Alzheimer’s disease (AD) pathology progresses in stages across anatomically connected regions of the brain, with certain regions affected before others. Why some brain regions are more vulnerable to AD than others has long remained a mystery. However, recent genomics research indicates that neurons with long axonal projections and many arbors exhibit selective neuronal vulnerability (SNV) to AD pathology. If large projection neurons are more vulnerable to AD, they should also be among the earliest affected. The cholinergic neurons of the basal forebrain (BF) are known to have large projections, though recent work indicates that they are much larger than was previously appreciated: In humans a single cell’s full arborisation measures ~100 meters in length.

Under the SNV hypothesis, this emerging evidence places the cholinergic BF neurons as likely targets in the earliest stage of AD. A core challenge for human AD research therefore is to devise strategies for detecting cell-type specific degeneration, even when individual cell types are not directly observable in vivo. For example, based on structural magnetic resonance imaging (sMRI) data alone, we cannot infer that gray matter decreases in the BF, as a whole, reflects degeneration of its constituent cholinergic neurons per se. We therefore integrated a cerebrospinal fluid biomarker (CSF) of AD pathology with neuroimaging and genomic data to triangulate in vivo cell-type specific degeneration of human cholinergic BF neurons across early (preclinical) stages of AD.

To accomplish this objective, we capitalized on the rich array of data available from the Alzheimer’s Disease Neuroimaging Initiative (ADNI). We first integrated measures of
neuropsychological status with the CSF amyloid-beta 1-42 biomarker (CSF Aβ) within the same individuals. This strategy allows for precise demarcation of cognitively normal (CN) adults with either normal CSF Aβ (CN NAβ) or abnormal CSF Aβ (CN Aβ+). The latter constitutes our preclinical AD group. We also delineated a third group of older adults with mild cognitive impairment (MCI) and abnormal CSF Aβ (MCI Aβ+). In these three groups, we then examined longitudinal changes in (1) structural MRI indices of gray matter volume and (2) gene expression derived from peripheral blood cells.

Our work provides unprecedented evidence that cell-type specific degeneration of the cholinergic BF system can be triangulated from subregional volumetric analysis of structural MRI data, in combination with gene expression data. Moreover, our work demonstrates further evidence supporting the SNV hypothesis, which proposes that cholinergic cells are among the most vulnerable to, and thus earliest affected by, AD pathology.