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Regional Exceptions to the "High Amyloid-Low Metabolism" Expectation in Preclinical Alzheimer's Disease

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Introduction

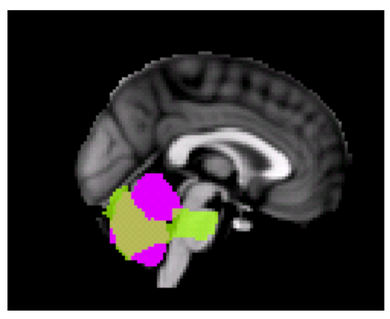
The amyloid cascade hypothesis of Alzheimer's disease (AD) holds that fibrillar deposits of amyloid are an early, driving force in pathological events leading to neurofibrillary tangles, neuronal dysfunction, and neuronal death. The advent of amyloid imaging—by highlighting regions like the medial temporal lobe which, though pathologically affected early in AD, show little amyloid deposition and other regions, like the prefrontal cortex which are relatively spared early in AD yet show prominent amyloid deposition—necessitates a critical re-analysis of this hypothesis. In the current study, we use a whole-brain, region-of-interest (ROI) approach to examine data from the AD Neuroimaging Initiative (ADNI) [1] with a focus on regional patterns of amyloid deposition and glucose metabolism in the same subjects, using florbetapir (AV45) PET and FDG PET, respectively. We identify three sets of regions: those showing the expected association between high amyloid signal and reduced metabolism, those showing high amyloid signal and normal metabolism, and those showing no statistical dependency between amyloid signal and metabolism.

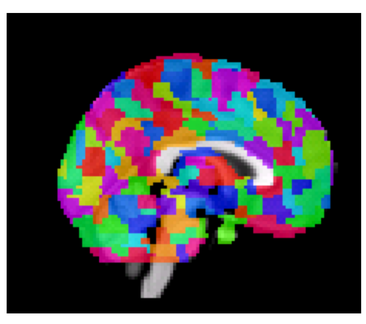
Methods

Image data. N=396 individuals from the ADNI database who have a baseline **FDG-PET scan**, a baseline **AV45-PET scan**, a baseline **structural T1 scan** and baseline **CSF biomarker levels**. Both baseline PET scans were at most 60 days apart. Moreover, the analysis was restricted to healthy controls and MCI patients. Subjects were dichotomized into CSF Ab- and CSF Ab+ groups based on their CSF Abeta value using the ADNI threshold of 192 pg/ml [2].

	HC	MCI
CSF Ab-	91	140
CSF Ab+	41	119

Image Processing. PET images were spatially normalized to MNI152 using the individuals' structural T1 image and FSL FNIRT. Then, PET images were normalized with respect to marker uptake in a reference region. Briefly, for FDG PET data a joint Pons-Vermis ROI was used for normalization, and for AV45 PET the whole cerebellum was used.





Parcellation. We employed a whole brain region of interest (ROI) approach. We derived an atlas with fine brain division on the basis of resting state functional MRI data. Voxel time courses across healthy subjects were concatenated and the brain was functionally parcellated into 500 parcels using Ward clustering.

Statistical Analysis. For each of these 500 ROIs we extracted the average signal intensity per subject per modality. Signal intensities were scaled to z-scores using mean and standard deviation (SD) of all Ab- subjects.

For the statistical analysis of the data we defined **high amyloid** levels as **z-score > 1.5** and **low FDG** levels as **z-scores < -1.5**. Fisher's Exact test (FET) was used to test for statistical dependency of high amyloid and low FDG in the same ROI.

	Norm AV45	High AV45
Low FDG	58	2
Norm FDG	227	104

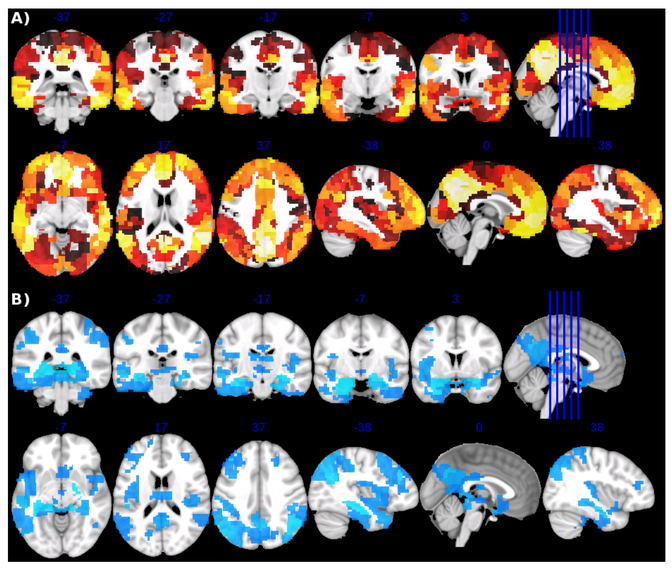
Fisher P-value: 4.6×10^{-7}
Amyloid protective?

	Norm AV45	High AV45
Low FDG	24	42
Norm FDG	203	122

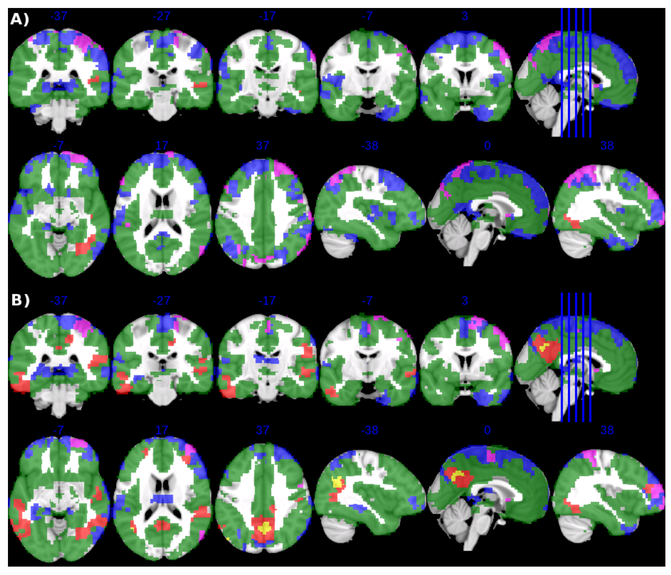
Fisher P-value: 0.0001145
Amyloid harmful?

In order to limit the number of tests to relevant regions, we focused on ROIs in which at least 40% of the Ab+ individuals exhibited high amyloid or ROIs where at least 15% of the Ab+ individuals showed reduced glucose metabolism. The test was carried out for the Ab+ group and separately for all subjects.

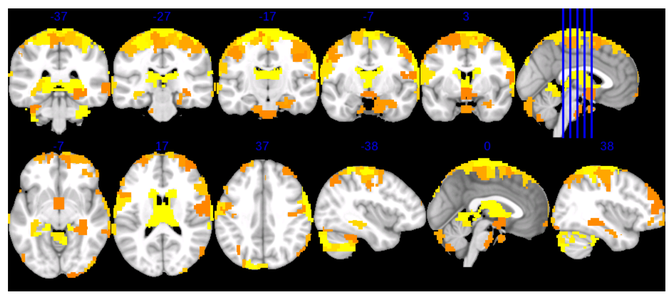
Results



Fraction of Ab+ individuals exhibiting high amyloid levels (a) and low FDG signal (b). For a) Hotter colors represent more individuals showing high amyloid in a given parcel [40%-85%]. For b) Colder colors indicate a larger fraction of individuals with low FDG in a given parcel [15%-35%].



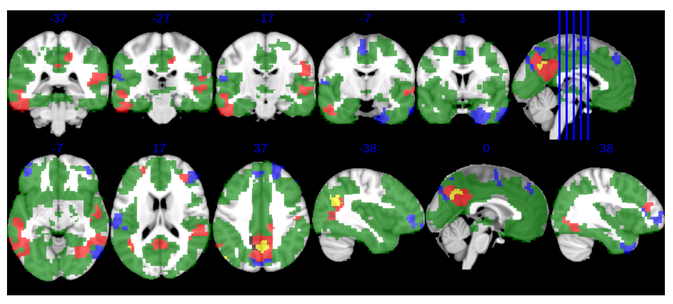
Results of the Fisher's Exact test. ROIs showing more events of low FDG than expected in the presence of high amyloid levels are **red** (nominal) and **yellow** (corrected p<.05). ROIs showing fewer events are **blue** (nominal) and **violet** (corrected p<.05). (A) Only CSF Ab+ subjects. (B) All N=396 subjects.



ROIs with high positive correlation (r>0.3) between amyloid burden and glucose metabolism computed across all subjects (N=396).

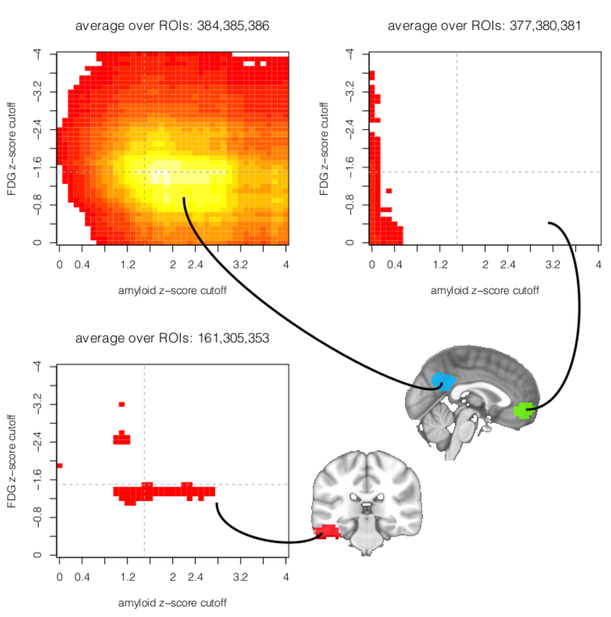
Conclusions

Few ROIs show classic high amyloid low FDG pattern. With the exception of a few regions, fibrillar amyloid deposition appears to have little association with local metabolism.



"Protective" amyloid effect only in ROIs close to the surface. Protective effects of amyloid detected by FET may be artifacts due to signal processing.

Results are independent of selected cutoffs. We screened for optimal thresholds for amyloid burden and glucose metabolism. Three ROIs in the cingulate (post)/ precuneous cortex (384-386), three ROIs in the cingulate (ant) (377,381,382), and three more ROIs (161, 305, 353) FET was computed for all combinations of cutoffs for low FDG [-4; 0] and high amyloid [0; 4].



References

1. Mueller SG, Weiner MW, Thal LJ, Petersen RC, Jack C, Jagust W, Trojanowski JQ, Toga AW, Beckett L. (2005) The Alzheimer's disease neuroimaging initiative. Neuroimaging Clin N Am. 15(4):869-77, xi-xii.
2. Shaw LM, Vanderstichele H, Knapik-Czajka M, Clark CM, Aisen PS, Petersen RC, Blennow K, Soares H, Simon A, Lewczuk P, Dean R, Siemers E, Potter W,Lee VM, Trojanowski JQ; Alzheimer's Disease Neuroimaging Initiative (2009) Cerebrospinal fluid biomarker signature in Alzheimer's disease neuroimaging initiative subjects. Ann Neurol. 65(4):403-13.

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