Neuronal dysfunction and disconnection of cortical hubs in non-demented subjects with elevated amyloid burden.

Disruption of functional connectivity between brain regions may represent an early functional consequence of ?-amyloid pathology prior to clinical Alzheimer's disease. We aimed to investigate if non-demented older individuals with increased amyloid burden demonstrate disruptions of functional whole-brain connectivity in cortical hubs (brain regions typically highly connected to multiple other brain areas) and if these disruptions are associated with neuronal dysfunction as measured with fluorodeoxyglucose-positron emission tomography. In healthy subjects without cognitive symptoms and patients with mild cognitive impairment, we used positron emission tomography to assess amyloid burden and cerebral glucose metabolism, structural magnetic resonance imaging to quantify atrophy and novel resting state functional magnetic resonance imaging processing methods to calculate whole-brain connectivity. Significant disruptions of whole-brain connectivity were found in amyloid-positive patients with mild cognitive impairment in typical cortical hubs (posterior cingulate cortex/precuneus), strongly overlapping with regional hypometabolism. Subtle connectivity disruptions and hypometabolism were already present in amyloid-positive asymptomatic subjects. Voxel-based
morphometry measures indicate that these findings were not solely a consequence of regional atrophy. Whole-brain connectivity values and metabolism showed a positive correlation with each other and a negative correlation with amyloid burden. These results indicate that disruption of functional connectivity and hypometabolism may represent early functional consequences of emerging molecular Alzheimer’s disease pathology, evolving prior to clinical onset of dementia. The spatial overlap between hypometabolism and disruption of connectivity in cortical hubs points to a particular susceptibility of these regions to early Alzheimer’s-type neurodegeneration and may reflect a link between synaptic dysfunction and functional disconnection.