Fibrillar Amyloid: Thinking Globally, Not Acting Locally

Andre Altmann[1], Bernard Ng[1], Susan Landau[2], William Jagust[2], Michael D. Greicius[1] for the ADNI Investigators

1. Functional Imaging in Neuropsychiatric Disorders (FIND) Lab, Department of Neurology and Neurological Sciences, Stanford University, Stanford, CA, USA
2. Helen Wills Neuroscience Institute, University of California, Berkeley, CA, USA.

P5 021

Introduction

The amyloid cascade hypothesis of Alzheimer's disease (AD) holds that fibrillar deposits of amyloid are an early, driving force in pathological events leading ultimately to neuronal death. Studies investigating the local dependency between metabolism and amyloid plaque deposition have arrived at conflicting results. E.g., Furst et al. (2012) report that "*there were no associations between regional PIB [Pittsburgh compound B] and FDG uptake*", while Lowe et al. (2014) report "*that the association of hypometabolism and amyloid accumulation also occurs in a regional, individual ROI basis*". Using the imaging data from the AD Neuroimaging Initiative (ADNI) we aim to analyze regional patterns of amyloid deposition and glucose metabolism in the same subjects, using florbetapir and FDG PET, respectively.

Methods

Data. We obtained structural T1-weighted MRI scans and date-matched florbetapir and FDG PET scans for N=661 subjects from the AD Neuroimaging Initiative (ADNI).

	N	Sex (males)	Age	Education	MMSE	APOE4 carrier
HC	227	111	75.3 (6.7)	16.3 (2.6)	29.1 (1.2)	61
MCI	434	245	72.5 (8.0)	16.1 (2.7)	28.1 (1.7)	200
P-value	-	0.077	$2.4x10^{-6}$	0.25	$<2.2x10^{-6}$	$2.3x10^{-6}$

Image Processing. Voxelwise gray matter (GM) density was computed using the VBM8 toolbox and corrected for intracranial volume (ICV). PET data were analyzed in subject space by projecting regions-of-interest (ROIs) from MNI space into subject space using SPM8. PET intensity values were re-scaled to a joint pons-vermis ROI (FDG) or whole cerebellum ROI (florbetapir).

Statistical Analysis. For each of the 404 ROIs (Figure 1a) we estimated the effect of diagnosis on the three imaging modalities (Figure 1b-c) using linear regression and correcting for age, sex, education, ICV and APOE-e4 status. Further, using linear regression we estimated the association of global amyloid burden or CSF $Abeta_{42}$ levels (available for N=544 subjects) on glucose metabolism (Figure 2). In the model we corrected for diagnosis, age, sex, education and gray matter. Regional association between amyloid plaques and glucose metabolism was estimated using linear regression (Figure 3a) with the same covariates. In order to test for local specificity of the association we corrected in addition for global amyloid (Figure 3b) and used a permutation test (Figure 3c).

For more information contact Andre Altmann: altmann@stanford.edu

Results (I)

Figure 1: The 404 regions of interest (ROIs) used in this study (a). Compared to HCs, MCIs show significant (P_{bonf} < 0.05) reductions in **gray matter (b)** and in **glucose metabolism (c)** in AD-related regions. **Amyloid plaque deposition (d)** is significantly increased in MCIs throughout the cortex.

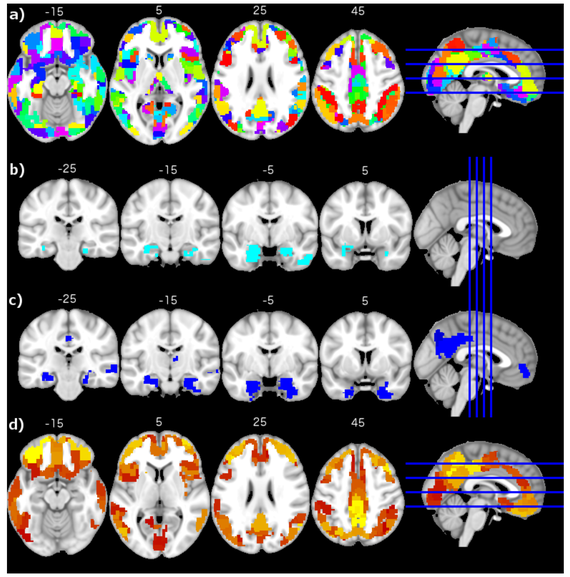
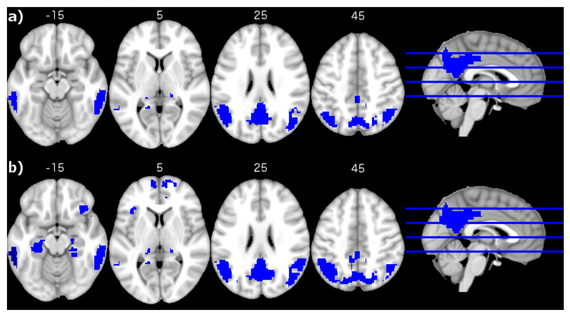


Figure 2: Key ROIs in AD show significantly (P_{bonf} < 0.05) decreased glucose metabolism with increased **global amyloid plaque burden (a)** and decreased **CSF $Abeta_{42}$ levels (b)**.



References

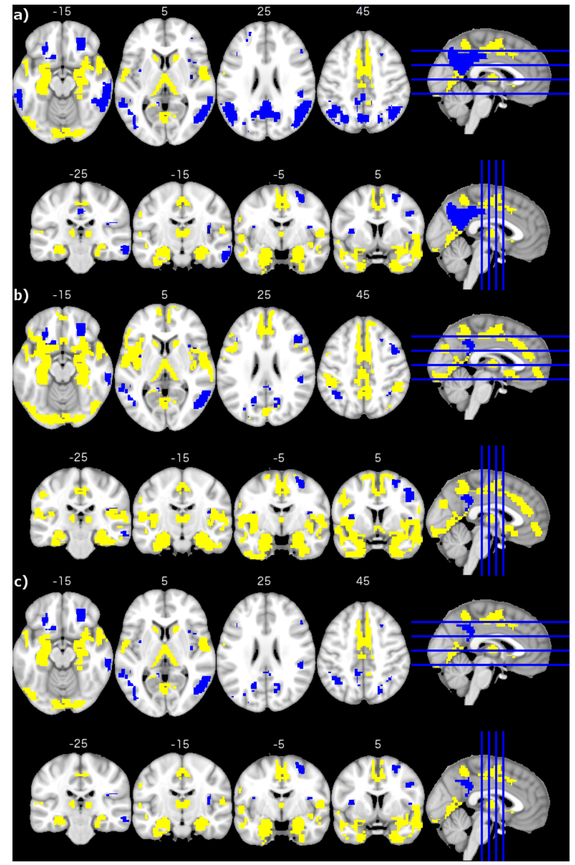
Furst et al. Cognition, glucose metabolism and amyloid burden in Alzheimer's disease. Neurobiol Aging (2012) vol. 33 (2) pp. 215-25.
Lowe et al. Association of hypometabolism and amyloid levels in aging, normal subjects. Neurology (2014) vol. 82 (22) pp. 1959-67.

Disclosure

The authors have nothing to disclose.

Results (II)

Figure 3: Regional association of amyloid plaque deposition and glucose metabolism (a). Significant (P_{bonf} < 0.05) negative associations (increase in regional amyloid and decrease in metabolism) are depicted in blue. Significant positive associations in yellow. After **correction for global amyloid burden (b)** negative associations in many AD key regions disappear. Likewise, most negative associations do not survive a **permutations test for local specificity of the associations (c)**.



Conclusions

Given the wide-spread distribution of amyloid plaques, if the canonical cascade hypothesis were true, we would expect wide-spread, cortical hypometabolism. Instead, cortical hypometabolism appears to be linked to global amyloid burden. Thus we conclude that regional fibrillar amyloid deposition has little to no association with regional glucose metabolism.