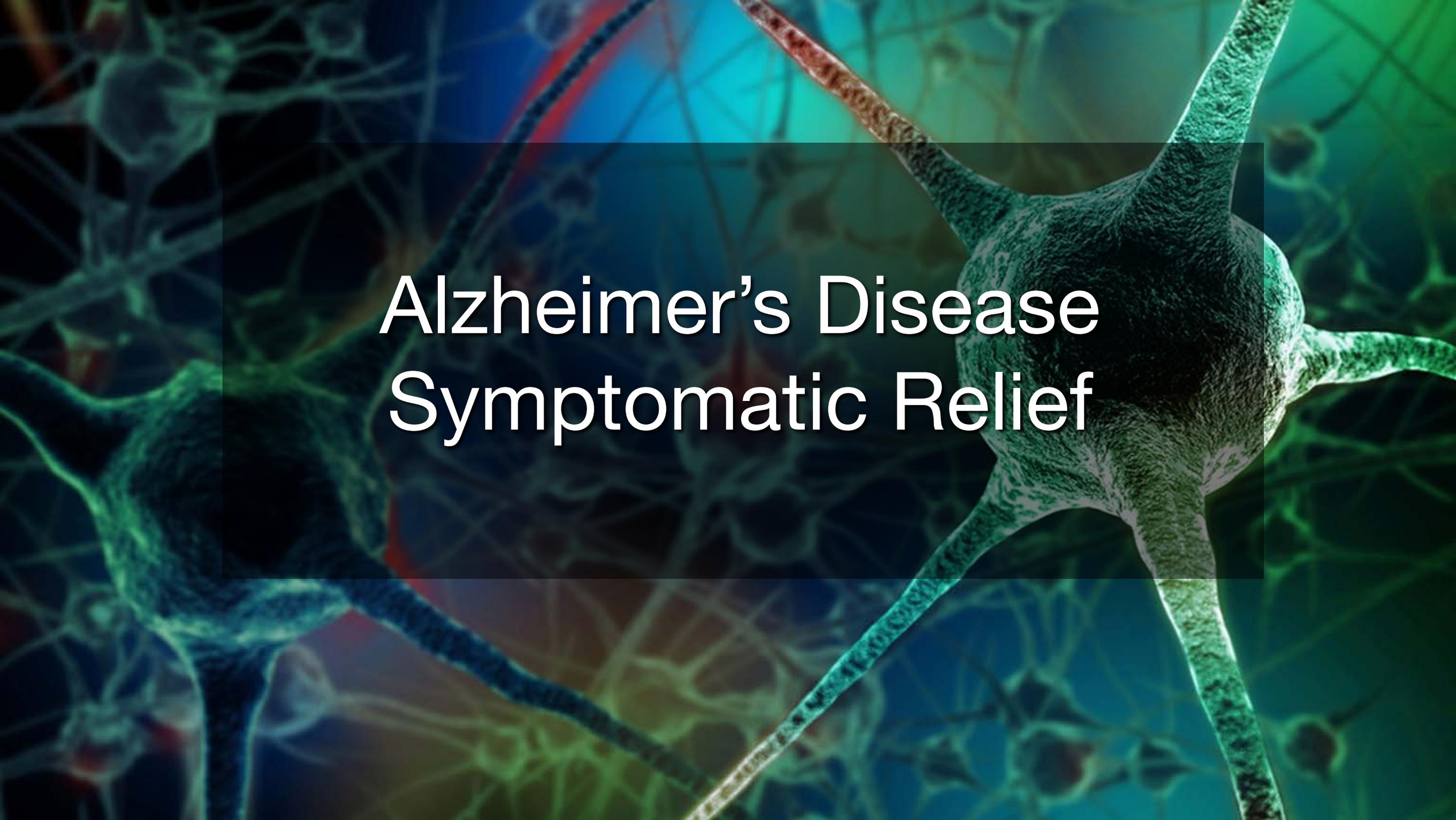




# COGNIGENICS

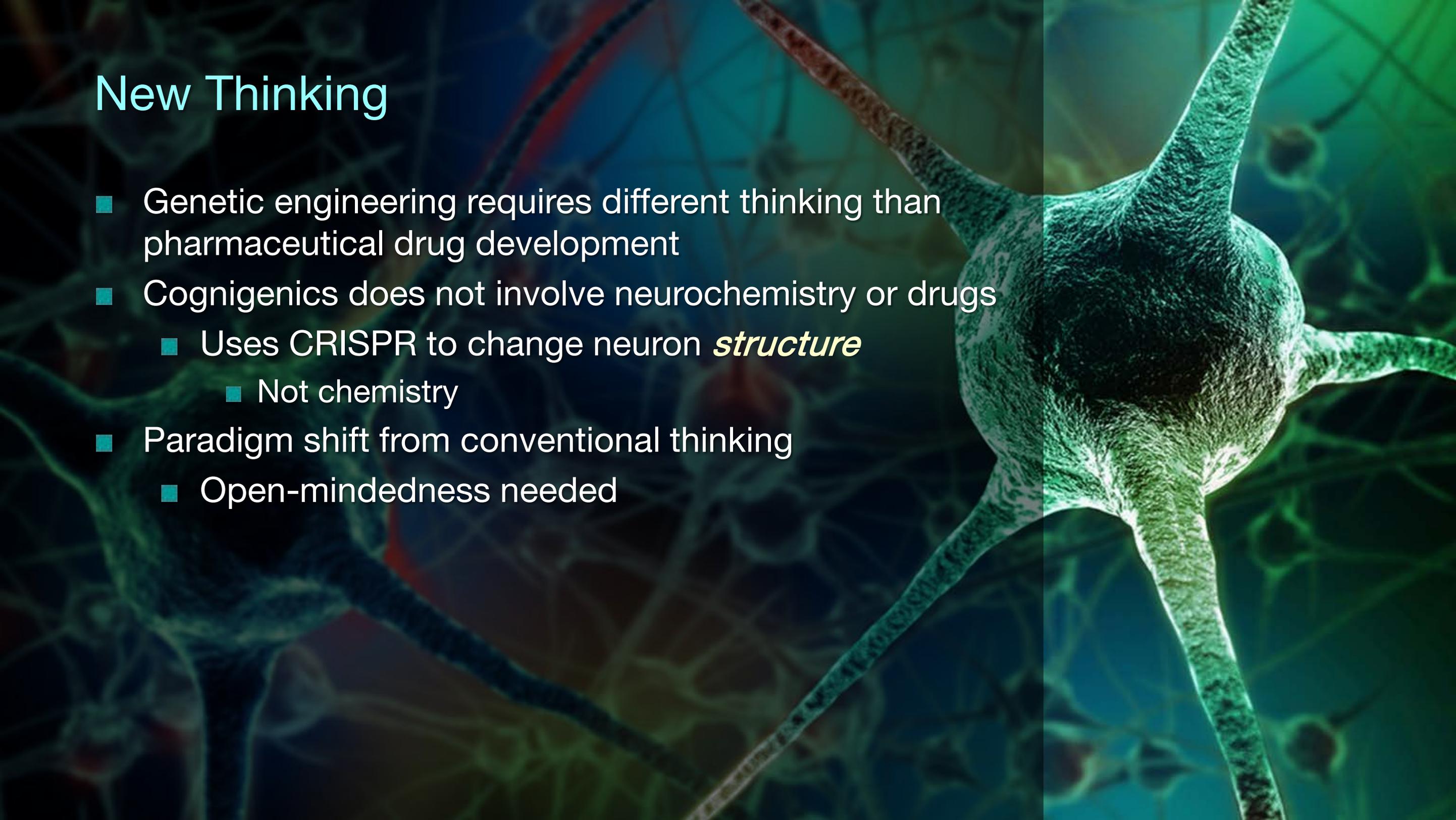
*Improving human cognition*

## Science Overview

A microscopic view of neurons, showing their cell bodies and branching processes. The image is rendered in a dark, teal, and blue color palette, giving it a scientific and somewhat ethereal appearance. The neurons are interconnected, forming a complex network. A semi-transparent dark rectangle is overlaid in the center, containing the text.

# Alzheimer's Disease Symptomatic Relief

# New Thinking

A microscopic image of neurons, showing a large central cell body with several long, thin processes extending outwards. The image is overlaid with a green, semi-transparent grid or mesh pattern, giving it a digital or scientific appearance.

- Genetic engineering requires different thinking than pharmaceutical drug development
- Cognigenics does not involve neurochemistry or drugs
  - Uses CRISPR to change neuron *structure*
    - Not chemistry
- Paradigm shift from conventional thinking
  - Open-mindedness needed

# Novel Approach

- Target symptomatic relief
  - Much simpler than cure
- Modify neuron performance with CRISPR to enhance cognition
- Edit RNA to reduce gene expression (1)
  - No changes to genome
- RNA editing approach for treating Alzheimer's validated by Feng Zhang
  - Broad Institute at Harvard / MIT in July, 2019 (2)
  - “REPAIR” system uses Cas13 RNA editor
  - Targets different gene but uses same mechanism

(1) IP covers all CRISPR flavors. Currently Cas13 for RNA is preferred.

(2) <https://www.fiercebiotech.com/research/crispr-pioneer-zhang-targets-brain-diseases-new-rna-editing-system>

# Alzheimer's Symptomatic Relief Strategy

- Reduce stress
  - Promote alpha frequency brainwaves
    - Induce relaxation
- Sharpen mental acuity
  - Increase theta frequency brainwaves
    - Enhance mental clarity
- Raise conscious attention
  - Lower brainwave activity
    - Expand available cognitive resources



# Alpha / Theta States

- Reduce AD risk factors
  - Lower hypertension, anxiety and stress
- Decrease cortisol levels
- Upregulate insulin pathway genes
- Slow down cognitive decline
- Ameliorate some Alzheimer's symptoms
- Enhance cognition
  - Improve mental acuity, focus, concentration, mindfulness and cognitive performance

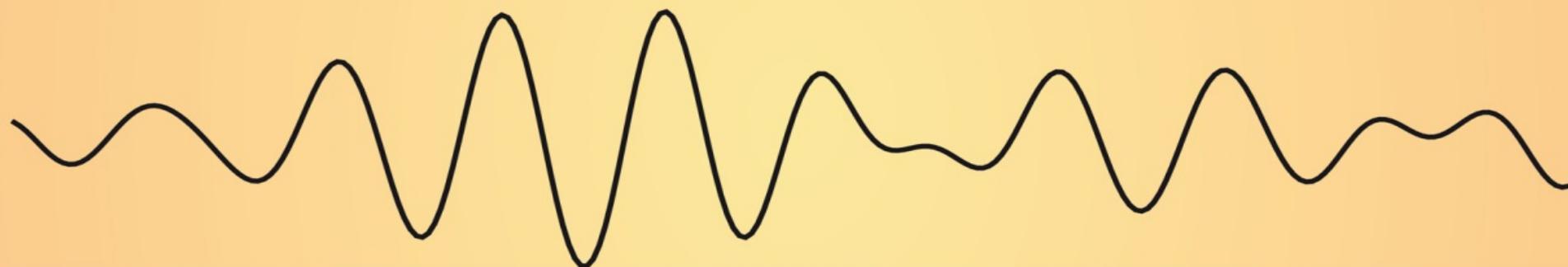
Source: Mindfulness and Meditation: Treating Cognitive Impairment and Reducing Stress in Dementia, Reviews in Neurosciences, Feb, 2018, Russell-Williams, et al

**BETA**  
16 - 30 Hz



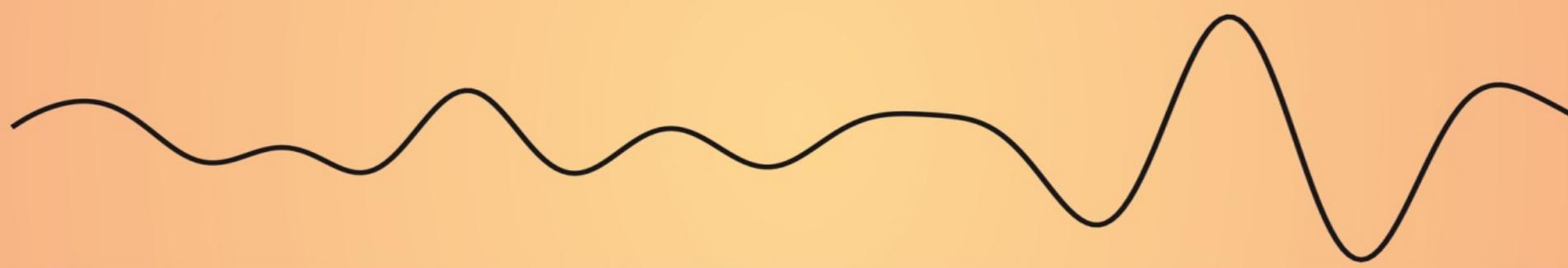
**Thinking**  
**Planning**  
**Analyzing**

**ALPHA**  
8 - 15 Hz



**Relaxation**  
**Reflection**  
**Peaceful**

**THETA**  
4 - 7 Hz



**Awareness**  
**Clarity**  
**Memory**

**DELTA**  
0.1 - 3 Hz

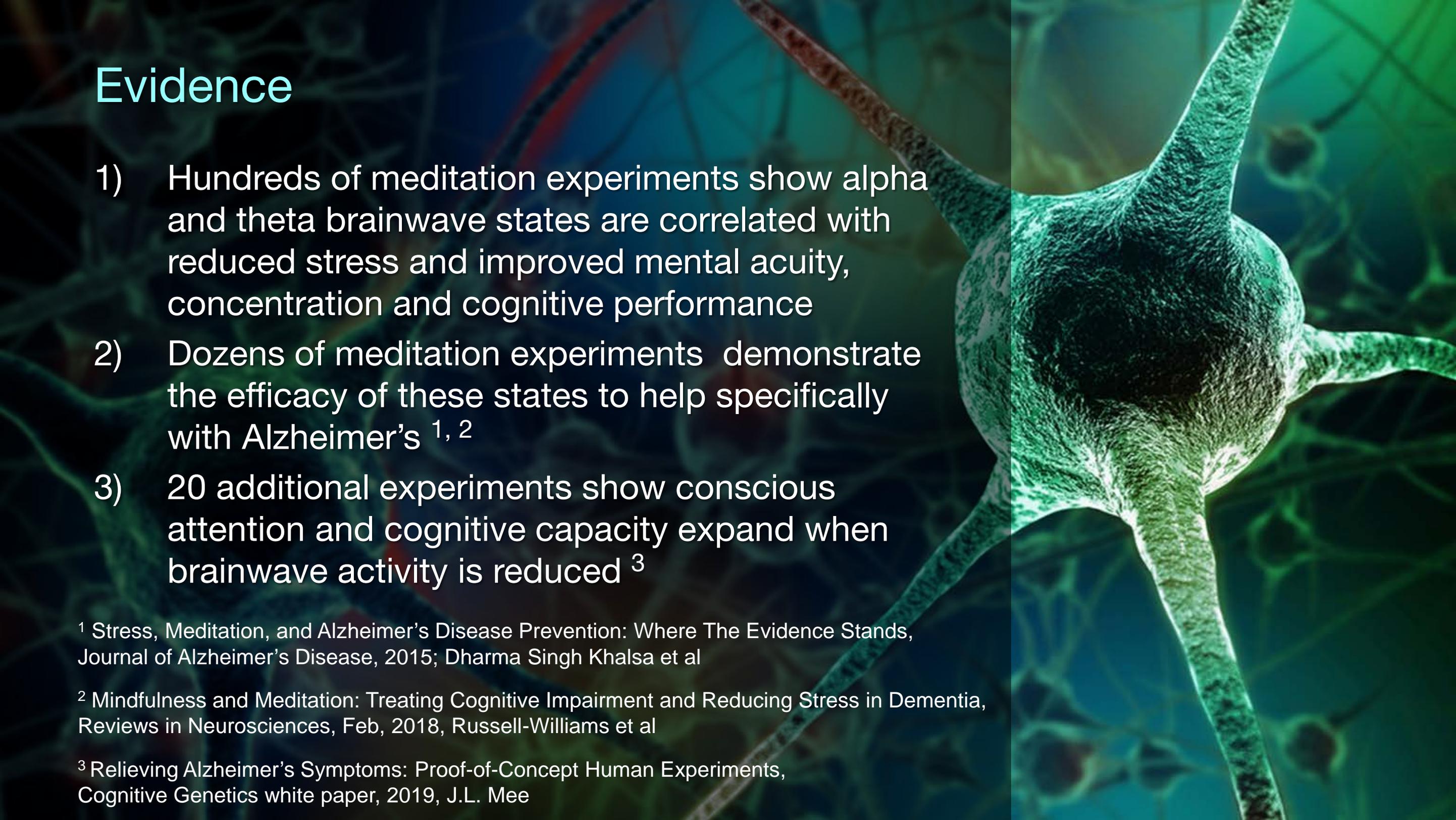


**Sleep**  
**Healing**

0.0                      0.2                      0.4                      0.6                      0.8                      1.0

*(Seconds)*

# Evidence



- 1) Hundreds of meditation experiments show alpha and theta brainwave states are correlated with reduced stress and improved mental acuity, concentration and cognitive performance
- 2) Dozens of meditation experiments demonstrate the efficacy of these states to help specifically with Alzheimer's <sup>1, 2</sup>
- 3) 20 additional experiments show conscious attention and cognitive capacity expand when brainwave activity is reduced <sup>3</sup>

<sup>1</sup> Stress, Meditation, and Alzheimer's Disease Prevention: Where The Evidence Stands, Journal of Alzheimer's Disease, 2015; Dharma Singh Khalsa et al

<sup>2</sup> Mindfulness and Meditation: Treating Cognitive Impairment and Reducing Stress in Dementia, Reviews in Neurosciences, Feb, 2018, Russell-Williams et al

<sup>3</sup> Relieving Alzheimer's Symptoms: Proof-of-Concept Human Experiments, Cognitive Genetics white paper, 2019, J.L. Mee

# CRISPR Strategy

- Use CRISPR to lower neuron excitability
  - Slow down brain currents
  - Shift brainwaves into lower frequencies
    - Alpha and theta bands
- Reduced brainwave activity enhances cognitive capacity
  - Counterintuitive but experimentally verified <sup>1</sup>
- Help relieve symptoms of Alzheimer's

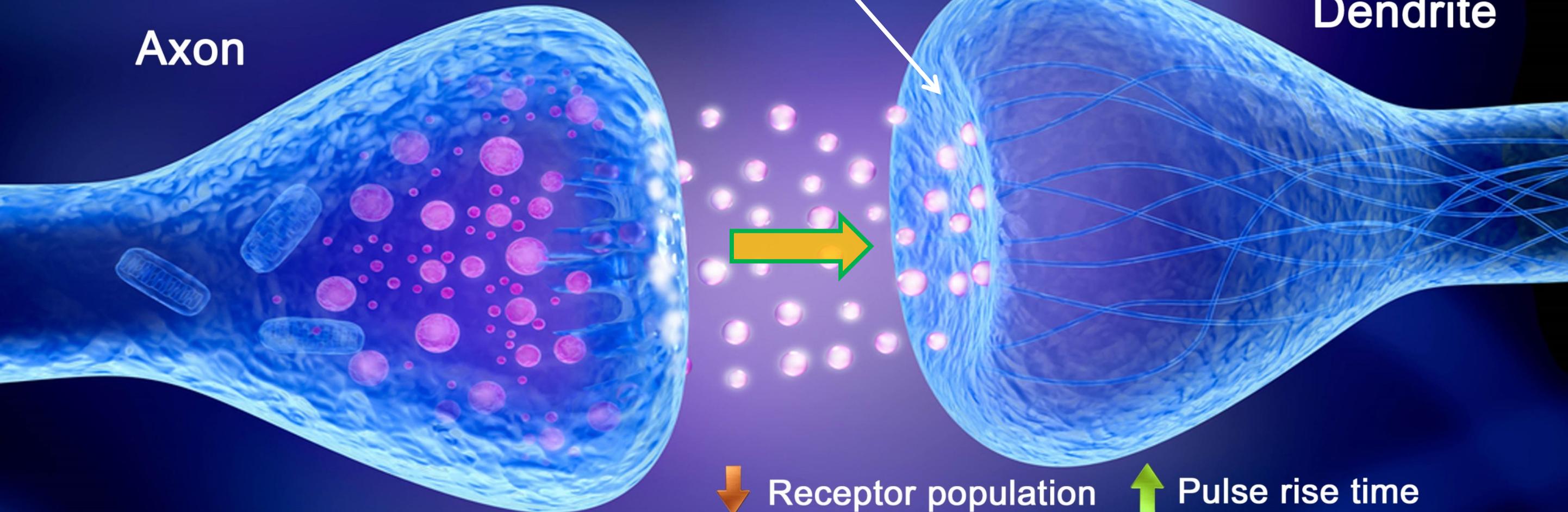
<sup>1</sup> Refer to "Evidence" slide

# Mechanism of Action

CRISPR instructs neuron to build fewer receptors

Axon

Dendrite



- Lowering receptor population raises neural resistance
  - Fewer “doors” for current to enter neuron
- Higher resistance lowers current flow, brainwave activity and frequency

↓ Receptor population  
↑ Electrical resistance  
↓ Neuron excitability

↑ Pulse rise time  
↓ Firing rate  
↓ Brainwave frequency  
↓ Brainwave activity

# Mechanism of Action

- Human experiments show attention, focus and cognitive capacity expand when brainwave activity is attenuated <sup>1</sup>
- Brainwave activity can be lowered by reducing the accompanying brain currents
  - Moving electrical currents generate electromagnetic waves <sup>2</sup>
- Brain currents can be decreased by raising neuron resistance
  - Higher resistance impedes the flow of electrical current <sup>3</sup>

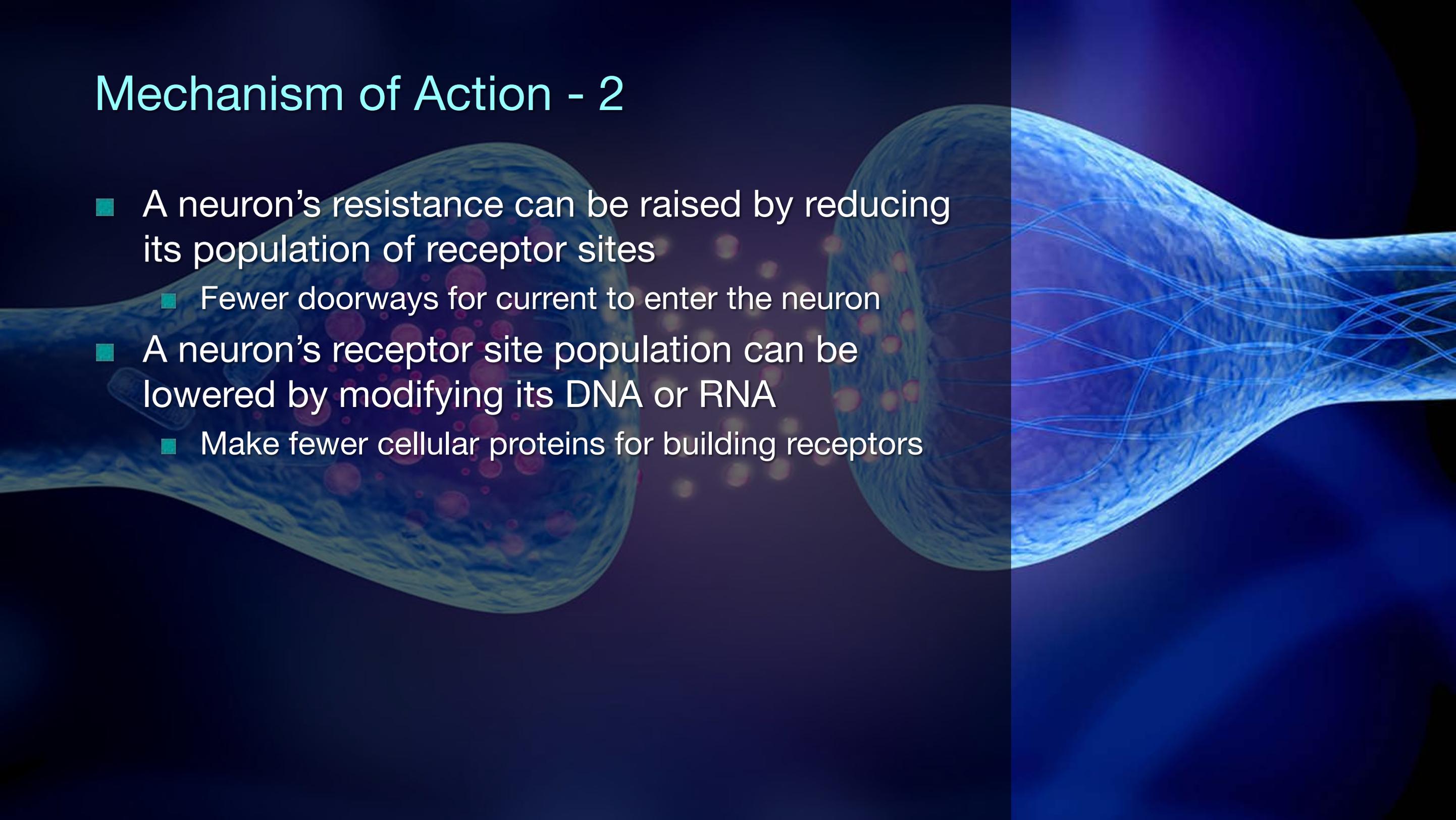
<sup>1</sup> Relieving Alzheimer's Symptoms: Proof-of-Concept Human Experiments, Cognitive Genetics white paper, 2019, J.L. Mee

<sup>2</sup> Ampere's Law

<sup>3</sup> Ohm's Law

## Mechanism of Action - 2

- A neuron's resistance can be raised by reducing its population of receptor sites
  - Fewer doorways for current to enter the neuron
- A neuron's receptor site population can be lowered by modifying its DNA or RNA
  - Make fewer cellular proteins for building receptors

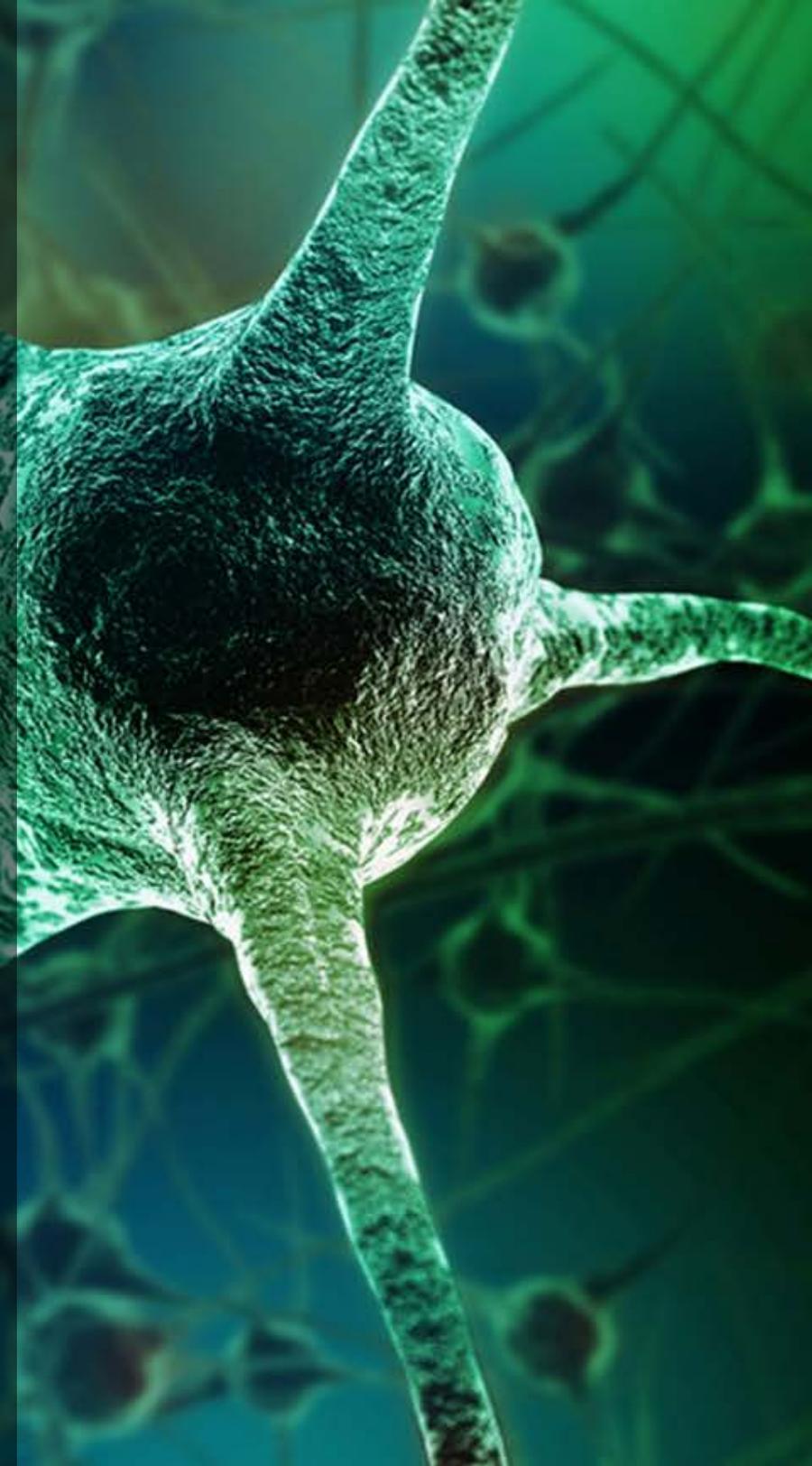


# Feasibility

- Over 30 published studies on CRISPR/Cas9 with AAV vectors *in vivo* genome editing in mice
- Max Planck Florida Institute for Neuroscience and University of Beijing have edited mice neurons *in vivo* with CRISPR
- CRISPR – AAV experiments demonstrated precise editing in mature mouse neurons *in vivo*
  - Regardless of cell maturity, brain region or age
  - AAV virus provides donor template for homology-directed repair (HDR)
- Tested well in an aged Alzheimer's disease mouse model even at advanced ages

CRISPR interference-based specific and efficient gene inactivation in the brain, Yi Zheng et al Nature Neuroscience volume 21, 2018 (University of Beijing)

Virus-Mediated Genome Editing via Homology-Directed Repair in Mitotic and Post-mitotic Cells, Jun Nishiyama et al, Neuron, October 19, 2017 (Max Planck Institute)





# Therapeutic Treatment

# I. Slowing Dementia Progression

Cognigenics treatments can slow Alzheimer's and MCI progression in 3 ways:

## 1. Reducing stress

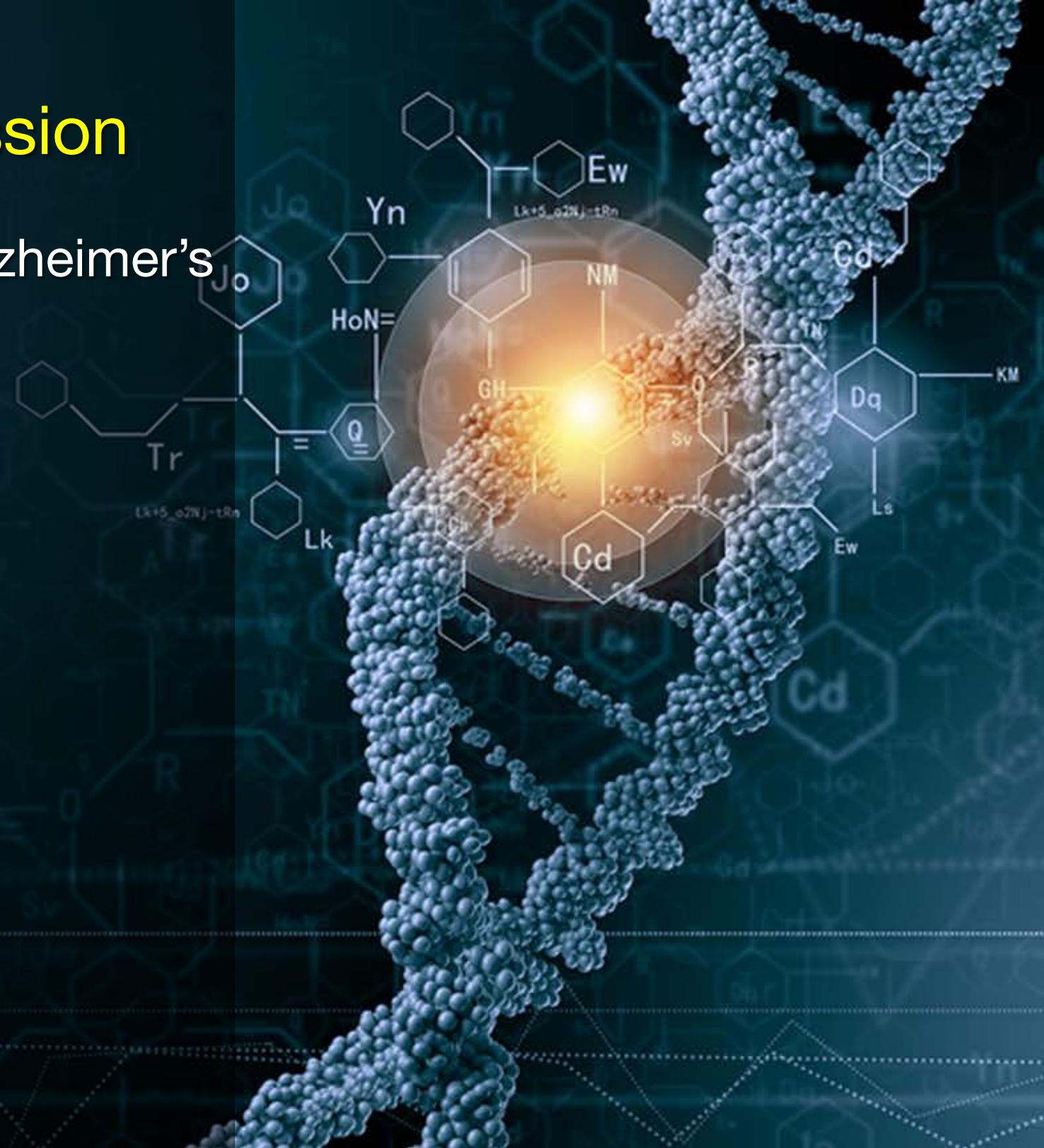
- Lower cortisol and inflammation

## 2. Promoting longevity

- Foster healthier neuronal activity

## 3. Halting AD & MCI progression

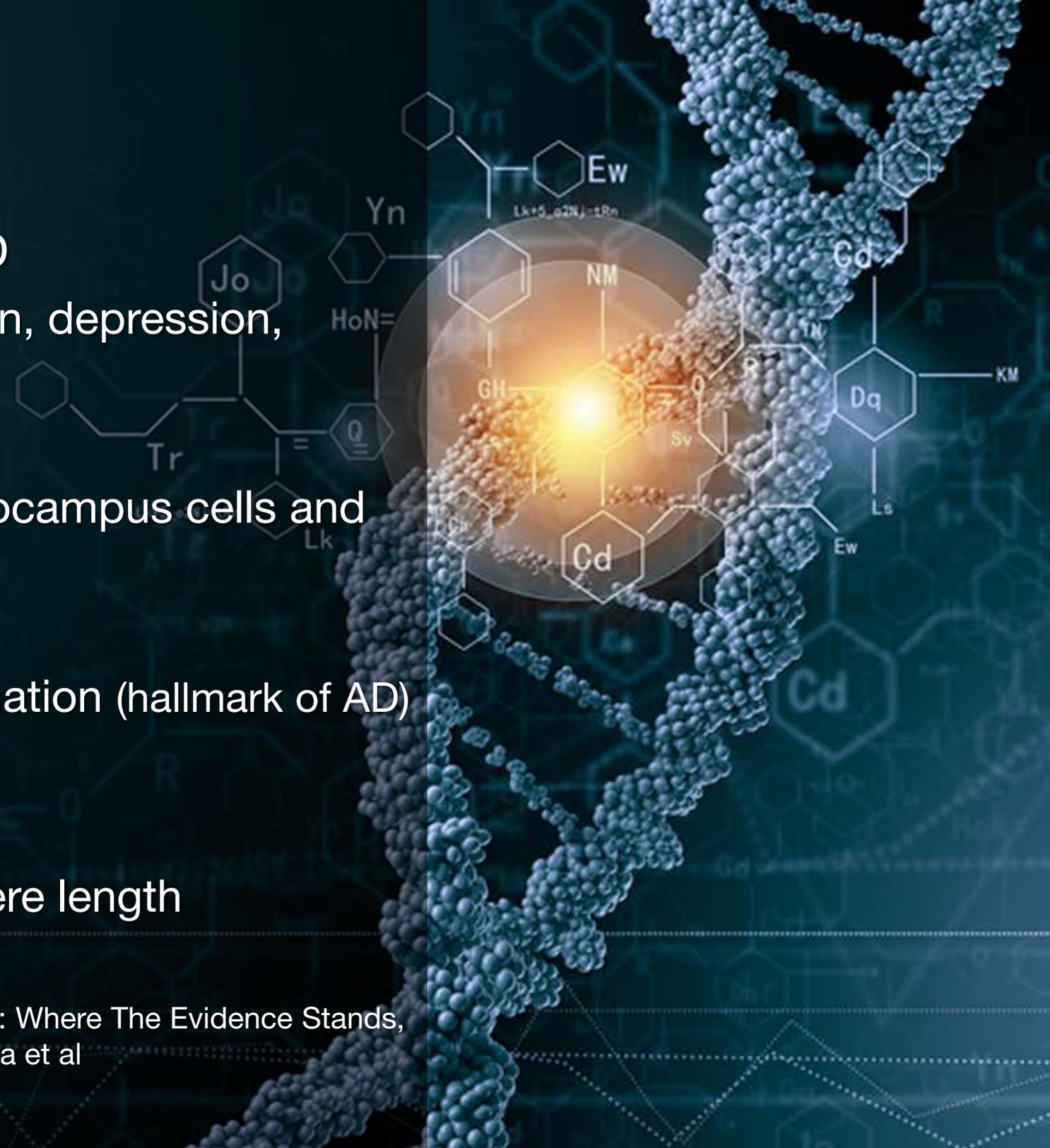
- [Unpublished technology]



# 1. Reducing Stress

- Mitigates multiple risk factors for AD
  - Inflammation, calcium dysregulation, depression, anxiety, insomnia, inactivity
- Lowers cortisol levels
  - Avoids neurotoxic damage to hippocampus cells and other neurons
- Decreases inflammatory mediators
  - Prevents widespread brain inflammation (hallmark of AD)
  - Especially in the hippocampus
- Improves genetic health
  - Raise telomerase levels and telomere length

Source: Stress, Meditation and Alzheimer's Disease Prevention: Where The Evidence Stands, Journal of Alzheimer's Disease, 2015; Dharma Singh Khalsa et al



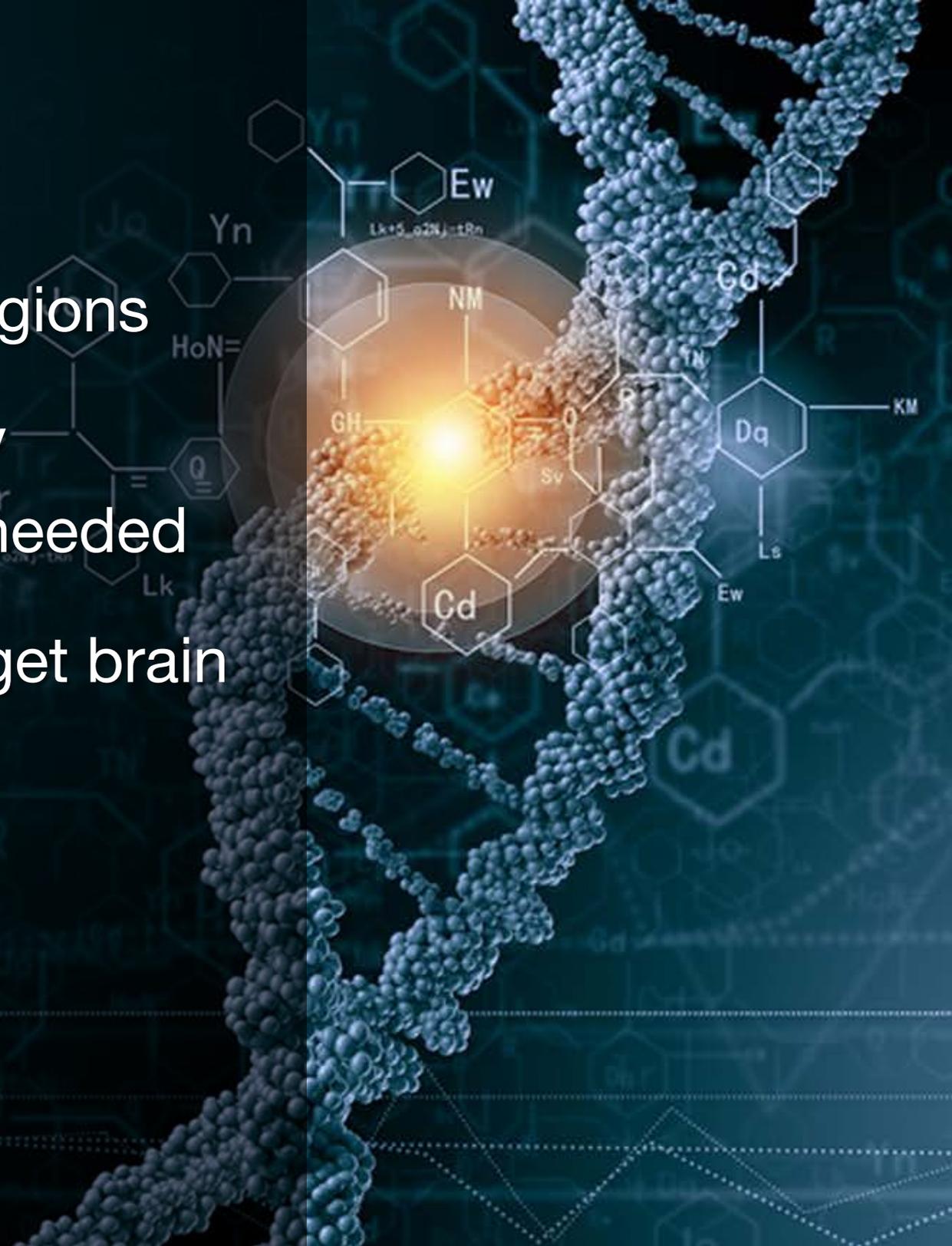
## 2. Promoting Longevity

- Cognigenics treatments will increase alpha and theta frequency brainwaves
  - Induce states of relaxation and cognitive clarity
- Method generates lower-frequency brainwaves by selectively decreasing neuronal activity
- Experimental evidence suggests reducing neuronal activity extends longevity



## II. Treating Neurological Disorders

- Caused by over- or under-active brain regions
- Crispr can normalize brain region activity
  - Raise or lower neuron excitability as needed
- CRISPR-T delivers Crispr to specific target brain regions as required by individual needs



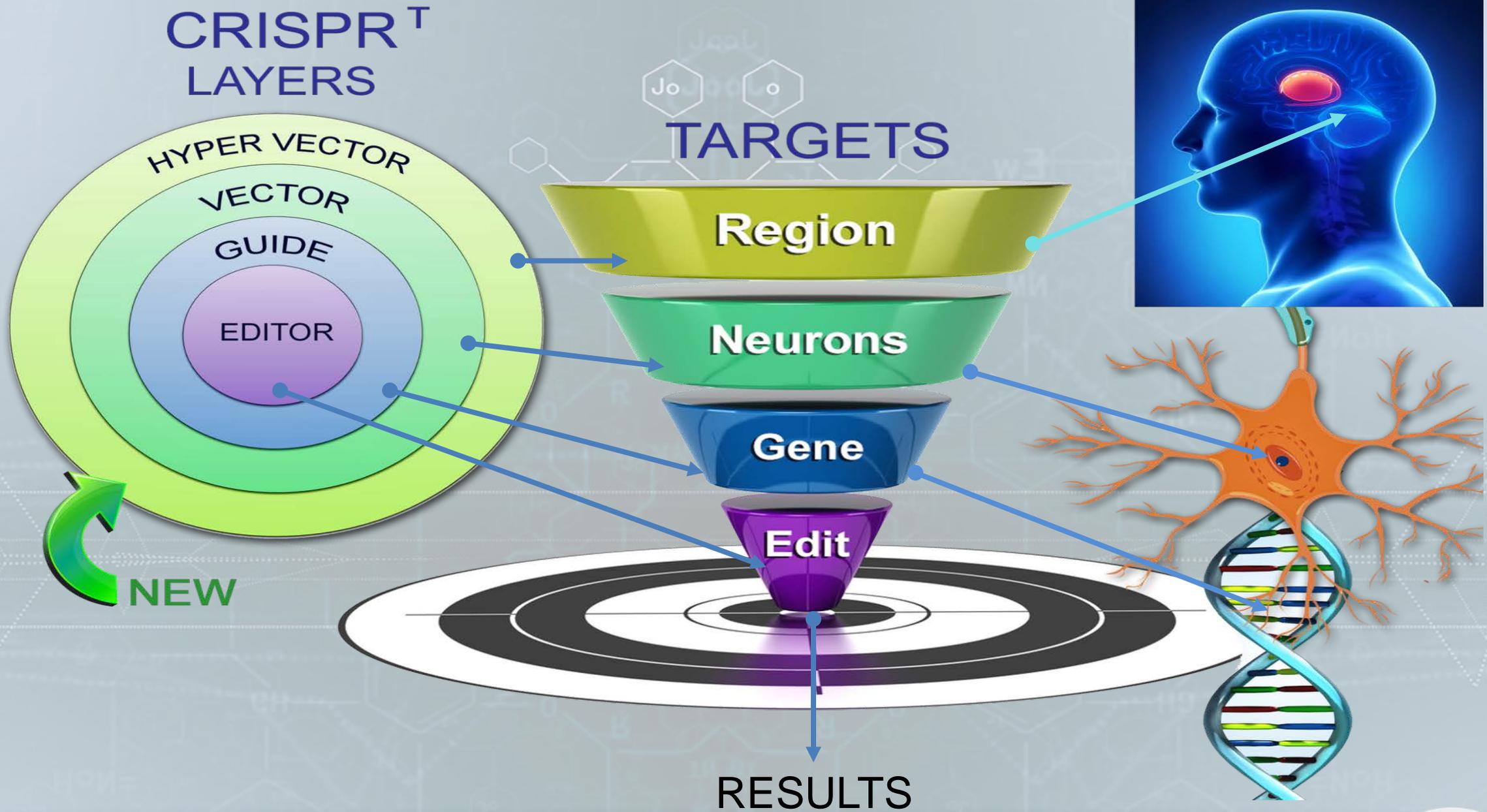
Treatable Neurological Condition	Regional Anomaly	
	Over-Active	Under-Active
Alzheimer's disease / MCI	Hippocampus	
ADD / ADHD	Dorsal attention and default mode networks	Amygdala, ventromedial prefrontal cortex, hippocampus
PTSD	Amygdala, hippocampus	Ventromedial prefrontal cortex
OCD	Orbital gyrus, caudate nucleus, dorsal anterior cingulate cortex	
Stress disorders	Amygdala, hypothalamus	
Anxiety	Amygdala	
Depression	Amygdala, hippocampus, anterior cingulate cortex	Posterior cingulate cortex, prefrontal cortex
Sleep issues	Prefrontal and parietal cortex, precuneus, anterior cingulate, mesial temporal, thalamus and hypothalamic arousal centers, default-mode network	
Memory concerns		Hippocampus, amygdala
Concussions		Frontal and temporal lobes
Psychosomatic issues	Amygdala, hippocampus	Ventromedial prefrontal cortex

# CRISPR-T

- New technology for delivering CRISPR biologics to any targeted brain region
- Enables hundreds of new CRISPR applications targeting specific brain areas
  - Treat neurological conditions
  - Enhance cognitive functions
- Highly flexible technology
  - Any form of CRISPR
  - Any neuron gene or RNA transcript
  - Any brain region

## CRISPR-T Components

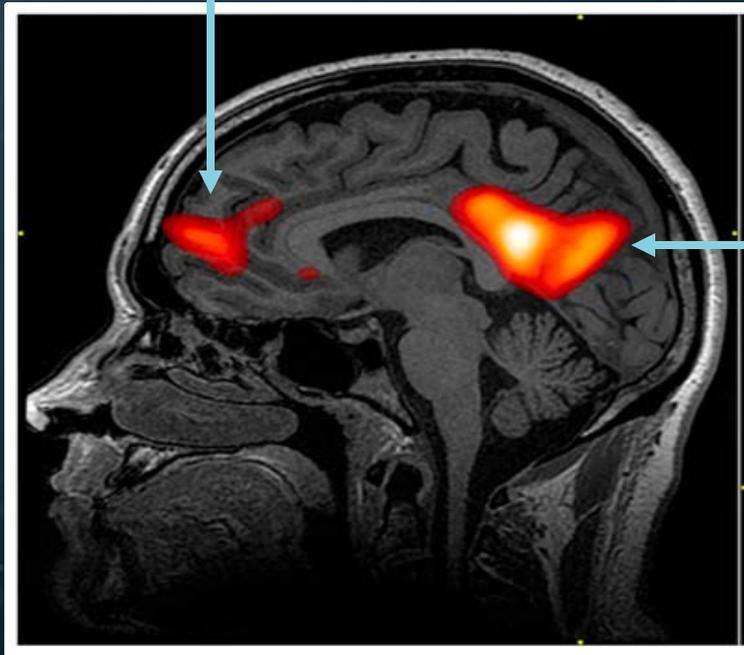




# Selective Activation Example

- Default mode network
- fMRI scan shows active areas

Medial prefrontal cortex



Posterior cingulate cortex



# Risk Mitigation

- Prototype all treatments with RNA before committing to DNA
- Use gene silencing for DNA edits
  - Not knockout
  - Reversible



# Conclusions

- Opportunity to improve millions of lives
- Innovative, unique new approach
- No known competition
- Patents pending
- Low R&D costs
- Large market
- Manageable risks
- Significant rewards
- Fast results



# Contact

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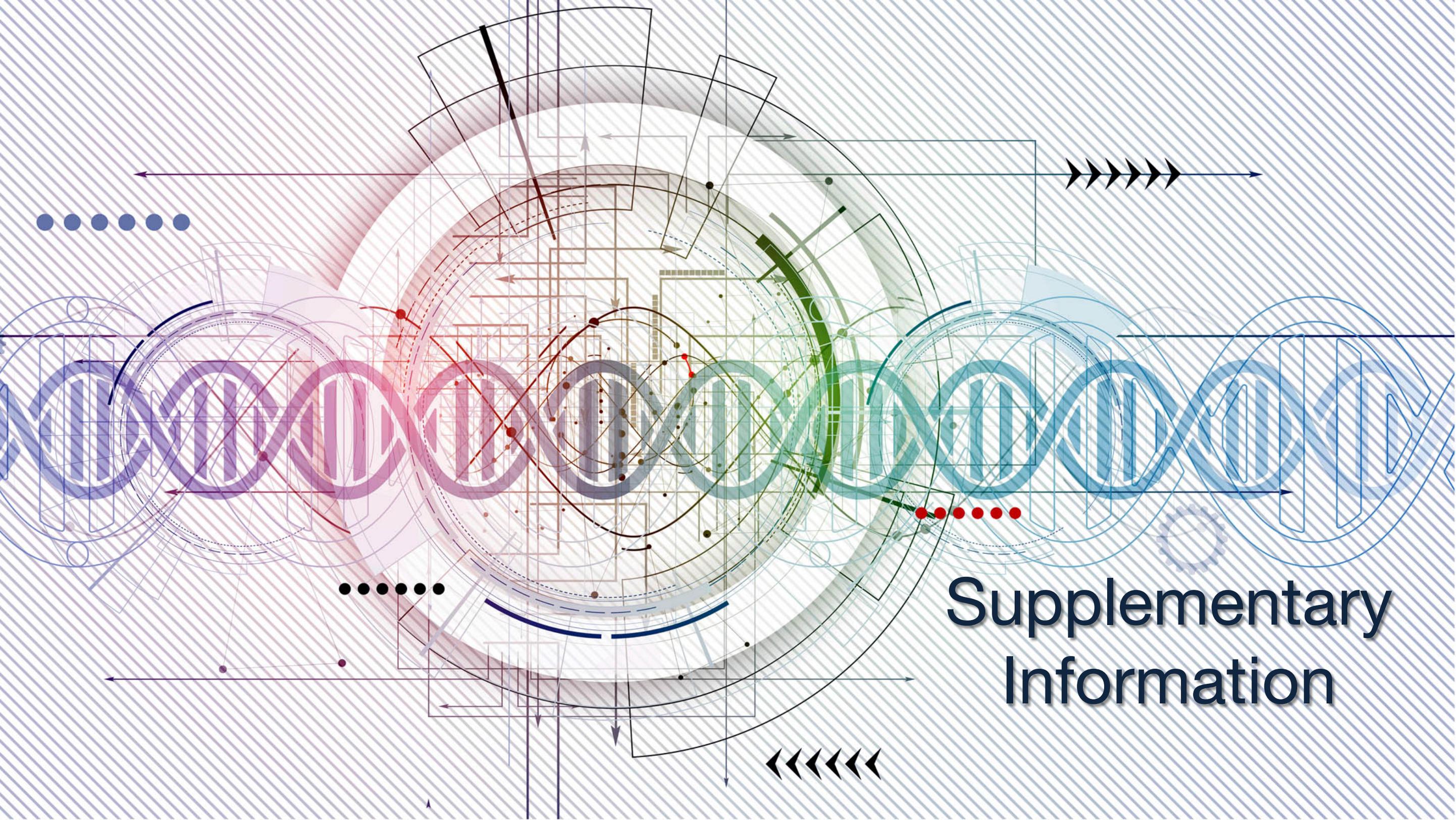
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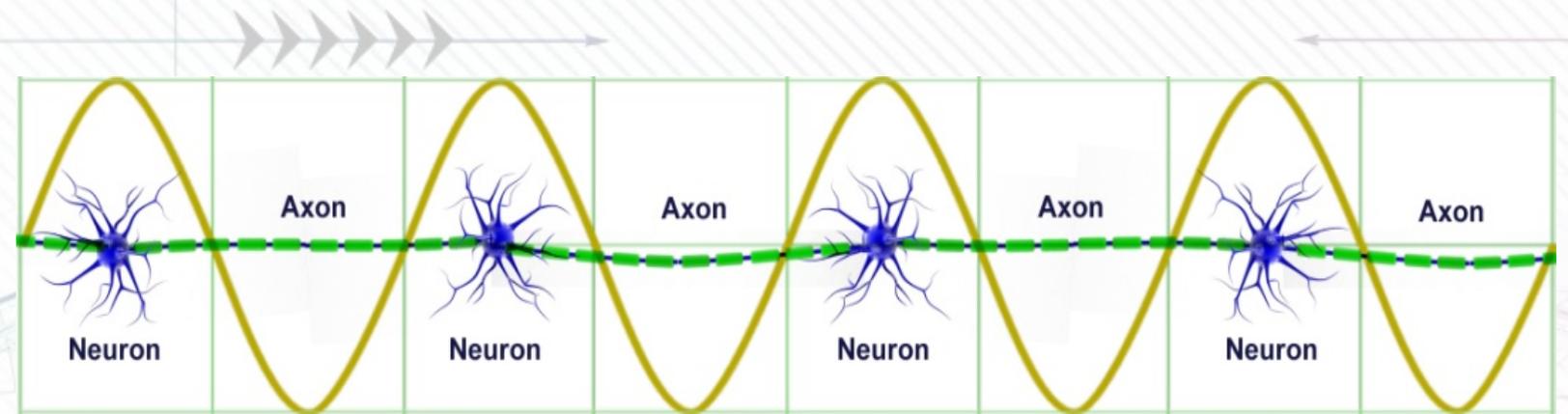
**Supplementary  
Information**

# Meditation Experiments

- Meditation works by calming down brainwaves
  - Slowing frequency from *beta* to *alpha* and *theta*
- Benefits claimed for meditation are actually the result of alpha and theta states
- Meditation is merely a set of practices and techniques for generating lower frequency brainwaves
- *These calmer brainwave states are the active agent of physiological change.*

# Neuron Level Brainwaves

## “Neurowaves”



- Electrical currents moving through the brain generate cellular-level brainwaves
- Reducing the flow of brain currents lowers brainwave frequency and activity

Source: *Electrophysiology of the Neuron*, Huguenard and McCormick, Oxford University Press, 1994



# Reducing Stress and Enhancing Cognitive Clarity

- Neurons with higher resistance take more time to excite
  - Lowers their activity per second (frequency)
- Lower neuron activity per second shifts overall brainwave activity
  - Out of higher “beta” frequencies
  - Into lower “alpha” and “theta” frequency bands
- Alpha frequency brainwaves characterize relaxation
  - Experimentally proven to lower stress in Alzheimer’s patients <sup>1</sup>
  - Mitigates symptoms and promotes brain health
- Theta frequency brainwaves signify states of enhanced cognitive clarity
  - Ameliorates Alzheimer’s symptoms <sup>1</sup>

<sup>1</sup> Mindfulness and Meditation: Treating Cognitive Impairment and Reducing Stress in Dementia, Reviews in Neurosciences, Feb, 2018, Russell-Williams et al



# Cognitive Enhancement

General-purpose cognitive boost is also feasible

- Raise conscious awareness
- Decrease inattention
- Reduce mind-wandering
- Lower craving
- Sharpen mental focus and concentration
- Enhance mindfulness and meditation
- Turbocharge cognitive behavioral therapy
- Promote desired behaviors
- Mitigate unwanted behaviors
- Alleviate cognitive impairment symptoms
- Raise creativity, imagination and ESP