

Identification of circuits that benefit from cholinergic intervention in cognitive decline during Alzheimer Disease progression.

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Research question and background

Despite well characterized neurodegeneration of cholinergic neurons in the vaguely labeled 'basal forebrain' and nucleus basalis, the integrity of cholinergic transmission in the specific septal nuclei and substantia innominata is unclear. The drugs currently approved for Alzheimer's treatment mostly act on these regions which contain the majority of the cholinergic neurons in the brain. Interestingly, each of these regions projects preferentially to different cortical and subcortical structures that play distinguishable roles in learning and memory. In order to understand the limitations and potentials of the current drugs, and to define the specific circuits that most directly benefit from cholinergic intervention to influence cognition, we will characterize the loss of cholinergic neurons in the specifically defined nuclei mentioned above. We will also establish the extent of Alzheimer disease (AD)-associated neuropathology (neurofibrillary tangles and neuritic plaques) in these regions and correlate it with Braak and Braak cortical stage and Clinical Dementia Rating (CDR) score. Following these results we will determine if we should look for changes in other Alzheimer's related proteins or other pathological features of the disease not previously characterized in these regions, and test our hypotheses in mouse models.

Methods and tissues used

Immunofluorescence on paraffin and frozen blocks of hippocampi and amygdala from AD patients and controls processed in "CLARITY" (a relatively novel, patented protocol to make blocks of tissue transparent and amenable to immunofluorescence labeling and confocal microscopy).

Results and conclusion

The study is still in progress.