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Berkeley Scientific Journal

Title

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Permalink

<https://escholarship.org/uc/item/42j5c473>

Journal

Berkeley Scientific Journal, 30(1)

ISSN

1097-0967

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Publication Date

2026-10-30

DOI

10.5070/BS3.69918

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Enlightenment: Understanding Alzheimer's Disease

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AN OVERVIEW

Age and death are defining variables of life, and for many, the transition from living to dying is the slow deterioration of physical and cognitive abilities. Memory is one of the most noticeable features of cognitive decline and is often associated with neurodegenerative diseases. In fact, over 57 million people worldwide are living with dementia 6, and more than seven million Americans are living with a certain type of dementia known as Alzheimer's disease. Conducting extensive research regarding the origins of the disease is not only an ambitious journey, but an essential one should cures be discovered. In recent years, optical methods have been utilized to illuminate the pathology of Alzheimer's disease. These approaches combine genetic techniques with light to control the activity of specific brain cells, allowing scientists to observe how harmful biostructures form in the brain. As a result, optogenetics has emerged as a promising tool for the future of neurological research.

THE PROGRESSION OF ALZHEIMER'S DISEASE

To understand the implications of optogenetics, it is important to be familiar with the diagnostic components of Alzheimer's disease. By definition, the disease involves the gradual decline of memory through the slow death of neurons, otherwise known as brain cells. A decrease in neuronal count compromises both the cognition and be-

havior of a person, culminating in the symptoms that heavily characterize Alzheimer's disease. Many people associate Alzheimer's disease with age, and while this tends to be true, the chronic origin of the disease begins far earlier than previously understood. From beginning to end, an individual with Alzheimer's disease experiences seven stages of decline.

The first stage of Alzheimer's disease is

considered baseline. The person in question is healthy and can comprehend and remember information in an organized fashion.²

The second stage is characterized by subjective memory loss, where cognitive ability becomes unstable.² As semantic information becomes lost, simple facts like the capital of the state where someone grew up or the name of a fruit become difficult

7 STAGES OF DEMENTIA						
		MEMORY IMPAIRMENTS	SPEECH IMPAIRMENTS	PHYSICAL IMPAIRMENTS	BEHAVIORAL IMPAIRMENTS	EMOTIONAL IMPAIRMENTS
STAGE 1 No Dementia <i>No cognitive decline</i>	Normal cognitive functioning	No noticeable signs of memory loss	No loss of cognitive skills	Can continue working and maintaining normal activities	None	None
STAGE 2 No Dementia <i>Very mild cognitive decline</i>	Symptoms not noticed by loved ones or doctor. Mild behavioral changes associated with aging	Forgetting where they placed items	Trouble finding the right words	Can continue working and maintaining normal activities	Mild behavioral changes associated with aging	Normal behavioral changes associated with aging
STAGE 3 No Dementia <i>Mild cognitive decline</i>	Loved ones begin to notice. Consult healthcare provider for evaluation	Increased forgetfulness. Trouble remembering names of people they just met	May have difficulty finding right words	Decreased work performance. Still able to go to bathroom, get dressed	Slight difficulty concentrating. May get lost more often	Increased frustration, irritability
STAGE 4 Early Stage <i>Moderate cognitive decline</i>	A physician can detect clear cognitive problems	Forgetfulness and misplaced items	Slowed speech	Gait impairment. Poor coordination	Depression. Lack of Personal Care. Collecting/Hoarding	Anxiety. Mood swings
STAGE 5 Mid Stage <i>Moderately severe cognitive decline</i>	Major memory deficiencies. Supervision required. Consider Assisted Living	Repeating themselves. Inability to do activities or read	Substituting words. Incomplete sentences	Parkinsonism. Clumsiness/falls. Poor coordination	Wandering. Delusion/Paranoia. Confusion	Anxiety. Agitation. Mood swings
STAGE 6 Mid Stage <i>Severe cognitive decline</i>	Full-time care needed	Unable to dress unassisted. No name recognition. Loss of spatial awareness	Incomprehensible speech	Visual impairment. Depth and contrast perception. Severely decreased motor skills	Wandering/Anxiety. Hallucinations/Paranoia. Sleep apnea	Apathy. Aggression
STAGE 7 Late Stage	Individuals lose all mental abilities	No short-term memory. Some long-term memory if any	Gibberish speech	Incontinence. Rigor mortis. Difficulty eating	Wandering	Agitation. Mood swings

Figure 1: A chart delineating the seven stages of dementia. Each stage leads to the regression of an individual's memory, speech, physique, behavior, and emotional well-being.

to recall.

At stage three, the patient has mild cognitive impairment. It is difficult for them to organize and concentrate on critical information and activities. In the workforce, job performance tends to suffer due to poor execution of hard skills. Individuals in this stage often have elevated stress levels.²

At stage four, moderate cognitive impairment settles in, otherwise known as dementia. A person with dementia will struggle to complete activities of daily living such as changing clothes, preparing meals, or keeping a clean living space.² As a result, external assistance is needed in the home.

At the fifth stage, moderately severe cognitive decline occurs.² Individuals are unable to recall current information, such as recounting the events of their day. Additionally, responsibilities such as paying bills or making critical decisions that require contextual interpretation cannot be executed.

Stage six is composed of multiple parts—largely because the time during which a person may suffer from moderately severe dementia is subject to sporadic change.² An individual will require constant assistance with activities of daily living, especially personal hygiene. These patients will have a difficult time verbally communicating, often stuttering or inventing new vocabulary.

At the last and seventh stage of Alzheimer's disease, the brain is incapable of coherent communication, and the body begins to shut down. Individuals lose the bulk and strength of their muscles, and many succumb to pneumonia or other infections as the body's immune system weakens.²

A vast and diverse range of symptoms encapsulate the progression of Alzheimer's disease. Therefore, a research strategy like optogenetics is necessary to learn more about the underlying mechanisms of the illness.

THE BIOLOGY OF ALZHEIMER'S DISEASE

Alzheimer's disease begins in the region of the brain responsible for memory recollection: the hippocampus. The symptoms of the disease progress upon the abnormal increase of two key proteins, amyloid-beta and tau. An excess of amyloid-beta leads to plaque accumulation around and between neurons. This disrupts cell signaling and triggers a cascade that promotes the expanse of tau, a protein normally responsible for stabilizing the microtubules that

provide structural support to neurons.⁵ Within the neuron, tau becomes hyperphosphorylated, meaning kinase enzymes add excessive phosphate groups to the protein. As a result, tau detaches from the microtubules, misfolds, and fuses as neurofibrillary tangles.⁵ The combined buildup of amyloid-beta plaque and neurofibrillary tangles ultimately impairs neural communication and leads to progressive memory loss.

HOW OPTOGENETICS WORKS

Through harnessing optogenetics, researchers can learn more about the biochemical mechanisms of Alzheimer's disease and its progression. Optogenetics is an experimental research technique that uses light-sensitive proteins called opsins to precisely control the activity of neurons.¹ To introduce opsins into neural cells, researchers employ viral vectors that deliver the genes into neurons.³ Once genetically expressed, the newly produced opsins can be activated by blue and green light. When researchers shine blue light on these engineered neurons, an opsin called channelrhodopsin is triggered. This causes an influx of positively charged ions to rush into the neuron, thus inducing electrical excitation. On the other hand, green light triggers the opsin halorhodopsin, resulting in an influx of negatively charged ions, which has an inhibitory effect on the neuron. The capacity to manipulate neuronal activity makes optogenetics a powerful tool to explore Alzheimer's disease at a biochemical level.¹

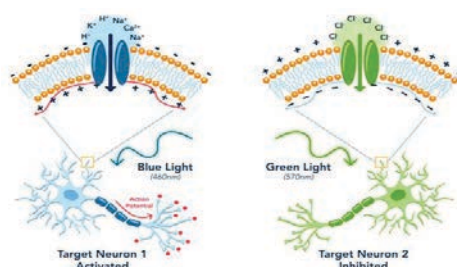


Figure 2: An image of the effect of light on neurons. In optogenetics, blue light excites and activates neurons, while green light inhibits neurons.

MODULATING NEURONS WITH LIGHT

Based on experimental findings, the ability to enable light-based modulation of neuronal activity has helped researchers

understand the pathology of Alzheimer's disease. In one study, scientists manipulated cholinergic neurons. These neurons are found in the cortex of the basal forebrain and are integral for memory, learning, attention, and motor function.³ CPBPGs, a specific subset of cholinergic neurons, regulate gamma-band oscillations (GBOs)—rhythms generated by the interaction of excitatory and inhibitory neurons previously discussed.³ When CPBPGs malfunction, GBOs slow, and working memory diminishes, as seen in many Alzheimer's patients. In a brain full of harmful biostructures like amyloid-beta plaques, the effect of a faulty cholinergic system is only amplified.³ By varying the activity levels of cholinergic neurons with light, the brain's ability to create and rearrange synaptic pathways is compromised.³ CPBPGs stimulated in the cortex lead to an increase in GBOs, ultimately improving memory. By contrast, inhibiting CPBPGs decreases the level of GBOs, leading to impaired memory. Scientists continue to employ optical methods to modulate the rates of neuronal activity, providing insight into the complex processes underlying Alzheimer's disease.

RECREATING ALZHEIMER'S DISEASE WITH LIGHT

Examinations of the neurodegenerative abnormalities in Alzheimer's disease are ongoing, and such initiatives have entertained research with therapeutic intent. In one instance, scientists theorized that if plaque and tangled fibers can form under light therapy, the same structures might be reduced under a different wavelength of light⁵; in other words, if optogenetics can be used to create a visual progression of Alzheimer's disease, alleviating symptoms of the disease may be possible. When researchers combined the light-protein Cryptochrome 2 (CRY2) with amyloid-beta and a fluorescent marker called mCherry, then injected the conjugate into neural cells, the pieces of amyloid-beta oligomerized (joined together to form a larger compound) upon exposure to blue light. The resulting formation mimicked the plaque characteristic of Alzheimer's.⁵ The same optogenetic methodology has been conducted with tau to form pseudo-neurofibrillary tangles.⁴ Researchers realized that the degree of aggregation depends on light frequency and continue to explore how light-sensitive proteins enable amyloid-beta and tau aggregati

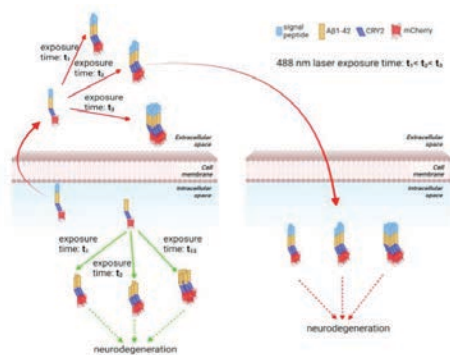


Figure 3: An image of varying amyloid-beta aggregation through light. Amyloid-beta levels are changed inside and outside of the cell upon CRY2's exposure to light.

THE LIGHT AT THE END OF THE TUNNEL

In summary, Alzheimer's disease is long and complicated. There are seven stages of memory loss, and a variety of other symptoms contribute to an individual's decline. Optogenetics, a gene therapy that uses light-sensitive proteins to control neurons, has been used to limit neuron communication and replicate neurofibrillary tangles and amyloid-beta plaque in the brain. By stimulating the recreation and growth of structures responsible for memory loss, scientists have opened the doors to a new realm of theory and understanding surrounding the complex pathology of Alzheimer's disease. In the end, it seems that the scientific application of light has revealed that the greater part of human discovery lies in the inquiry of our own fragility.

ACKNOWLEDGEMENTS

I would like to thank Linda Wilbrecht, a professor and researcher in the Department of Psychology at the University of California, Berkeley, for giving her time to provide expert feedback in support of this article.

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