

### Optogenetics Shed Light on Alzheimer's Disease

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#### COLUMN ARTICLE

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by the presence of amyloid plaques and neurofibrillary tangles in the brain ultimately leading to cell death and dementia. Currently there is no cure for AD. A number of research groups reported disruptions in neuronal activity preceding neuronal cell death. Disruptions in default mode network activity have been reported in asymptomatic cognitively normal adults [1,2]. Additionally disruptions in neuronal oscillations, such as gamma oscillations and corticothalamic slow wave activity, important for consolidation of memories during sleep have been reported in humans and animal models of AD [3-8]. Interestingly, oscillatory activity disruptions precede the onset of AD symptoms, and occur during the preclinical stages of disease, such as Mild Cognitive Impairment (MCI) [4].

A number of clinical trial failures underscores the need for further insight into the etiology and mechanisms of AD progression. Furthermore, intervention during the early disease stages, prior to substantial neuronal loss will provide for more efficient therapeutic alternatives. Transgenic

mice yield valuable animal models to gain insight into the cellular and molecular mechanisms of neuronal activity disruptions early in the disease progression. Until recently it has been difficult to address the cause and effect questions when it comes to neuronal activity disruptions and how to best restore neuronal circuit function in AD.

The advent of optogenetics provides a valuable tool to ask these questions in animal models of disease in the *in vivo* context critical for understanding the interplay of molecules and circuits. Optogenetics involves genetically targeted optical and relatively noninvasive manipulation of neuronal activity with light activation [9,10]. It allows scaling of neuronal activity manipulation from individual neurons to that of entire neuronal networks. This methodology is more precise than other means of neuronal stimulation, such as use of electrodes, since optogenetics provides temporal and spatial resolution comparable to the elementary building blocks of neural codes. The duration and the pattern of light pulses can be varied with millisecond-scale temporal precision. Furthermore, specific cell type targeting is achieved with cell-type specific promoters. Neuronal activity can be facilitated with light activation of Channelrhodopsins or inhibited with light activation of Halorho-

dopsins and Archaelhodopsins [11-15]. Recently a number of Channelrhodopsin and Halorhodopsin derivatives have been developed, including red-light-drivable ones that enable large-volume, even noninvasive neural control [16,17]. Thus optogenetics serves as an excellent toolset to study neuronal activity disruptions and to provide insight into promising approaches to restore those activity aberrations.

Recently a number of studies have been conducted implementing optogenetics in investigating AD progression and pathogenesis. An important outstanding question in the AD field was whether increasing neuronal activity leads to exacerbation of amyloid and tau pathology *in vivo*. Yamamoto, *et al.* have reported that increasing neuronal activation in hippocampi of AD mice leads to increased amyloid production and deposition [18]. Also, optogenetic increases in neuronal activity result in elevated tau production and pathology [19]. Consequently, optogenetics allowed establishing a direct causal link between hyperactivity and amyloid as well as tau pathology.

Recent and exciting work aimed to address the question of whether encoding or retrieval of memories is impaired in AD mice. Hippocampus plays a critical role in encoding and retrieval of episodic memories, which are disrupted in early stages of AD progression. Optogenetic activation of memory engrams restored memory retrieval in AD mice, suggesting that memory encoding was intact [20].

Additionally, efforts have been made to highlight the importance of neuronal oscillatory activity in the brains of AD patients. Oscillations take form of periodic and repetitive electrical activity generated by neurons. Gamma oscillations generated in the hippocampus are important during sharp-wave ripples. Disruptions in gamma waves have been reported in AD animal models prior to amyloid deposition [7]. Interestingly, restoration of gamma oscillations with light activation of Channelrhodopsin-2 resulted in decreased amyloid beta production and overall amyloid beta levels. Furthermore, normalization of gamma wave activity led to morphological changes in microglia [7]. Intriguingly, optogenetic stimulation at a random frequency failed to reduce amyloid burden in these mice. Thus, normal gamma oscillation activity is likely to prevent pathological AD advancement.

Another form of oscillatory activity that has been implicated in AD pathogenesis is slow wave activity. Slow oscillations important for consolidation of memories during sleep are disrupted in early stages of AD in humans [4]. Animal studies have recapitulated these disruptions [5,6]. However, it was unclear whether slow wave activity disruption is an epiphenomenon of AD progression or slow waves play an active role in AD pathogenesis. To address this question, slow oscillations were rescued with light activation of Channelrhodopsin-2 and determined that it halted amyloid plaque deposition and restored calcium homeostasis, which is disrupted in AD [6]. Thus the normal activity of slow oscillations is crucial to prevent AD progression. Therefore, amyloid impairs neuronal circuits, such as those generating gamma and slow oscillations, while disruptions in oscillatory activity further exacerbate amyloid aggregation, resulting in a vicious feedback loop that ultimately leads to breakdown of neuronal networks.

In addition to shedding light onto the mechanisms of AD progression, use of optogenetics can provide insight into the best strategies aimed to tackle neuronal activity disruptions in AD patients. Use of noninvasive brain stimulation methodologies, such as Transcranial Magnetic Stimulation (TMS) and transcranial direct current stimulation (tDCS) have shown great promise in treatment of Parkinson's disease and neuropathic pain among other disorders. These tools provide promising venues for future treatment options for AD patients. However, it will be important to determine the stage of the disease progression at which these treatments will be most effective. Also the patterns of stimulation and the specific brain regions targeted will have to be carefully selected to maximize benefit to risk ratio. Use of optogenetics in animal models of AD will provide great insight into these questions that will help streamline clinical trials using TMS and tDCS.

In conclusion, neuronal activity disruptions comprise an early event and an integral part of the progression of AD. Use of optogenetics has supplied a valuable tool to investigate the pathology and progression of AD as well as the potential to provide insight into the design of treatments intended at restoring neuronal activity disruptions.

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