Prefrontal hypometabolism in Alzheimer disease is related to longitudinal amyloid accumulation in remote brain regions.

In PET studies of patients with Alzheimer disease (AD), prominent hypometabolism can occur in brain regions without major amyloid load. These hypometabolism-only (HO) areas may not be explained easily as a consequence of local amyloid toxicity. The aim of this longitudinal multimodal imaging study was the investigation of locoregional and remote relationships between metabolism in HO areas and longitudinal amyloid increase in functionally connected brain areas, with a particular focus on intrinsic functional connectivity as a relevant linking mechanism between pathology and dysfunction. Fifteen AD patients underwent longitudinal examinations with (11)C-Pittsburgh compound B ((11)C-PiB) and (18)F-FDG PET (mean follow-up period, 2 y). The peak HO region was identified by the subtraction of equally thresholded statistical T maps (hypometabolism minus amyloid burden), resulting from voxel-based statistical parametric mapping group comparisons between the AD patients and 15 healthy controls. Then functionally connected and nonconnected brain networks were identified by means of seed-based intrinsic functional connectivity analysis of the resting-state functional MRI data of healthy controls. Finally, network-based, region-of-interest-based, and
voxel-based correlations were calculated between longitudinal changes of normalized (11)C-PiB binding and (18)F-FDG metabolism. Positive voxel-based and region-of-interest-based correlations were demonstrated between longitudinal (11)C-PiB increases in the HO-connected network, encompassing bilateral temporoparietal and frontal brain regions, and metabolic changes in the peak HO region as well as locoregionally within several AD-typical brain regions. Our results indicate that in AD amyloid accumulation in remote but functionally connected brain regions may significantly contribute to longitudinally evolving hypometabolism in brain regions not strongly affected by local amyloid pathology, supporting the amyloid- and network-degeneration hypothesis.