

TRANSCRANIAL ULTRASOUND AS THERAPY FOR PATIENTS WITH ALZHEIMER'S
DISEASE AND OTHER DEMENTIAS

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A Thesis Submitted to The Honors College
In Partial Fulfillment of the Bachelors degree
With Honors in
Physiology

THE UNIVERSITY OF ARIZONA

M A Y 2 0 1 7

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Abstract

Alzheimer's disease is a progressive disorder that can affect cognitive and mental functions, and is the most common form of dementia. In upcoming years, the number of people expected to get Alzheimer's disease is expected to increase significantly due to so-called 'baby boomers' reaching advanced age. Clinical trials regarding dementia are critical in advancing Alzheimer's therapy, but drugs have been ineffective thus far. Rather than drugs, non-invasive brain stimulation techniques have had encouraging results. In animals, low to moderate transcranial ultrasound ('TUS') improves memory, and in humans, TUS causes improvements in mood. The application of TUS in humans is a promising therapy for neuronal growth, cognitive function, and mental state of mind. This paper reviews potential use of TUS for Alzheimer's disease and dementia.

Overview of Dementia, specifically Alzheimer's disease

Patients with dementia have cognitive or memory impairments that may affect their lifestyle, ability to care for themselves, communicate and enjoy life. Dementia has cognitive impairment characteristics such as alertness, difficulty in motor activities, object recognition, and memory loss, and difficulties in social and occupational aspects as well. Individuals sixty-five years or older in particular have a prevalence rate for dementia of about 6-10%. As prevalence increases with age, it becomes increasingly important to recognize and intervene appropriately to ensure the best care for elders with dementia.

Although Alzheimer's disease is the most common form of dementia, it is different from other forms because it is a progressive disease. Depression, insomnia, hallucinations, sudden muscle contractions, and even gait disturbances are all possible as the disease progresses. It is key for an individual who presents Alzheimer's disease to have a close friend or family member provide information in the early stages of the disease since the disease can be subtle in the beginning.

In an adult healthy brain, there are billions of neurons with axonal and dendritic extensions that allow it to make connections with other nearby neurons. These connections, known as synapses, allow information to travel in small bursts of neurotransmitters that are released by one neuron and sensed by another neuron. These synapses connect neurons into networks from which emotions, movements, memories, and sensations somehow arise.

Alzheimer's disease is a degenerative neurological disease that can be detrimental to most parts of the brain. The five stages associated with the disease include pre-clinical Alzheimer's disease, mild cognitive impairment, mild dementia, moderate dementia, and severe dementia.

Although these stages exist, they are generalizations since the disease is progressive. Every individual experiences dementia and its symptoms differently.

In the preclinical stage of the neurodegenerative disease, symptoms are not recognized immediately, and thus this stage may last for years. Technology today allows for identifying protein deposits (amyloid beta), and this early identification can be vital in determining future treatments. Genetic testing is also common for determining if an individual is at risk for the disease.

In the mild cognitive impairment stage, there exists a slight alteration in memory and reasoning abilities, but the individual is still capable of maintaining relationships and continue working. Memory lapses may occur for information that is often easily recalled (i.e. important events, appointments). Not all subjects with mild cognitive impairment have this form of dementia.

Alzheimer's disease usually first becomes diagnosed in the mild dementia stage. In this phase, the individual tends to have substantial trouble with memory and reasoning, and therefore, daily functioning becomes affected. Personality changes, such as less motivation for task completion and feelings of irritability, also begin to occur.

Next is the moderate dementia stage. During this stage, individuals become more easily lost and even begin to forget where items are placed. Individuals with Alzheimer's disease need more monitoring as they tend to wander in their surroundings more. Individuals begin to need help with daily functioning (i.e. choosing clothes) as well as believing information that may be untrue.

In the severe stage of the disease, mental function begins to deteriorate, and the individual is unable to properly communicate. At this stage, personal assistance is necessary as

physical abilities tend to decline. The individual with Alzheimer's disease may have difficulty controlling bowel and bladder functions.

Alzheimer's disease progresses differently for individuals. Typically, affected individuals live about eight to ten years after they have been diagnosed, although some survive up to twenty years and more. As the disease progresses, people with this form of dementia may have difficulty swallowing, which ultimately can lead to aspiration pneumonia and cause death.

In individuals with Alzheimer's disease, there are two types of brain lesions. Plaques made of the protein fragment beta-amyloid collect outside neurons and intervene in neuronal communication at the synapses. Also, inside neurons, the microtubule associated protein 'tau' is dislodged from microtubules and form neurofibrillary tangles, resulting in cognitive impairment.

The *APOE* gene, which has three forms (e2, e3, and e4) is associated with the protein that carries cholesterol in the bloodstream. Although the e3 form is most common, it is the e4 version that can create a higher risk of getting Alzheimer's, and it can help develop the dementia at a younger age. Inheriting this gene version, however, does not guarantee the development of Alzheimer's disease—in fact, it is quite rare and at most increases risk of getting dementia only slightly.

Physicians collaborate with neurologists and geriatricians, among other specialties, to make a diagnosis for Alzheimer's disease. Analyzing appropriate family medical history is crucial and includes psychiatric history, cognitive history, and behavioral changes. Healthcare professionals also ask family members to provide insight on behavioral changes. Additionally, cognitive tests and neurological examinations are conducted to check for dementia. Blood tests and neuroimaging are also conducted to determine the causes of dementia. Pinpointing

dementia's exact cause is more difficult than figuring out if an individual has dementia in the first place.

There is an indirect relationship between numbers of formal education and risk of getting Alzheimer's disease. Individuals with more years of schooling tend to have a reduced risk for being diagnosed with dementia than those people with less schooling. Some believe this is because more years of education creates a cognitive reserve that lets people with dementia make up for the neurological changes they experience as part of Alzheimer's disease.

The cognitive reserve hypothesis indicates that greater education strengthens neuronal connection, thus giving the brain multiple paths of neuronal communication to finish cognitive tasks, especially when there exists neuronal gaps in the usual routes due to dementia.

Those with fewer years of schooling tend to have higher chances of getting dementia for other reasons as well. One reason is that their jobs tend to be less mentally stressful, and fewer years of schooling is often linked with being on the lower end of the socioeconomic ladder, potentially leading to lack of medical treatments and poor nutrition. Individuals with fewer years of schooling often are more prone to cardiovascular risk factors for Alzheimer's disease.

There is little to no medication for Alzheimer's dementia that aids in stopping or slowing the neuronal destruction that ultimately makes the disease fatal. There are certain drugs that are shown to temporarily enhance symptoms by producing more chemicals in the brain known as neurotransmitters. From 2002-2012, one drug out of a total of two hundred and forty four drugs for Alzheimer's received approval from the U.S. Food and Drug Administration. Some factors that make it hard to create effective Alzheimer's disease treatments include drug development costs, the time needed to determine if a treatment affects the progression of the disease, and the brain structure since very specific molecules can cross the blood-brain barrier.

Non-pharmacologic therapies are used to help enhance cognitive function, do everyday tasks, and improve quality of life. This form of therapy may also help lower symptoms of depression, agitation, uncomfortable sleep, and aggression. Some forms of this therapy include specific lighting for more comfortable sleep, listening to pleasant music to improve recall, and even computerized memory training.

It has been shown that aerobic exercise and a mix of aerobic and non-aerobic exercise can enhance cognitive function. Exercise improves overall cognitive performance and can reduce rate of cognitive decline in Alzheimer's disease patients, although the extent to which it can slow cognitive deterioration is not fully known.

Although there exists limited number of therapies that aid in Alzheimer's disease, pro-actively managing the disease and other forms of dementia can enhance quality of life for both caregivers and the patients. Some ways to become pro-active include using treatments appropriately and coordinating between health care professionals and family members, including caregivers. For individuals with Alzheimer's disease, participating with their loved ones in activities that give them a sense of purpose are integral for daily function, mental health, and allows them to connect with others who have dementia.

Many Alzheimer's patients have caregivers, or a person dedicated to attending others' health needs. It involves aid with daily activities (bathing & dressing) and running errands. Additionally, caregivers provide emotional support and help make patients' with Alzheimer's have a better quality of life. Many caregiver duties lie outside everyday tasks as well, and their roles sometimes delve into supporting organizations for people with dementia. Family caregivers who help people with Alzheimer's disease are more likely than family caregivers of those without dementia to aid with emotional and mental distress.

A caregiver's role is important for individuals with dementia as it presents challenges as well. As the disease progresses, people experience difficulty communicating and reasoning, and it becomes the caregiver's duty to manage the issues. As the disease symptoms get worse, the care required becomes more time intensive and there is often more emotional discomfort that arises. The shared memories between the Alzheimer's patient and the caregiver could become jeopardized because of changes in behavior and loss of memory and function. Although some experiences may become jeopardized if the patient does not remember them, caregivers often find this relationship to be meaningful.

There exist strategies to help family caregivers, and it is intended to help enhance caregivers' overall well-being to alleviate the stress from taking care of a patient with dementia. Counseling is one effective intervention that helps find solutions to personal problems that caregivers face with the person they are looking after. Support groups are another popular intervention that allow for a comfortable space in which caregivers can express their concerns about their experience and feel more connected to others who are in a similar position.

Although the specific cause of Alzheimer's disease is not clear, there is still no way to prevent it. There are ways to delay cognitive decline. Exercise and other forms of physical activities can help lower an individual's risk for Alzheimer's disease and delay cognitive decline in the elderly. Animal studies have demonstrated that exercise causes higher small blood vessels that provide blood to the brain, and raises connections between nerve cells. Also, research indicates that exercise increases nerve growth factor levels, and this protein aids in learning and memory. Diet equally plays an important role in lowering the rate of cognitive decline. A vegetable rich diet, especially one filled with lots of greens, are helpful in lowering rate of cognitive deterioration. The Mediterranean diet in particular is known to be effective in lowering

the risk for dementia. The diet consists of legumes, vegetables, fruits, fish, whole grains, and olive oil is the main cooking fat used.

Some scientists believe that participating in social or intellectual activities helps the brain adjust in certain mental capabilities in order to make up for decline in other functions.

Individuals engaged in such activities also may have other contributing lifestyle factors that prevent Alzheimer's disease. The more mentally, socially, and physically active an individual is, the less likely they are to develop dementia.

Transcranial Ultrasound Clinical Study

Treatments available for those who have Alzheimer's disease are minimally effective. Better methods are needed. These conditions lower the quality of life for individuals who have them, and also for their loved ones.

Non-invasive brain stimulation techniques are also being considered. These techniques include transcranial direct current electrical stimulation (tDCS), transcranial magnetic stimulation (TMS), transcranial infra-red photons, and transcranial ultrasound (TUS).

Ultrasound, often used for medical imaging, has megahertz mechanical vibrations and has been safely used in medicine for numerous years. A clinical study led by Dr. Stuart Hameroff at the University of Arizona in 2013 looked at effects of ultrasound delivered non-invasively from the scalp on mood effects in human volunteers in a pilot study, the first clinical trial of transcranial ultrasound on mental states of participants. In a double blind study, it was found that fifteen seconds of sub-thermal eight megahertz ultrasound on the fronto-temporal scalp can cause about forty minutes of enhancement in mood when compared with the placebo.

Low intensity transcranial ultrasound goes through the skull and into the brain and echoes back painlessly. The technique appears to be completely safe and painless when used at low to moderate, sub-thermal intensities.

There are gaps in understanding how the brain properly functions, and how memory, cognition, mood, and consciousness arise. New evidence currently suggests that mental states can rely, to a certain degree, on vibrations and megahertz resonances that lie within microtubule networks inside neurons. These microtubules, stabilized by tau proteins, are disrupted specifically in those experiencing traumatic brain injury and Alzheimer's disease. As a result, tau proteins are released and form neurofibrillary tangles.

In normal conditions, the microtubules aid in synaptic and neuronal growth, are vital in repair and synaptic plasticity, and may themselves encode memory. They have been shown to have vibrational resonances in megahertz.

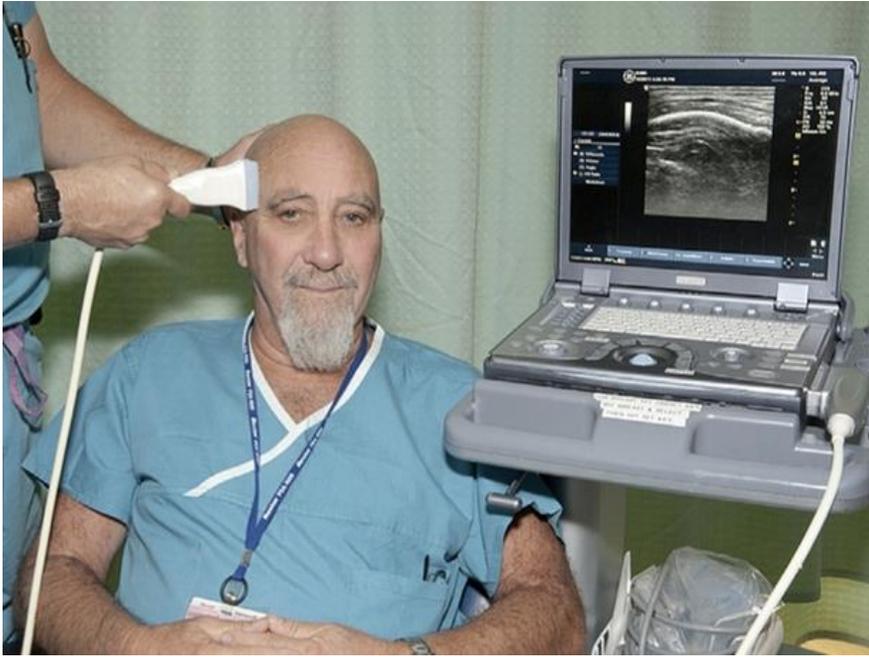
In two studies, mice with genetically-induced Alzheimer's disease were given transcranial ultrasound and found to have significant improvement in cognition, and reduction in brain pathology. In one of the studies, the results suggested that frequent scanning ultrasound helps remove amyloid-beta in the mouse brain and there is no obvious harm done. The waves stimulate the microglia, a cell that removes undesired items in the brain and improves the immune system. About three-fourths of the mice that experienced the treatment had significant plaque decrease. The mice demonstrated better performance on memory tasks as well. In the other study, the dendritic morphology and neuronal spine densities were examined. There were less apical dendritic spine densities, and the study indicated that ultrasound can be resourceful to avert age-related dendritic structure without compromising neuronal excitability. Scanning ultrasound is a non-invasive method that can reestablish memory functions in mouse models with Alzheimer's disease.

Since high intensity ultrasound is capable of damaging tissues and is used to ablate tumors and other brain lesions, TUS uses low-intensity (sub-thermal) ultrasound. The low-intensity sub-thermal ultrasound is known to encourage regeneration of peripheral neurons after an injury, and two megahertz electrical stimulation causes optimal microtubule polymerization. The low-intensity transcranial ultrasound will be performed on the scalp region, and is approved by the U.S. Food and Drug Administration for brain imaging. Transcranial ultrasound at low intensity is versatile in that it can be used anywhere in adult brains.

Previous studies suggest that transcranial ultrasound encourages vibrations in a continuum of extracellular, intra-neuronal, and intra-membrane structures, including microtubules. It is believed that transcranial ultrasound may enhance endogenous microtubule megahertz resonances. The University of Arizona group led by Hameroff is planning clinical trials of TUS to examine its role in neuronal repair for individuals with traumatic brain injury, and memory turnover for people with post-traumatic stress disorder, as well as for Alzheimer's disease.

The transcranial ultrasound device to be used emits sub-thermal ultrasound at five to eight megahertz. Areas to be stimulated include temporal and frontal lobe regions.

Researchers believe that the ultrasound promotes microtubule vibrations, which affect neuronal and synaptic functions, mood, and memory. Eventually, the ultrasound devices may be wearable and portable, and capable of safely and non-invasively interacting with the brain to hopefully treat and improve symptoms of Alzheimer's disease.



Left: Dr. Stuart Hameroff, lead author on the first clinical study to demonstrate how transcranial ultrasound may impact mood.

Below: Jay Sanguinetti, a doctoral candidate at University of Arizona's Psychology department, administers brain ultrasound for a clinical trial.



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