Relieving Alzheimer's Symptoms

Mechanism of Action

Proof-of-Concept

Experiments

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I. Introduction

Cognigenics, LLC is developing genetic cognitive enhancement technology for raising conscious awareness, mental acuity, focus, attention and cognitive performance. Compassionate use of the company's technology dictates Alzheimer's disease as the first application.

Recent neuroscience experiments conducted at 15 universities in 8 countries including Yale, Columbia, MIT, Harvard, Brown and Stanford have uncovered the relationship between a person's level of consciousness and their brainwave activity. These experiments conclusively demonstrate that *higher states of awareness* are accompanied by *lower levels of brainwave activity*, and that *lower states of awareness* are accompanied by *higher levels of brainwave activity*. Although counterintuitive, there appears to be an inverse relationship between consciousness and brainwave activity.[1]

Cognigenics is applying these findings to develop new kinds of treatments for relieving symptoms of cognitive impairment in Alzheimer's patients. An Alzheimer's symptomatic reliever can improve the lives of 5 million patients whose quality of life has been marginalized by the disease. The genetic edit is straightforward and the neural targets are well known.

II. Human Brainwave Experiments

This section cites 20 neuroscience experiments with human subjects providing evidence that consciousness level varies inversely with brainwave power. The experiments are divided into 2 parts.

Part One presents 3 classes of experiments which demonstrate higher brainwave power accompanies reduced consciousness.

Part Two presents 3 classes of experiments which show that lower brainwave power is correlated with increased consciousness.

Part One – Higher brainwave power accompanies reduced consciousness BP ↑ C ↓

BP = brainwave power C = consciousness

1. Anesthesia Experiments

A team of researchers at M.I.T., Harvard, Brown and Boston University led by ShiNung Ching recorded the brainwaves of subjects as they received anesthesia. They found that *loss of consciousness was accompanied by an increase in low beta and high alpha band brainwave power*. (Ching et al, 2010) (1)

Neuroscientists at Harvard, M.I.T. and Brown led by Patrick Purdon confirmed Ching's results by recording the brainwaves of 10 subjects as they were gradually given anesthesia. They noticed that *as the subjects lost consciousness, their brainwave power increased*. (Purdon et al, 2013) (2)

[1] One explanation may be that since most brainwaves reflect unconscious processes, reduced activity frees up a person's cognitive resources.

2. Fainting Experiment

A team of scientists in Rome tested 63 patients with a history of fainting, and induced unconsciousness using a tilt table. They observed that *loss of consciousness was accompanied by an increase in EEG brainwave amplitude*. When patients regained consciousness, their brainwave amplitude *diminished*. (Ammirati et al, 1998) (3)

3. Exercise Experiments

We can empirically observe that vigorous exercise temporarily reduces a person's cognitive capacity. For example, it much easier to recite the multiplication tables while comfortably seated than while running a hundred yard dash.

Researchers at Elon University in North Carolina tested 20 subjects during exercise on a recumbent bicycle. They discovered *brain EEG activity increased during exercise*, and may be related to exercise intensity. Brain EEG activity returned to resting levels quickly after the cessation of exercise. (Bailey et al, 2008) (4)

A team of exercise physiologists in Germany measured 11 subjects during exercises on a treadmill and a stationary bicycle. They found *exercising raised alpha and beta brainwave activity*. (Schneider et al, 2009) (5)

Part Two – Lower brainwave power accompanies increased consciousness BP ↓ C ↑

BP = brainwave power C = consciousness

4. Meditation Experiments

If brainwave activity increases when people become less conscious, what does it do when people enter into states of higher awareness? A natural starting point for this inquiry would be to study meditation.

Neuroscience researchers at Yale, Columbia and the University of Oregon tested the brainwaves of 12 subjects during meditation. They deliberately restricted their sample to very experienced meditators from a single practice tradition (mindfulness/insight meditation). This approach was intended to reduce heterogeneity in meditation practices. They found *meditation reduced brainwave activity* (Brewer et al, 2011). (6)

Subjective *experience of meditative states has also been associated with reduced activity* in the brain's default mode network in a study of 32 subjects conducted by researchers at the University of Massachusetts and Stanford (van Lutterveld et al, 2017) (7), as well as in four additional experiments cited by van Lutterveld and Brewer in their 2015 paper (8), including Brewer et al, 2011 (6), Pagnoni et al, 2012 (9), Brewer and Garrison 2013 (10) and Garrison et al, 2015 (11). *The opposite effect – distracted awareness with higher default mode network activity – has also been observed* by Brewer and Garrison, 2013 (10).

5. Experiments with Psychoactive Compounds

Searching the neuroscience field for laboratory experiments which measure the brainwaves of people in higher states of consciousness also reveals a large body of literature on experiments with psychoactive compounds, which are known to expand consciousness and promote metacognition.

Neuroscientists from four universities in the UK tested 15 subjects under psilocybin with functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG). They discovered that *expanded states of awareness* were accompanied by *large decreases in brainwave oscillatory power* and reduced neural activity. (Muthukumaraswamy et al, 2013) (12)

Neuroscience researchers at the Imperial College of London and three other UK universities summarized the results of several experiments which used different neuroimaging (brainscan) techniques – functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG) – to understand how psychedelics change brain functions to alter consciousness. They concluded that *consciousness-expanding psychedelics cause brain activity, functional connectivity and oscillatory power to all decrease* in brain regions that are normally highly metabolically active. (Carhart-Harris et al, 2014) (13)

Neuroscientists at the Imperial College of London and two other UK universities administered psilocybin to 15 volunteers. They observed *profound* expansion of consciousness which was accompanied by significantly decreased brain activity. They noticed the magnitude of the reduction in brain activity correlated positively with the intensity of the drug's subjective effects. (Carhart-Harris et al, 2012) (14)

A team of neuroscientists in Switzerland tested the effects of psilocybin on 50 volunteers. They found the mind-expanding drug *reduced brainwave current.* They also noticed the intensity levels of psilocybin-induced consciousness expansion and insightfulness correlated with desynchronization of brainwaves (which reduces their voltage by wave interference). (Kometer et al, 2015) (15)

Researchers from universities in Spain and Austria tested the effects of the mind-expanding psychoactive beverage ayahuasca on 18 subjects. They found ayahuasca *decreased absolute brainwave power* across all frequencies. (Riba et al, 2002) (16)

Neuroscientists from four universities in the UK measured the effects of the psychoactive drug MDMA on 25 volunteers. They found MDMA *reduced brain activity*, and the magnitude of the reductions was highly correlated with the subjective intensity of the drug's mind-expanding effects. (Carhart-Harris et al, 2013) (17)

A study of 58 subjects conducted by Candace Lewis at the University of Zurich found oral psilocybin engendered *expanded states of consciousness* accompanied by *decreased absolute cerebral blood flow* in healthy participants. (18)

6. Intelligence Experiments

Lower brainwave current not only results in higher awareness, it also raises IQ. Scientists at the Ruhr University in Bochum, Germany have discovered that *higher IQ individuals have fewer dendrites in their brains*. A team of researchers led by Dr. Erhan Genc analyzed the brains of 259 subjects using neurite orientation dispersion and density imaging, which enabled them to measure the amount of dendrites in the cerebral cortex. All participants completed IQ tests which were correlated with their neuroimages. (19)

The results showed that the more intelligent a person is, the fewer dendrite connections there are between the neurons in their cerebral cortex. Using a database from the Human Connectome Project, Dr. Genc's team confirmed these results in a second sample of 500 individuals.

Receptors are located on dendrites. Fewer dendrites means fewer receptors Fewer receptors yields higher resistance, which makes neurons less excitable. Less excitable neurons fire less often, lowering brainwave activity.

Dr. Genc's report also cites other studies which have shown the *brains of highly intelligent people demonstrate less neuronal activity* during an IQ test than the brains of average individuals. Neuronal activity is measured in voltage.

One such experiment, conducted by Dr. Richard Haier at University of California Irvine, found *significantly lower brain activity* in subjects during an abstract reasoning test, as indicated by cortical metabolic rates measured with positron emission tomography (PET). (20)

III. Alzheimer's Experiments

Two meta-studies have compiled a large body of scientific evidence indicating lower frequency brainwave states ameliorate cognitive decline by promoting brain health and reducing stress, anxiety and cortisol.

A 2015 study by the Alzheimer's Research and Prevention Foundation in Arizona found 350 peer-reviewed research studies on *meditation* in 160 scientific journals confirming a *reduction in hypertension and anxiety*, which could help in the prevention of AD. (21) The paper also cites 2 experiments indicating meditation reduces *cortisol levels*, 3 studies showing it may counter-balance *stress* and protect the brain from age-related disorders, and 8 experiments showing relaxation decreases hypertension and maximizes gene expression.

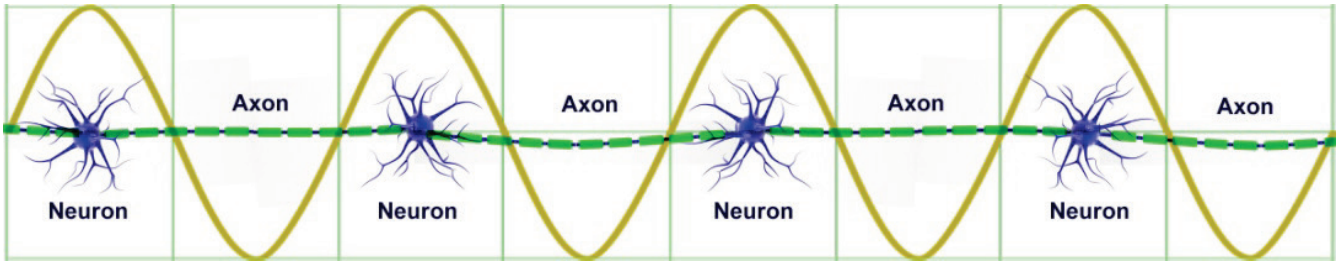
An team of five scientists from Australia, America and France reviewed ten scientific papers on using meditation and mindfulness to ameliorate dementia symptoms. These ten papers reported *significant reductions in cognitive decline and stress in Alzheimer's patients practicing meditation and mindfulness technqiues, along with increases in quality of life and functional brain connectivity*. (22)

The benefits claimed for meditation are actually the result of alpha and theta brainwave states. Meditation is merely a technique for calming down brainwaves; slowing their frequencies from beta to alpha and theta. The lower frequency brainwave states are the active agent of physiological change.

IV. Background

This section contains background information for marketing, finance or business managers reading this paper who may not be familiar with neuron electrodynamics.

Brainwaves are composed of millions of tiny, cellular-level electromagnetic waves. The illustration below shows one of these miniscule waves traveling through a series of neurons. Every one of these waves has a corresponding flow of electrical current which runs through neurons in the brain. [2]



Brain currents flow through neurons at different rates, depending on the neuron's physical properties. Neurons which have higher electrical resistance will impede the flow of current, while neurons with lower resistance will conduct current more readily. [3]

When the flow of a brain current is impeded, its associated brainwave slows down. Slower brainwaves exhibit lower overall activity per second. Refer to the Glossary for additional information.

V. Implementation

The research indicates Alzheimer's symptoms can be mitigated by:

A) Increasing the patient's available attention and cognitive resources
B) Reducing stress and enhancing cognitive clarity

A. Increasing attention and cognitive resources

1. Human brainwave experiments show consciousness and cognitive capacity expand when brainwave activity is reduced.

2. Brainwave activity can be lowered by reducing the accompanying brain currents, since moving electrical currents generate electromagnetic waves (per Ampere's Law).

3. Brain currents can be reduced by raising neuron resistance, since higher resistance impedes the flow of electrical current (per Ohm's Law).

[2] *Electrophysiology of the Neuron*, Huguenard and McCormick, Oxford University Press, 1994
[3] Ohm's Law

4. Experiments in China and the US have shown that CRISPR can precisely edit genes in neurons.

5. CRISPR can be used to increase neural resistance to attenuate brainwave activity, yielding expanded cognitive capacity, mental acuity and conscious awareness.

B. Reducing stress and enhancing cognitive clarity

1. Neurons with higher resistance are harder to excite, which reduces their activity per second.

2. Lower neuron activity per second shifts overall brainwave activity from the higher "beta" frequencies into the lower "alpha" and "theta" frequency bands.

3. Alpha frequency brainwaves characterize relaxation and have been experimentally proven to lower stress in Alzheimer's patients, which mitigates their symptoms and promotes brain health.

4. Theta frequency brainwaves signify states of enhanced cognitive clarity and have been shown to ameliorate Alzheimer's symptoms.

VI. CRISPR Experiments

This section recaps recent experiments in China and the US which demonstrate CRISPR's ability to precisely edit neurons *in vivo*.

Chinese researchers are already using CRISPR to reduce neuron activity in mice. A team of scientists at Tsinghua University in Beijing used dCas9-based CRISPR interference (CRISPRi) to efficiently silence genes in neurons, demonstrating that CRISPRi shows superior targeting specificity without detectable off-target activity. (23)

Also, the Max Planck Florida Institute for Neuroscience has demonstrated precise CRISPR editing in mature mouse neurons *in vivo* regardless of cell maturity, brain region or age. Jun Nishiyama, Takayasu Mikuni, and Ryohei Yasuda used a packaging technique called vSLENDR to provide CRISPR with templates which raise its editing efficacy, achieving extremely efficient results in mouse neurons. They also tested their system in an aged Alzheimer's disease mouse model showing that the vSLENDR technique can be applicable in pathological models even at advanced ages. (24)

Editing RNA as a strategy for treating Alzheimer's has been validated by CRISPR co-inventor Feng Zhang at the Broad Institute at Harvard / MIT. Zhang and his colleagues used the CRISPR Cas13 RNA editor to convert the gene variant APOE4—a risk factor for late-onset Alzheimer's disease—into the non-pathogenic variant APOE2. (25)

VII. Summary

Unconscious brainwave activity can be reduced by lowering neuron excitability. Genome editing can dampen neuron excitability by modifying neurons to raise their electrical resistance.

Many kinds of unconscious brainwave activity are vital, but certain types of activity are superfluous. Great care must be exercised in selecting neuron editing strategies which attenuate only unnecessary brainwave activity without interfering with essential neurosignaling pathways.

Our design affects neuron structures which have been extensively studied in 600 drug discovery experiments and are safe to modify in limited dosages. These structures are most densely expressed in a brain region experimentally correlated with distraction, inattention, mind-wandering and craving. Lowering neural activity in this region provides an extra boost to attention, focus and mental clarity. The primary gene of interest is minimally polymorphic and is chemically dissimilar to its neighbors on the chromosome.

VIII. References

(1) Thalamocortical model for a propofol-induced alpha-rhythm associated with loss of consciousness
ShiNung Ching, et al
Proceedings of the National Academy of Sciences vol. 107 no. 52, 22665-22670
http://www.pnas.org/content/107/52/22665.abstract

(2) Electroencephalogram signatures of loss and recovery of consciousness from propofol
Patrick Purdon, et al
Proceedings of the National Academy of Sciences vol. 110 no. 12, E1142-E1151
http://www.pnas.org/content/110/12/E1142.full

(3) Electroencephalographic Correlates of Vasovagal Syncope Induced by Head-Up Tilt Testing
Fabrizio Ammirati, et al
Stroke 1998 Nov;29(11):2347-51
http://www.ncbi.nlm.nih.gov/pubmed/9804646

(4) Changes in EEG During Graded Exercise on a Recumbent Cycle Ergometer
Stephen P. Bailey, et al
Journal of Sports Science and Medicine (2008) 7, 505 - 511
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3761919/

(5) Changes in brain cortical activity measured by EEG are related to individual exercise preferences.
S. Schneider, et al
Journal of Physiological Behavior 2009 Oct 19;98(4):447-52.
http://www.ncbi.nlm.nih.gov/pubmed/19643120

(6) Meditation experience is associated with differences in default mode network activity and connectivity
Judson A. Brewer, et al
Proceedings of the National Academy of Sciences USA 2011 Dec 13; 108(50): 20254–20259.
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3250176/

(7) Source-space EEG neurofeedback links subjective experience with brain activity during effortless awareness meditation
Remko van Lutterveld et al, 2017
Neuroimage, 2017 May 1;151:117-127. doi: 10.1016/
https://www.ncbi.nlm.nih.gov/pubmed/26921712

(8) Neurofeedback from the Posterior Cingulate Cortex as a Mental Mirror for Meditation.
Remko van Lutterveld and Judson Brewer
Biofeedback: Fall 2015, Vol. 43, No. 3, pp. 117-120.
http://dx.doi.org/10.5298/1081-5937-43.3.05

(9) Dynamical Properties of BOLD Activity from the Ventral Posteromedial Cortex Associated with Meditation and Attentional Skills
Giuseppe Pagnoni, 2012
Journal of Neuroscience 11 April 2012, 32 (15) 5242-5249;
http://www.jneurosci.org/content/32/15/5242.full

(10) Effortless awareness: using real time neurofeedback to investigate correlates of posterior cingulate cortex activity in meditators' self-report
Kathleen A. Garrison, et al 2013
Frontiers in Human Neuroscience v.7; 2013 Aug 6 PMCID: PMC3734786
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3734786/

(11) Meditation leads to reduced default mode network activity beyond an active task
Kathleen A. Garrison, et al 2015
Cognitive, Affective, & Behavioral Neuroscience
September 2015, Volume 15, Issue 3, pp 712–720
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4529365/

(12) Broadband Cortical Desynchronization Underlies the Human Psychedelic State
Suresh D. Muthukumaraswamy, et al
Journal of Neuroscience, 18 September 2013, 33(38): 15171-15183;
http://www.jneurosci.org/content/33/38/15171.full

(13) The entropic brain: a theory of conscious states informed by neuroimaging research with psychedelic drugs
Robin L. Carhart-Harris, et al
Frontiers in Human Neuroscience 2014; 8: 20.
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3909994/

(14) Neural correlates of the psychedelic state as determined by fMRI studies with psilocybin
Robin L. Carhart-Harris, et al
Proceedings of the National Academy of Sciences USA 2012 Feb 7; 109(6): 2138–2143
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3277566/

(15) Psilocybin-induced spiritual experiences and insightfulness are associated with synchronization of neuronal oscillations
Michael Kometer, et al
Psychopharmacology (Berlin). 2015 Oct;232(19):3663-76.
http://www.ncbi.nlm.nih.gov/pubmed/26231498

(16) Topographic pharmaco-EEG mapping of the effects of the South American psychoactive beverage ayahuasca in healthy volunteers
Jordi Riba, et al
British Journal of Clinical Pharmacology 2002 Jun; 53(6): 613–628.
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1874340/

(17) The effects of acutely administered 3,4- methylenedioxymethamphetamine on spontaneous brain function in healthy volunteers
Robin Carhart-Harris, et al
International Journal of Neuropsychopharmacology 2013 10.1017/S1461145713001405
Biological Psychiatry 2015 Oct 15;78(8):554-62
http://www.ncbi.nlm.nih.gov/pubmed/24495461

(18) Two dose investigation of the 5-HT-agonist psilocybin on relative and global cerebral blood flow
Candace R. Lewis, Katrin H.Preller, et al
NeuroImage Volume 159, 1 October 2017, Pages 70-78
https://doi.org/10.1016/j.neuroimage.2017.07.020

(19) Diffusion markers of dendritic density and arborization in gray matter predict differences in intelligence
Erhan Genc, Christoph Fraenz, et al
Nature Communications, 2018, volume 9, Article number 1905
doi:10.1038/s41467-018-04268-8
http://www.nature.com/articles/s41467-018-04268-8
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5954098/

(20) Cortical glucose metabolic-rate correlates of abstract reasoning and attention studied with positron emission tomography. Haier RJ, et al, Intelligence. 1988; 12:199–217.
doi: 10.1016/0160-2896(88)90016-5
https://doi.org/10.1016/0160-2896(88)90016-5

(21) Stress, Meditation, and Alzheimer's Disease Prevention: Where The Evidence Stands
Journal of Alzheimers Disease 2015; 48(1): 1–12.
Dharma Singh Khalsa, J. Wesson Ashford New Mexico
doi: 10.3233/JAD-142766 / PMCID: PMC4923750 / PMID: 26445019
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4923750/

(22) Mindfulness and meditation: treating cognitive impairment and reducing stress in dementia.
Reviews in Neurosciences, 2018 Feb 21. pii:
doi: 10.1515/revneuro-2017-0066.
https://www.ncbi.nlm.nih.gov/pubmed/29466242
Russell-Williams, Jaroudi W, Perich T, Hoscheidt S, El Haj M, Moustafa A.

(23) CRISPR interference-based specific and efficient gene inactivation in the brain
Yi Zheng, Wei Shen, Jian Zhang, Bo Yang, Yao-Nan Liu, Huihui Qi, Xia Yu, Si-Yao Lu, Yun Chen
Nature Neuroscience volume 21, pages447–454 (2018)
https://www.nature.com/articles/s41593-018-0077-5

(24) Virus-Mediated Genome Editing via Homology-Directed Repair in Mitotic and Postmitotic Cells in Mammalian Brain.
Jun Nishiyama*, Takayasu Mikuni*, and Ryohei Yasuda
Neuron, October 19 2017,
DOI: 10.1016/j.neuron.2017.10.004
https://www.maxplanckflorida.org/news-and-media/news/gene-editing-in-the-brain-gets-a-major-upgrade/

(25) CRISPR pioneer Zhang targets brain diseases with new RNA-editing system
Fierce Biotech, Arlene Weintraub, July 11, 2019
https://www.fiercebiotech.com/research/crispr-pioneer-zhang-targets-brain-diseases-new-rna-editing-system

IX. Glossary

This section contains definitions to assist marketing, finance or business managers reading this paper who may not possess neuroscience backgrounds.

brainwave amplitude	a measurement of brainwave strength
brainwave current	the brain's electrical currents which accompany brainwaves
brainwave power	a measurement of the strength of the brain's electromagnetic field over time
brainwave voltage	a measurement of the strength of the brain's electromagnetic field
default mode network	a large scale brain network normally active during the resting state
EEG	a brainwave measuring device (electroencephalogram)
EEG activity	brainwave activity as measured by EEG
Metacognition	advanced cognitive functions such as self awareness, mindfulness and higher-order thinking skills
Neuroimaging	producing images of brain activity by techniques such as magnetic resonance imagining
neuronal activity	brain activity at the neuron level (also called neural activity)
oscillitory power	brainwave power
PET	positron emission tomography; a nuclear functional neuroimaging technique

X. Exhibits

This section contains additional information about Alzheimer's, meditation and brainwaves.

Exhibit I – Meditation Dementia Experiments

Stress, Meditation, and Alzheimer's Disease Prevention: Where The Evidence Stands

Journal of Alzheimers Disease 2015; 48(1): 1–12. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4923750/
Published online 2015 Aug 28. doi: 10.3233/JAD-142766 / PMCID: PMC4923750 / PMID: 26445019
Dharma Singh Khalsa[a,b,*] J. Wesson Ashford
Correspondence to: Dharma Singh Khalsa, MD, Founding President, Alzheimer's Research and Prevention Foundation, P.O. Box 30783, Tucson, AZ 85751-0783,

Stress, via the cortisol connection, causes neurotoxic damage to cells in the hippocampus and elsewhere in the brain which may increase AD risk. Beyond that, stress has a causative association with multiple risk factors for AD, including inflammation, calcium dysregulation, cardiovascular disease including hypertension, diabetes/insulin resistance, depression, anxiety, physical inactivity, sleep deprivation, and smoking [7, 8]. A recent study of 1,796 elderly people with AD compared to 7,184 without an AD diagnosis highlighted the direct connection between anxiety, insomnia, benzodiazepine use, and AD [9]. Previously, a number of these drugs were shown to turn on AD promoting genes [10].

How meditation acts to reduce stress and cortisol levels and improve multiple aspects of health and cognition will then be reviewed.

Furthermore, aging is a time of decreased ability to handle stress and, untreated, chronic stress accelerates many of the degenerative aspects of aging, including cognitive decline. In contrast, meditation may counter-balance many aspects of the stress response and protect the brain specifically from the ravages of aging combined with stress overload [11, 18, 19].

Stress may injure hippocampal cells via the release of the hormone cortisol from the adrenal gland in response to hypothalamic and pituitary stimulatory signals, such as CRF and ACTH. Such injury could lead to dysfunction and atrophy of that critically important memory and emotional brain structure [20, 21]. Beyond that, hippocampal cellular loss is dramatically exacerbated because of the destruction of the specific neurons that control cortisol secretion from the adrenal gland [14].

This loss of feedback inhibition may lead to a persistent toxic cortisol level, thus causing the further injury or death of hippocampal cells by activating NMDA receptors, which may allow excessive extracellular calcium ion to pass through now open channels, flooding the interior of the cell with markedly excessive calcium ion. This excessive intracellular calcium leads to cytosolic injury, mitochondrial damage, severe oxidative stress, and possibly inflammation, which may ultimately lead to significant cognitive decline [22]. Current research also indicates that chronic stress arousal activates multiple inflammatory mediators, including the NF-κB system, leading to widespread brain inflammation, especially in the hippocampus [8, 23–25]. These disturbances of central inflammation have been shown to be a hallmark of AD [26].

Chronic stress is associated with multiple brain anatomic abnormalities, including a decreased size of the anterior cingulate cortex, which leads to impaired hypothalamic-pituitary-adrenal axis regulation and perhaps an increased vulnerability to the effects of chronic stress [36].

Finally, recent stress research by Epel and Blackburn shows that stress has a pronounced negative effect on genetic health, diminishing telomerase levels, the enzyme responsible for maintenance of telomere length, the protective cap of DNA. Shorter telomeres are associated with inflammation, accelerated aging, and AD [37, 38].

Elicitation of the Relaxation Response (RR), regardless of the technique used, has been proven to have multiple general and cognitive health benefits from decreasing hypertension to maximizing gene expression including the upregulation of insulin pathway genes, which could help prevent dementia, as insulin resistance may be risk factor for AD [19, 44–47, 53–55].

RR practice enhanced gene expression associated with energy metabolism and mitochondrial function, thus improving mitochondrial energy production and resiliency. Mitochondrial energy dysfunction has also been postulated to be an associated causative factor of AD development [56].

Meditation studies have been shown to lower cortisol levels [57, 58].

More than 350 peer-reviewed research studies on the TM technique have been published in over 160 scientific journals. Studies confirmed its effect on hypertension, and a reduction of anxiety [60]. Reducing these risk factors may help in the prevention of dementia and AD

Exhibit II – Mindfulness and meditation: treating cognitive impairment and reducing stress in dementia

Rev Neurosci. Reviews in Neurosciences, 2018 Feb 21. pii:

doi: 10.1515/revneuro-2017-0066. https://www.ncbi.nlm.nih.gov/pubmed/29466242
Russell-Williams J[1], Jaroudi W[1], Perich T[1], Hoscheidt S[2], El Haj M[3], Moustafa AA[1].
Author information

Abstract

This study investigates the *relationship between mindfulness, meditation, cognition and stress in people with Alzheimer's disease (AD),* dementia, mild cognitive impairment and subjective cognitive decline. Accordingly, we explore how the use of *meditation* as a behavioural intervention *can reduce stress and enhance cognition, which in turn ameliorates some dementia symptoms*. A narrative review of the literature was conducted with any studies using meditation as an intervention for dementia or dementia-related memory conditions meeting inclusion criteria. Studies where moving meditation was the main intervention were excluded due to the possible confounding of exercise. *Ten papers were identified and reviewed*. There was a broad use of measures across all studies, with cognitive assessment, quality of life and perceived stress being the most common. Three studies used functional magnetic resonance imaging to measure functional changes to brain regions during meditation. The interventions fell into the following three categories: mindfulness, most commonly mindfulness-based stress reduction (six studies); Kirtan Kriya meditation (three studies); and mindfulness-based Alzheimer's stimulation (one study). Three of these studies were randomised controlled trials. *All studies reported* significant findings or trends towards significance in a broad range of measures, including *a reduction of cognitive decline,* reduction in perceived stress, increase in quality of life, as well as increases in functional connectivity, percent volume brain change and cerebral blood flow in areas of the cortex.

Exhibit III – Meditation Brainwave Experiment & Articles

Increased Theta and Alpha EEG Activity During Nondirective Meditation

The Journal of Alternative and Complementary Medicine Vol. 15, No. 11 Original Articles
https://www.liebertpub.com/doi/abs/10.1089/acm.2009.0113
Published Online:18 Nov 2009https://doi.org/10.1089/acm.2009.0113

Abstract

Objectives: In recent years, there has been significant uptake of meditation and related relaxation techniques, as a means of alleviating stress and maintaining good health. Despite its popularity, little is known about the neural mechanisms by which meditation works, and there is a need for more rigorous investigations of the underlying neurobiology. Several electroencephalogram (EEG) studies have reported changes in spectral band frequencies during meditation inspired by techniques that focus on concentration, and in comparison much less has been reported on mindfulness and nondirective techniques that are proving to be just as popular.

Design: The present study examined EEG changes during nondirective meditation. The investigational paradigm involved 20 minutes of acem meditation, where the subjects were asked to close their eyes and adopt their normal meditation technique, as well as a separate 20-minute quiet rest condition where the subjects were asked to close their eyes and sit quietly in a state of rest. Both conditions were completed in the same experimental session with a 15-minute break in between.

Results: Significantly increased theta power was found for the meditation condition when averaged across all brain regions. On closer examination, it was found that theta was significantly greater in the frontal and temporal–central regions as compared to the posterior region. There was also a significant increase in alpha power in the meditation condition compared to the rest condition, when averaged across all brain regions, and it was found that alpha was significantly greater in the posterior region as compared to the frontal region.

Conclusions: These findings from this study suggest that nondirective *meditation techniques alter theta and alpha EEG patterns significantly* more than regular relaxation, in a manner that is perhaps similar to methods based on mindfulness or concentration.

Alpha Brain Waves Boost Creativity and Reduce Depression

Increasing alpha brain waves can stimulate creativity and minimize depression.

Apr 17, 2015 Psychology Today
https://www.psychologytoday.com/us/blog/the-athletes-way/201504/alpha-brain-waves-boost-creativity-and-reduce-depression

Neuroscientists recently made a correlation between an increase of alpha brain waves—either through electrical stimulation or mindfulness and meditation—and the ability to reduce depressive symptoms and increase creative thinking.

When alpha oscillations are prominent, your sensory inputs tend to be minimized and your mind is generally clear of unwanted thoughts.

When your brain shifts gears to focus on a specific thought—in either a positive or negative way—alpha oscillations tend to disappear and higher frequency oscillations begin running the show.

Alpha wave biofeedback has been shown to be a useful tool for treating anxiety and depression. Because alpha waves are linked with relaxed mental states, an increase in alpha wave activity is the goal of most biofeedback training. EEG can be used to provide moment-to-moment feedback when alpha waves increase or decrease.

Mindfulness training and meditation tend to produce noticeably more alpha waves without the use of technological machinery.

How Meditation Changes Your Brain Frequency

By Ashley Turner, Mind Body Green
February 5, 2014 — 8https://www.mindbodygreen.com/0-12491/how-meditation-changes-your-brain-frequency.html

As yogis have known for centuries and scientists can now prove, the benefits of meditation are profound. Meditation is perhaps the most crucial instrument to harness the power of thought, cultivate more peace, clarity and happiness.

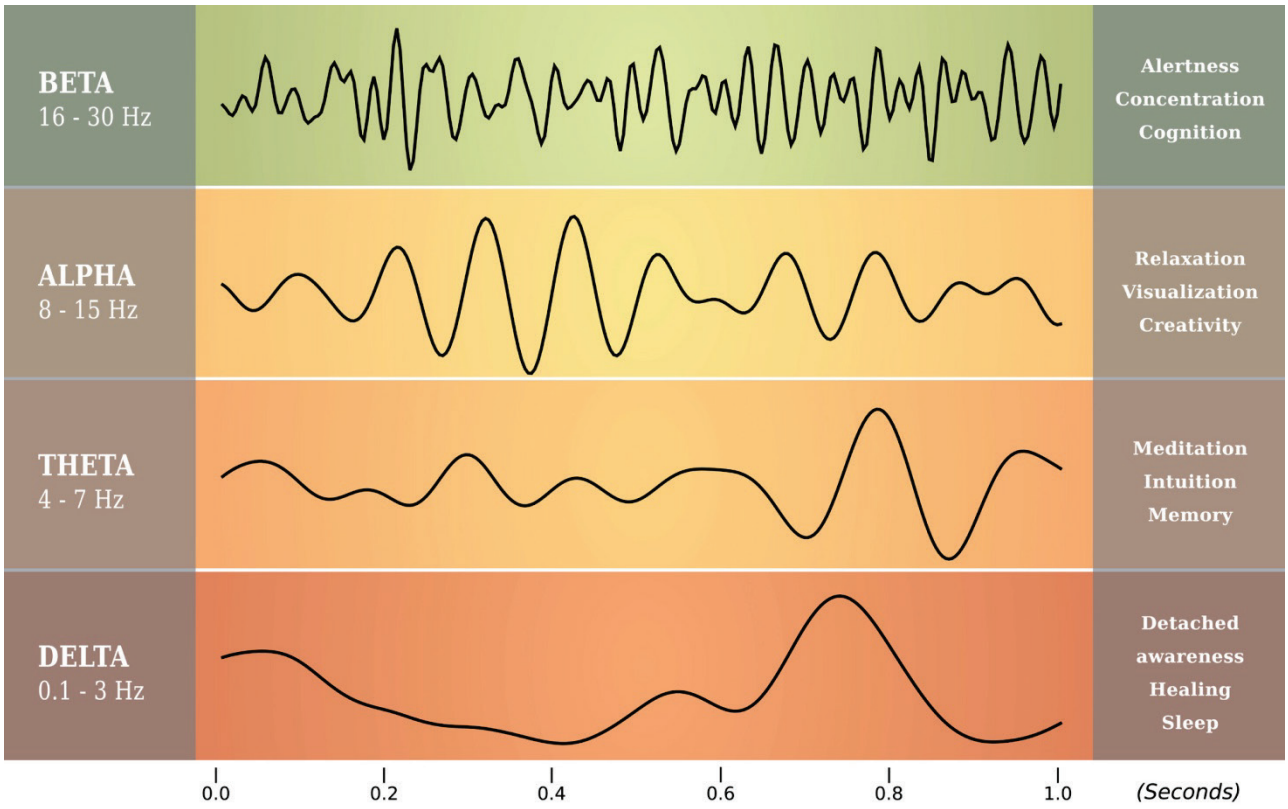
Learning to train the brain and focus our attention is crucial to thriving and cultivating a peak performance in any endeavor.

Longtime psychotherapist Dr. Ron Alexander, author of *Wise Mind, Open Mind,* speaks of mind strength, or the resiliency, efficacy and emotional intelligence that arise as we begin the process of controlling the mind. Mind strength is one of the most empowering tools we can employ to impact and improve all aspects of life.

There are five major categories of brain waves, each corresponding to different activities. *Meditation enables us to move from higher frequency brain waves to lower frequency, which activates different centers in the brain.*

Slower wavelengths = more time between thoughts = more opportunity to skillfully choose which thoughts you invest in and what actions you take.

Exhibit IV – Categories of Brain Waves



1. Beta State: (16 to 30 Hz) Beta waves are associated with the alert mind state of the prefrontal cortex. This is a state of the "working" or "thinking mind": analytical, planning, assessing and categorizing, where we function for most of the day, Excess beta is associated with stress.

2. Alpha State: (9 to 15 Hz) In this state, our thinking and our brain waves start to slow down. We feel more calm, peaceful and grounded. We often find ourselves in an "alpha state" during a yoga class, spending time in Nature, or any activity that helps relax the body and mind. We are lucid, relaxed and reflective.

3. Theta State: (4 to 8 Hz) Here the verbal thinking mind transitions to the meditative mind. We begin to move from the planning mind to a deeper state of consciousness, with stronger intuition, and greater capacity for clarity, visualization and problem-solving.

4. Delta State: (1 to 3 Hz) Tibetan monks who have been meditating for decades can reach this in an alert, wakened phase, but most of us experience this state during deep sleep.

5. Summary: Alpha = relaxation (stress reduction) / Theta = meditation (cognitive clarity)

Exhibit V – Relieving Stress

Stress

- Associated with multiple risk factors for AD
    - Inflammation, calcium dysregulaton, 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

Stress is a major contributing factor to AD

Alpha / Theta States

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

Reduce AD risk factors and boost cognitive functioning