



COGNIGENICS

**New Approaches For
Treating Alzheimer's Symptoms
Science Overview**

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Research Objectives

- Treat Alzheimer's symptoms
 - Lucidity, clarity, focus, mental acuity, attention, memory (short/intermediate)
- Produce a safe and effective treatment with no known side effects
- Aim to achieve proof of concept quickly at minimum cost
- Use state-of-the art technology

New 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

(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>

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 ^{1, 2}
- 3) 20 additional experiments show conscious attention and cognitive capacity expand when brainwave activity is reduced ³

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

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

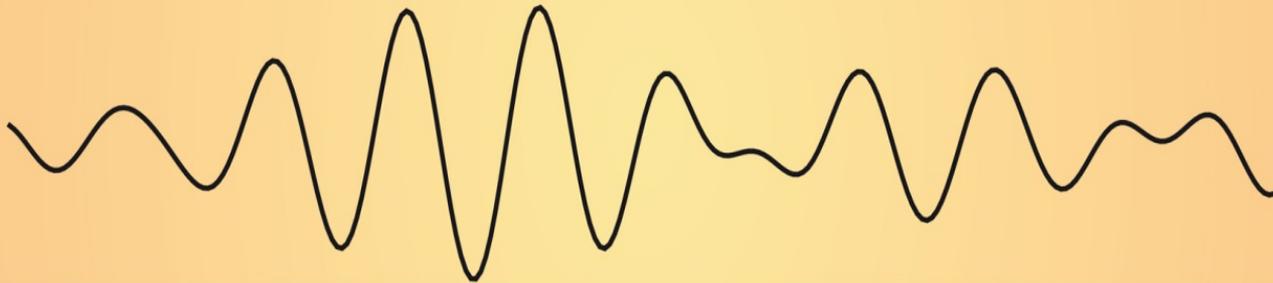
³ Relieving Alzheimer's Symptoms: Proof-of-Concept Human Experiments, Cognitive Genetics white paper, 2019, J.L. Mee

BETA
16 - 30 Hz



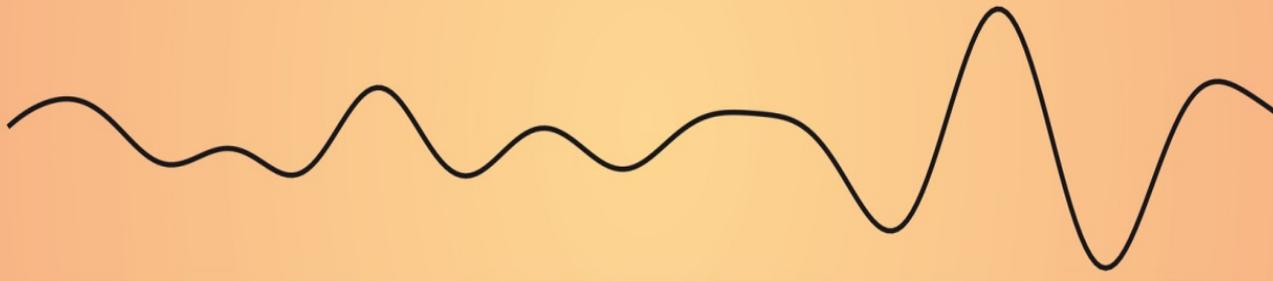
Thinking
Planning
Analyzing

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)

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

AD Symptom 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

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 ¹
- Help relieve symptoms of Alzheimer's

¹ Refer to "Evidence" slide.

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)

Roadmap

Stage	Edit Type	Target	Current Tools	Effect	Remarks
Preclinical	Gene knockout	DNA	CRISPR Cas9	Permanent	Lowest cost way to demonstrate mechanism of action
Preclinical	RNA interference	RNA	CRISPR Cas13	Temporary	
Human	RNA interference	RNA	CRISPR Cas13	Temporary	Safest method for first human trials
Preclinical	Gene silencing	DNA	CRISPR dCas9	Permanent / Reversible	
Human	Gene silencing	DNA	CRISPR dCas9	Permanent / Reversible	Final product

Note: The roadmap mentions specific CRISPR tools for purposes of illustration. The field is moving so fast that by the time preclinical studies are complete and human trials begin, there will be a different set of tools than the ones we have today.

Conclusions

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



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Supplementary Information

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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.*

“Meditation Pill”

- Modify certain neurons to promote alpha and theta brainwave activity
- Generate cognitive advantages similar to those proven for meditation
 - But on a greater scale
- Deliver sustainable results throughout the day
 - Not just for 20 minutes

Pill Ease of Use

- Generate consistent, reproducible effects across a wide population
 - Regardless of concentration skills
- Patients effortlessly brought into more relaxed and lucid states
 - Without time-consuming work of daily meditation practice
- Patients not required to develop proficiency in meditation
 - Difficult even for healthy individuals
 - Problematic for people facing cognitive challenges

Increasing Attention and Cognitive Resources

- 1) Human experiments show consciousness and cognitive capacity expand when brainwave activity is reduced ¹
- 2) Brainwave activity can be lowered by reducing the accompanying brain currents
 - Moving electrical currents generate electromagnetic waves ²
- 3) Brain currents can be reduced by raising neuron resistance
 - Higher resistance impedes the flow of electrical current ³
- 4) A neuron's resistance can be raised by reducing its population of receptor sites
 - Fewer doorways for current to enter the neuron
- 5) A neuron's receptor site population can be lowered by modifying its DNA or RNA
 - Make fewer cellular proteins for building receptors

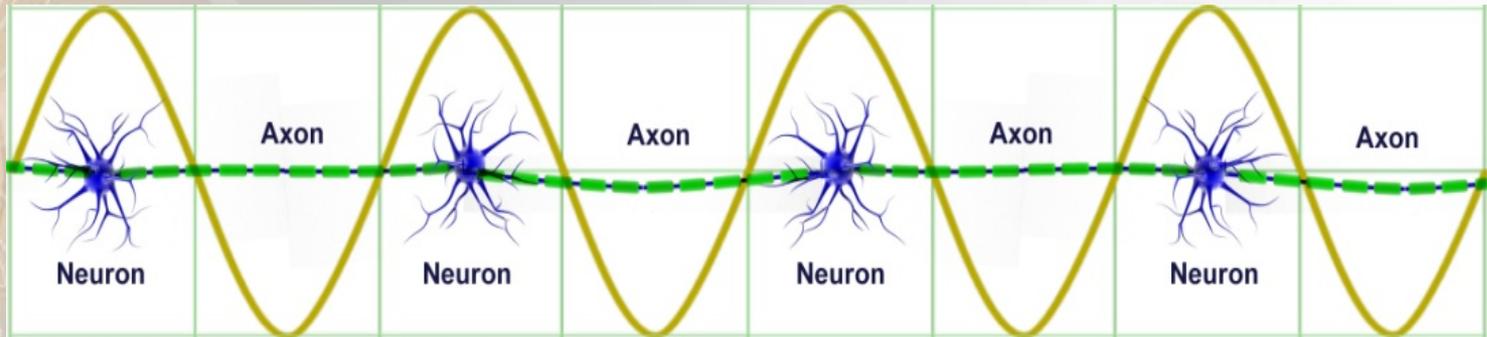
¹ Relieving Alzheimer's Symptoms: Proof-of-Concept Human Experiments, Cognitive Genetics white paper, 2019, J.L. Mee

² Ampere's Law

³ Ohm's Law

Neuron-Level Brainwaves

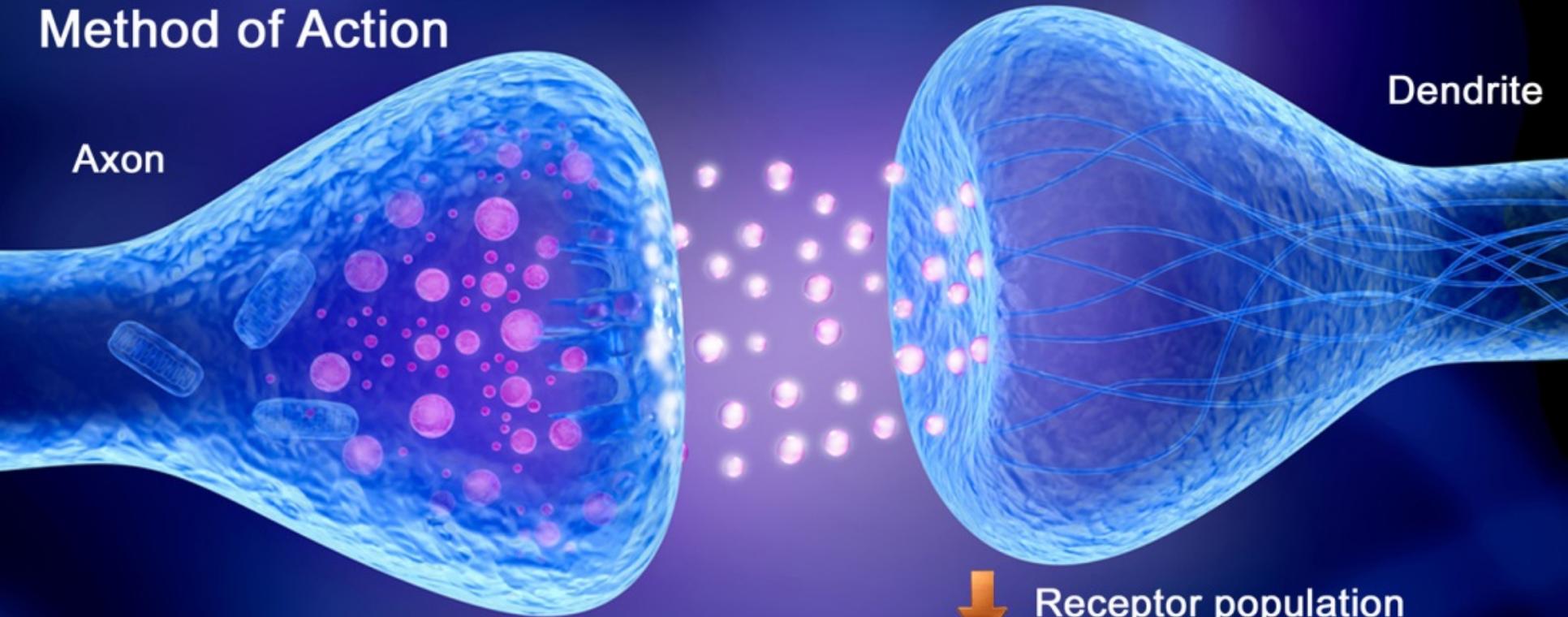
“Neurowaves”



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

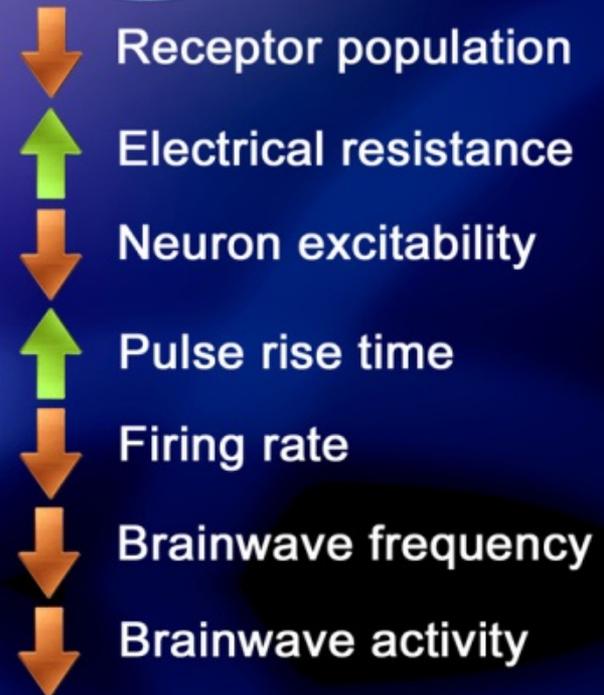
Source: *Electrophysiology of the Neuron*, Huguenard and McCormick, Oxford University Press, 1994

Method of Action



- Lowering receptor population raises neural resistance
 - Fewer “doors” for current to enter neuron
- Higher resistance lowers current flow, ¹ brainwave activity and frequency

¹ Ohm's Law



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 ¹
 - Mitigates symptoms and promotes brain health
- Theta frequency brainwaves signify states of enhanced cognitive clarity
 - Ameliorates Alzheimer’s symptoms ¹

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

Stress

- Associated with multiple risk factors for AD
 - Inflammation, calcium dysregulation, depression, anxiety, insomnia, inactivity
- Raises cortisol levels
 - Causes neurotoxic damage to hippocampus cells and other neurons.
- Activates inflammatory mediators
 - Leads to widespread brain inflammation
 - Especially in the hippocampus
 - Central inflammation is a hallmark of AD
- Impacts genetic health
 - Reduces telomerase levels and telomere length
 - Causes inflammation and accelerated aging

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

Cognitive Enhancement Strategy

20th Century

21st Century

Method

Alter
neurochemistry

Optimize
brainwaves

Technology

Pharmaceuticals

CRISPR

Focus

Matter

Energy