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

Vincent Kong[1,2], Raihaan Patel[1], Gabriel A. Devenyi[1], M. Mallar Chakravarty[1,2,3], Alzheimer's Disease Imaging Initiative

[1]Cerebral Imaging Center, Douglas Mental Health University Institute, Montreal, Canada. [2]Integrated Program in Neuroscience, McGill University, Montreal, Canada. [3]Departments of Psychiatry and Biomedical Engineering, McGill University, Montreal, Canada.

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 860 subjects (142 AD, 455 MCI, 263 NL; baseline to 3 years).

Florbetapir analysis data 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 cerebellum 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 and BEaST 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).

Diagnosis	MCI		NL		Test Statistic
Amyloid Classification	High	Low	High	Low	
n	250	205	88	175	
Sex					
Female	112	94	59	84	MCI - X^2(df=1) = 0.017 (p=0.897) NL - X^2(df=1) = 7.81 (p=0.005)
Male	138	111	29	91	
Age at baseline mean±SD	72.9±6.9	69.9±7.9	74.5±5.8	72.1±6.0	MCI - t=4.25 (p<0.001) NL - t=3.10 (p=0.002)
ADAS11 mean±SD	10.40±4.70	7.66±3.53	5.93±2.78	5.53±3.07	MCI - t=7.09 (p<0.001) NL - t=1.06 (p=0.29)
ADAS13 mean±SD	16.8±6.98	12.12±5.46	9.45±4.26	8.65±4.43	MCI - t=8.03 (p<0.001) NL - t=1.42 (p=0.16)
MMSE mean±SD	27.67±1.80	28.57±1.42	29.07±0.92	28.99±1.35	MCI - t=-5.98 (p<0.001) NL - t=0.60 (p=0.55)
n of APOE4 allele(s)					
0	82	154	47	140	MCI - X^2(df=2) = 84.13 (p<0.001) NL - X^2(df=1) = 19.24 (p<0.001)
1	129	44	36	32	
2	39	36	4	3	

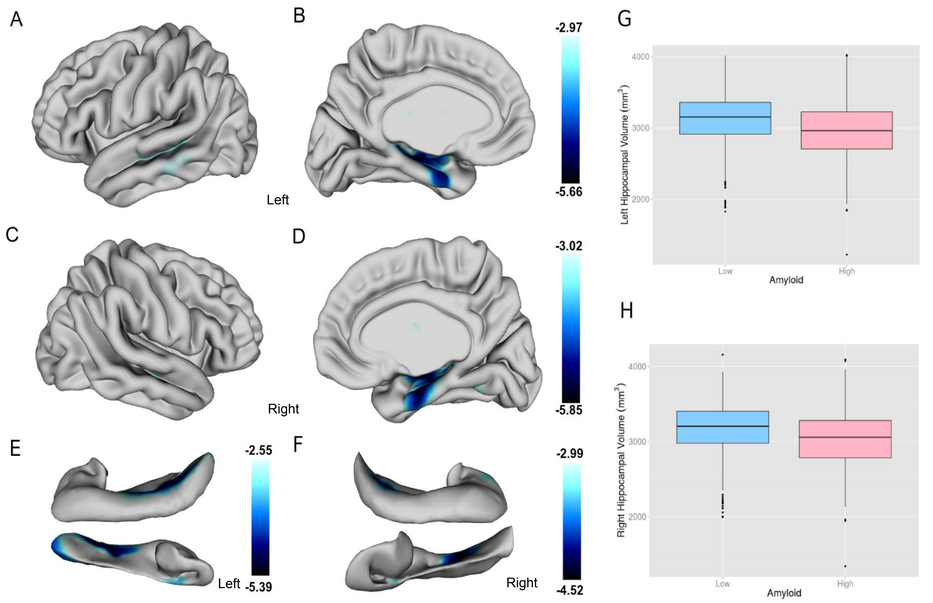

Figure 1. Cortical thickness, hippocampal surface and volume differences for subjects in all diagnostic group. Cortical thickness differences between subjects with high amyloid and low amyloid in the left hemisphere (A,B) and right hemisphere (C,D). The colourbars show t-values for the cut-off value after FDR correction of 5% on top and maximum difference at the bottom. Hippocampal surface area differences in subjects with high vs.low amyloid after 5% FDR correction for the left (E) and right (F) hippocampi. Hippocampal volumes in box and whisker plot against amyloid classification (G,H).

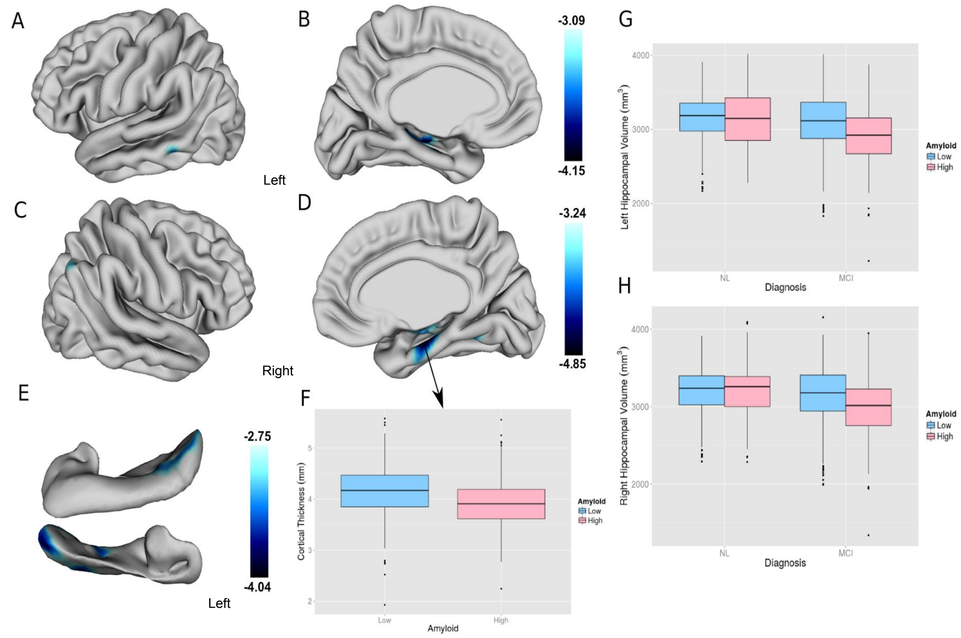

Figure 2. Cortical thickness differences between MCI subjects with high and low amyloid after FDR correction of 10% for the left hemisphere (A,B) and 5% for the right hemisphere (C,D). Left hippocampal surface area differences in MCI subjects with high vs. low amyloid after FDR correction of 5% (E). The colourbars show the t-values for the cut-off for 5% FDR correction (C,D,E) and 10% (A,B) at the top and t-value for maximum difference at the bottom. Cortical thickness plotted against amyloid classification at vertex chosen from the region with maximum difference in D (F). Volumes of left and right hippocampi of MCI and NL subjects plotted with amyloid classification (G,H).

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 q-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 of AD. The hippocampus and entorhinal cortex are the earliest sites of atrophy, followed closely by amygdala, parahippocampus before spreading to the neocortex.

References

1) Selkoe DJ. Amyloid beta protein precursor and the pathogenesis of Alzheimer's disease.Cell. 1989;58(4):611-2.
2) Huijbers W, Mormino EC, Sperling RA, et al. Amyloid-β deposition in mild cognitive impairment is associated with increased hippocampal activity, atrophy and clinical progression. Brain. 2015.138:1023-35.
3) Becker JA, Hedden T, Johnson KA, et al. Amyloid-β associated cortical thinning in clinically normal elderly.Ann Neurol. 2011.69 (6):1032-42.
4) Chan D, Fox NC, Rossor MN, et al. Patterns of temporal lobe atrophy in semantic dementia and Alzheimer's disease. Ann Neurol. 2001 Apr;49(4):433-42.