeT Brain algorithm for hippocampal volume (HV) and morphometry using surface area (HSA), and BESA for total brain volume.

Linear mixed-effects model is used to examine the effect of amyloid burden on CT, HV and HSA for all subjects (covaried for age, gender, baseline diagnosis and total brain volume) and within each diagnostic group (covaried for age, gender and total brain volume).

Results

AD subjects were not included in the analyses due to the insufficient number of subjects in the low amyloid group for power, when divided according to amyloid classification and diagnosis. When all diagnostic groups were considered, the high amyloid group, compared to the low amyloid group, has significant reductions in both left and right HV, HSA and CT (Figure 1). When subjects were stratified into diagnostic groups of MCI and NL, high amyloid NL subjects showed no significant difference in all measures when compared to low amyloid NL. High amyloid MCI subjects, however, had significant differences in both left and right HV and left HSA. For vertex-wise CT analysis, the right CT is significant with differences concentrated at the medial temporal lobe, while the left CT is marginally different with p-value of 0.064 (Figure 2).

Conclusions

Hippocampus was observed to be the most affected by amyloid burden, especially in the diagnostic group of MCI. High amyloid in MCI subjects is related to accelerated neurodegeneration and is consistent with the literature on the increased hippocampal atrophy and cortical thinning associated with amyloid-β. NL subjects were observed to have no difference with amyloid contrast. Even with high amyloid load, the neuroanatomical integrity of NL subjects were still intact and the hippocampal volumes and cortical thickness were not different from those with low amyloid load.

The pattern of neurodegeneration with more severe hippocampal atrophy and cortical thinning in the medial temporal region is consistent with the signature progression of AD. The hippocampus and entorhinal cortex are the earliest sites of atrophy, followed closely by amygdala, parahippocampus before spreading to the neocortex.

References