

Investigating the Role of the Lateral Entorhinal Cortex in Alzheimer's Disease

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The purpose of this study was to discover potential mechanisms that mediate the spread of Alzheimer's Disease (AD), a fatal neurodegenerative disease that affects 5 million U.S. citizens every year (Alzheimer's Disease facts and figures, Alzheimer's Association, 2019). AD disrupts and destroys normal neuronal function via the formation of beta-amyloid plaques (between neurons) and neurofibrillary tangles made of hyperphosphorylated tau protein (within neurons). One of the first brain regions to exhibit this pathology is the lateral entorhinal cortex (LEC); this study is aimed at understanding the role of this brain region in the progression of the disease.

We began by delivering mutant tau protein to the LEC in previously healthy mice via intracranial injection. After allowing sufficient expression time of four weeks, we assessed for learning and memory impairments in these mice using two memory tasks: object recognition and trace fear conditioning. At the conclusion of behavioral testing, we then assessed for the presence of tau pathology using immunohistochemical staining of brain slices. We found the presence of early tau pathology mice injected with mutant tau (AAV-TauP301L; data not shown). In addition, these mice had cognitive deficits (Figure 1), indicating that our experiment sufficiently modeled early stage disease alterations.

In AD, tau pathology beginning in the LEC eventually spreads to the hippocampus along a circuit called the perforant pathway. Evidence from the literature suggests that misfolded tau may be released into the space between neurons, or the synapse, due to increases in neuronal activity (Pooler et al., 2013). Once there, the misfolded tau can be taken up by nearby neurons, eventually compromising the healthy tau in these neurons. To determine if this was the case, we again delivered mutant tau protein to the LEC. In addition, we delivered a viral vector containing light-sensitive opsin receptor to neurons in the LEC. Neurons expressing this light-sensitive opsin receptor can then be activated by exposure to a certain wavelength of light. We implanted

a fiber optic cannula through which we exposed these neurons to light, resulting in increased neuronal activity. For our comparison, we increased neuronal activity (stimulated) in one hemisphere of the brain and not in the other hemisphere (non-stimulated). We determined that tau pathology spread further in the stimulated hemisphere, versus the non-stimulated hemisphere (Figure 2). These results indicate that increased neuronal activity resulted in increased spread of tau along connected neural networks. Currently, we are continuing work to determine if this increased spread of tau pathology also results in worsened pathology and memory deficits.

The LEC has been identified as the site where some of the first alterations appear in AD, but the role of the LEC in memory is poorly understood. Understanding the role of the LEC in memory would allow for creation of diagnostic tasks sensitive to these early alterations.

Statement of Research Advisor

Marissa's work strongly indicates that tau pathology in the LEC can induce detectable memory deficits and that increasing neuronal activity in the LEC can cause tau pathology to spread to connected neural networks. Future work will identify whether decreasing neuronal activity can prevent the spread of tau.

– *Miranda N. Reed, Drug Discovery and Development*

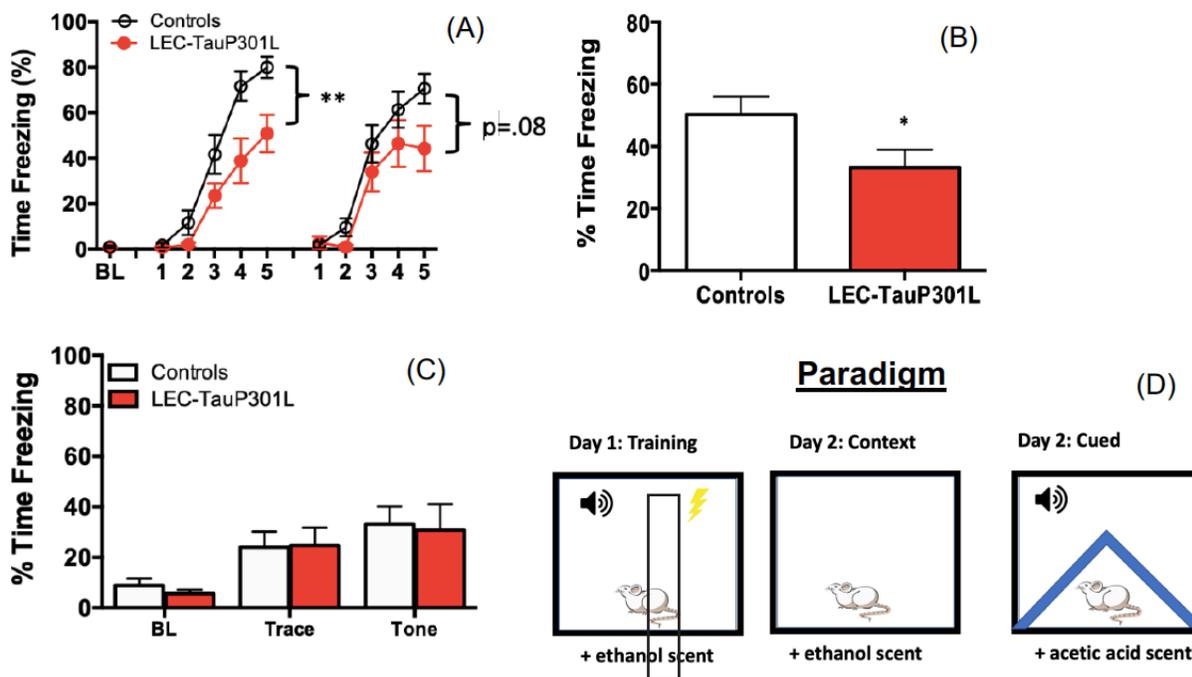


Figure 1. (A) AAV-TauP301L mice do not differ from controls in baseline freezing. AAV-TauP301L freeze significantly less than controls during trace and tone acquisition. (B) AAV-TauP301L mice freeze significantly less than controls during contextual testing. (C) AAV-TauP301L mice do not differ from controls in amygdala-based tone retention testing. (D) Representative paradigm. Data represented as means +/- SEM.

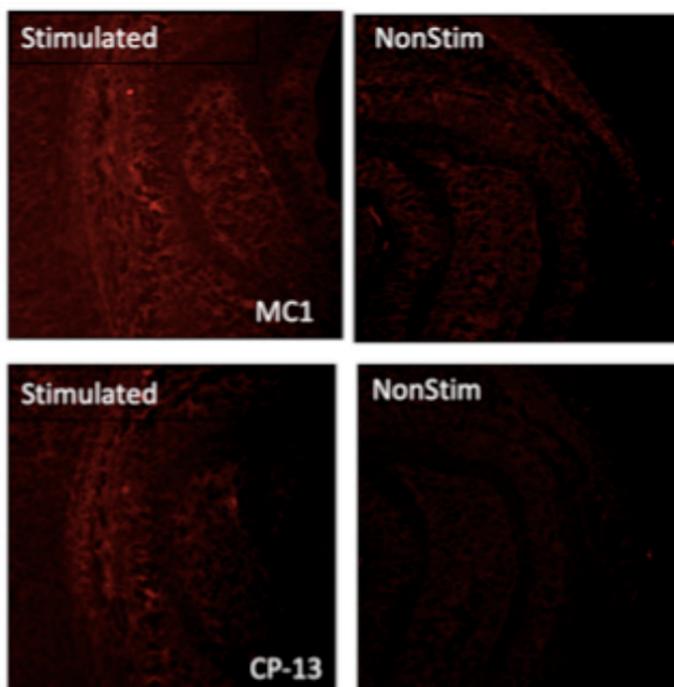


Figure 2. Presence of MC-1 and CP-13 in the hippocampus of stimulated brain regions but not non-stimulated brain regions.