EXPLORATIONS OF MULTISENSORY COGNITIVE APPROACHES IN ALZHEIMER’S DISEASE

by
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ABSTRACT

We experience the world through our senses. Our consciousness is the culmination of our recalled perceptual associations. Stimulating the senses can yield remarkable biological effects for cognitive recovery; this is the cornerstone of my thesis. Alzheimer’s is currently the 6th leading cause of death in the United States and impacts an estimated 50 million worldwide. Therefore, it is vital to develop an effective cure that goes beyond stalling symptoms, to reverse disease progression. My research contribution to the Aging Brain Initiative, reveals the importance of multi-modal gamma stimulation for human-centered applications. This takes form within a novel sensory taxonomy of the effects of gamma entrainment stimuli in humans. Simultaneously, groundbreaking multisensory testing methodologies are outlined to evaluate subtle cognitive changes in human participants. The amalgamation of this research is physically expressed in the design of a multisensory, interactive Gamma Instrument, designed to effect peak levels of gamma entrainment and sensory congruence. This work provides foundational components for future gamma research and broadens our understanding of the role of music in medicine and multisensory cognition.

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1.0 INTRODUCTION

1.1 PREFACE

Throughout the history of science, specific veins of thought culminating between vastly different fields, have launched our understandings into broader spectrums. Although still elusive, explorations of our senses will likely become an axis point of centrifugal explorations into higher dimensions of the neurosciences, contributing to the understanding of how we leverage our perception of the world. Although there is preliminary evidence revealing the capabilities of non-invasive sensory stimuli to modulate neuronal and biological changes in the brain, the medical community does not currently rely upon these modalities to treat pathologies. Through my research in exploring the use of non-invasive stimuli within a medical context, I seek to create a taxonomy of multisensory gamma experiences to contribute to the treatment of Alzheimer’s and our understanding of the role of multisensory stimuli in medicine.

Medications and treatments for Alzheimer’s are not currently able to approach the task of reversing disease progression. In 2016 the Aging Brain Initiative was sparked by a fundamental discovery (Iaccarino, Tsai, Boyden, 2016) evaluating the use of visual gamma frequencies to reverse beta-amyloid plaques in the brains of mouse models. Collaborators in the initiative include my lab group, led...
by Professor Tod Machover, Professor Edward “Ed” Boyden’s group, Synthetic Neurobiology and Li-Huei Tsai’s lab at Picower in conjunction with Brain and Cognitive Sciences. The goal of this initiative as described by the Picower website is to find novel treatments for brain pathologies.

“Our MIT scientists are opening the doors to an entirely new direction of brain research. It is a priority for me to support their efforts,” says Michael Sipser, MIT’s Dean of Science. “The tremendous need to address the burdens of the aging brain — memory loss, cognitive decline, and dementia — is what gave rise to an institute-wide call to action at MIT.”

Having worked on prior projects evaluating the effects of multimodal approaches in medical contexts, my PI Tod Machover and I sought to further explore the effects of multimodal gamma entrainment. In the 2016 study, visual stimuli was the modality of gamma entrainment and showed successful reduction of plaques in the visual cortex. These findings corroborate with a 2010 study where researchers at the University of Basel found that the visual stimuli and the resulting entrainment was relayed by the thalamus. Professor Sonja Hofer was able to determine that the thalamus not only sends out the visual signals from the eye to the visual cortex but that it was capable of transmitting these visual cues within a specific context. In Gottfried Schlaug’s 2009 book entitled “The Neurosciences and Music III: Disorders and Plasticity” he examines the effect of music on brain recovery in the chapter Listening to and Making Music Facilitates
Brain Recovery Processes. He shares how emerging research indicates music is capable of transmitting multi-modal information and not just transferring visual stimuli but, motoric and auditory signals as well. Schlaug et al. attributes the conduction of this multi sensory information to a plexus in the brain in which he refers to as the frontotemporo-parietal regions. “Furthermore, music might also provide an alternative entry point into a “broken” brain system to remediate impaired neural processes or neural connections by engaging and linking up brain centers that would otherwise not be engaged or linked with each other.” (Schlaug, 2009). Therefore by utilizing entrainment stimuli beyond the visual sense, more widespread plaque removal can be promoted. In newer mouse model studies with Boyden et al. using audio/visual adaptations of stimuli, mice also showed greater levels of beta-amyloid plaque clearance in further brain regions. This phenomenon has been identified to be a result of the audio and visual (audio-visual) approach to entrainment.

The process of plaque removal through gamma stimulation occurs through brainwave entrainment. Entrainment occurs frequently when humans are exposed to repetitious stimuli. Active and passive neurons (O’Connell, 2015) are capable of entraining to the given frequency. Through emitting stimuli of a certain tempo, the brain’s frequency following response is enacted, aligning with the given state. “Entrainment” (Figure 1) in itself is a longstanding principle first noted by mathematician and scientist Christian Huygens in 1665 when studying
pendulums. In 1973, Mt. Sinai Medical Center Doctor, Gerald Oster released a groundbreaking work evaluating the effects of presenting differently timed audio sources to each ear. This early work on binaural beats titled: “Beats on the Brain” (Oster, 1973) revealed how the brain entrained as though neurons were small-scale models of Huygens’ pendulums. The brain has numerous wave patterns associated with various states. For example, (Figure 2) the alpha wave pattern (8 – 12Hz) usually relates to a relaxed or resting state of brain activity, whereas theta waves (3 – 8Hz) indicate alertness and
concentrated attention. Gamma brainwaves (40Hz) are often associated with higher cognitive function and are known to play a role in recruiting microglial cells. In early work, Sir Francis Crick, Nobel prize winning scientist, theorized that the 40Hz brain frequency (Blanco, 2017) is likely the cornerstone of consciousness and cognition. Although the scientific community is still striving to understand the gamma frequency further, studies reveal individuals with Alzheimer’s lack the ability to enter the gamma brainwave state needed to recruit microglial cells. These cells are crucial in clearing beta-amyloid plaques (Figure 3). Beta-amyloid plaque build-up reduces synaptic connections, prevents them from repairing and keeps new ones from forming. By artificially instating gamma brainwaves through entrainment, microglial cells are recruited and dilated leading to increased plaque removal.

Figure 3: Gamma Wave Plaque Regulation Diagram
1.2 CONTRIBUTIONS

At the commencement of this research, gamma frequencies had not as yet been tested in humans, my research focused on initiating a human testing protocol to develop stimuli suitable for human perception. Mice have a smaller visual field (Figure 4), so a visual 40Hz flickering can remain diffuse when they are turned away from the light source. Humans (Figure 5) have a wider visual field and would experience the same stimuli as jarring. In light of this and other sensory differences between mice and humans, stimuli must be developed that has enough contrast to establish entrainability, as well as tolerability, better ensuring patient compliance (Krot, 2017). Patient compliance relates to how a patient willingly and correctly follows medical advice: coming in regularly for treatments or implementing prescribed care as directed as directed by the physician. Studies reveal, the more pleasant the treatment/experience is perceived, the higher the probability of a patient to be compliant. This is an integral...
aspect as a treatment shown to have efficacy can remain unsuccessful if a patient avoids it. Therefore, this is a foremost consideration in developing an instrument: both medical and musical to deliver the stimuli. Furthermore, it is currently unknown which precise sensorial pairings will ensure this. Therefore, I have created a sensorial taxonomy of multisensory gamma delivery through my research (Figure 6). Part of this exploration will also evaluate potential risks. In older individuals currently taking Alzheimer’s medication, there are some drug interaction concerns due to plaque clearance rates. However, as gamma therapy is noninvasive the risks remain notably minimal.

1.3 APPLICATIONS FOR FUTURE STUDY

It is my hope that this master’s thesis will contribute valuable information and continued longitudinal testing of gamma-based trials. The research presented in this thesis will fall within the greater context of my doctoral work over the coming years. This thesis explores a combination of designs, experiments, tests and
projects as well as the broader scope for which future testing will broach the overarching questions fueling the research.

2.0 BACKGROUND

2.1 GAMMA STUDY

This research is based in part on the initial 2016 gamma study (Iaccarino, Tsai, Boyden, 2016) This study, was conducted in mice with beta-amyloid plaques in various areas of their brains including the visual cortex region (Figure 7). These plaques resemble the beta-amyloid plaques noted in Alzheimer's disease in humans. The mice were exposed to flickering LED lights at oscillations of 40Hz for several hours daily. Following a period of this treatment, the plaques in the brains of the treated mice were greatly reduced. The study was originally developed, based on the recognition that individuals with Alzheimer's disease lack the gamma brain frequency. This frequency, although yet to be fully understood, is connected with many higher functions ranging from perception,
intuition and memory. In healthy cognitively normal adults the brain is able to merge into gamma oscillations and will frequently do so during times of intensive mental activity. As individuals age, a multitude of factors ranging from health challenges, bed rest and fatigue can tend to reduce normal activity. Therefore, there is some likelihood, that a lack of strenuous mental activity could exasperate the lack of gamma stimulation in individuals with Alzheimer’s. Despite this, individuals lacking in gamma waves, will find it more difficult to participate in activities requiring higher cognitive functions. I refer to this as the "gamma lacking cycle" (Figure 8) throughout this work. One needs gamma brainwaves to enact full cognitive function, yet cannot attain this state of cognition without these brain waves. Therefore the mouse model gamma study sought to artificially entrain these oscillations in the mouse models. The "gamma lacking cycle" is not the only aspect of gamma interaction within cognition.

Gamma brainwaves also hold a powerful role in recruiting microglial cells, vital in the process of plaque reduction. Artificially inducing these oscillations could be a vital step
towards reducing the beta-amyloid plaques (Figure 9) and fibrillary tangles ubiquitous in Alzheimer's disease.

In this study mice were exposed to the gamma light frequency. Following this treatment, researchers examined the levels of hippocampal beta-amyloid proteins. The findings revealed a reduction of 40% to 50% of these harmful protein levels. When experimenting with various frequencies of light oscillation in control groups researchers found no beta-amyloid decrease. This finding reveals possible promising results at the 40Hz oscillation level. A marked slowing was noted in the generation of beta-amyloid plaques following gamma replacement therapy (Figure 10). In Alzheimer's disease, microglial cells are often inflamed and unable to perform immune functions necessary in beta-amyloid clearance. An increase in gamma oscillation can recruit an abundance of microglial cells, leading to enhanced clearance of the amyloid plaque. Although these findings are fascinating, there is a lot left unanswered. For example, the mice are in early-stages of Alzheimer's, therefore it is not certain if there is a specific phase among the Alzheimer's stages where this intervention will be most effective or
concernedly ineffective. Furthermore as humans have extremely different sensory capacities in comparison to mice, humans will likely have varied responses to entrainment stimulation.

2.2 MULTIMODAL GAMMA APPROACH

Although the mouse model study from Iaccarino et al. relied upon a unimodal stimulation source, other cognitive studies reveal that brain entrainment can occur through multimodal stimuli. According to Harvard neuroscientist and professor, Gottfried Schlaug, music effects various regions of the brain, especially the frontotemparo-parietal regions. “Music is a strong multimodal stimulus that simultaneously transmits visual, auditory, and motoric information to a specialized brain network consisting of frontotemparo-parietal regions (Figure 11) whose components are also part of the putative human mirrorneuron system. Among other functions, this system might support the coupling between perceptual events (visual or auditory) and motor actions (leg, arm/hand, or vocal/articulatory actions). Music might be a special vehicle to engage components of this mirror-neuron system” (Schlaug, 2009). Therefore, in exploring gamma stimulation, it is vital to consider the
particularities of human perception. Humans perceive the world multi-modally. Every sensory stimuli is frequently accompanied by an association. Based on this research, it can be concluded that human subjects exposed to grating unimodal gamma stimulation, could experience incongruent associations out of phase with the gamma oscillation. Therefore by delivering the stimulation multi-modally with congruent associations, maximum entrainment can be induced (Figure 12). As seen in the study with the mouse model, light-based gammatherapy removed amyloid plaques mostly in the hippocampus region. This region is commonly linked with visual perception. Therefore, one can conclude that the region of plaque removal is indicated by the sensory modality through which the gamma is delivered. For example, one can assume that a tactile or vibration based gamma delivery could remove plaque buildup in motor cortex regions. As it is vital to take a holistic approach to plaque removal, multimodal stimuli transference systems are a focus of this work.
2.3 THE IMPACT OF ALZHEIMER’S DISEASE

Alzheimer’s disease is currently the 6th most leading cause of death in the United States. According the World Alzheimer’s Report, over 50 million people are living with Alzheimer’s worldwide. It is a difficult and painful trajectory that vastly changes daily life for the affected individual as well as their loved ones. It is a non-discriminating condition affecting even some of the greatest minds of our time from Rosa Parks to Ronald Reagan. One must wonder why the brain is so fragile that it can biologically dissolve. Family members are in the position where they must watch the person for whom they are caring, become less and less themselves. During my master’s thesis writing process, various notable individuals have lost their battles with Alzheimer’s disease including MIT’s former president Paul Gray ’54, SM ’55, ScD ’60. These notable individuals further displays how widespread and detrimental this condition is. As Alzheimer’s disease progresses, brain tissue shrinks (Figure 13). However, the ventricles and chambers within the brain that contain cerebrospinal fluid, are noticeably enlarged. In the early-stages of Alzheimer’s disease, short-term memory begins to
decline when the cells in the hippocampus degenerate. Those with the disease lose the ability to perform routine tasks. As Alzheimer’s disease spreads through the cerebral cortex (the outer layer of the brain), these three things occur: worsening of judgment, emotional outbursts and language impairment. Advancement of the disease leads to the death of more nerve cells and subsequent changes in behavior, such as wandering and agitation. In the final stages, people may lose the ability to feed themselves, speak, recognize people and control bodily functions. Memory declines and may become almost non-existent. Constant care is typically necessary. On average, those with Alzheimer's live for 8 to 10 years after diagnosis, but this terminal disease can last for as long as 20 years.

3.0 ALZHEIMER’S DISEASE

3.1 DISEASE ETIOLOGY OVERVIEW

Scientists are still working to gain a fuller scope of the multifold factors which contribute to the progression and development of Alzheimer’s disease and dementia. Factors related to genetics, health,
environment and age are currently known to contribute to the abnormal buildup of plaques in the brain. These plaques are clusters of beta-amyloid, sticky proteins which accumulate between nerve cells. When beta-amyloid accumulations increase, cell-to-cell signaling at the synaptic level becomes obstructed. The plaque congestion triggers immune cells leading to heightened inflammation as incapacitated cells are removed and absorbed (Figure 14). Disabled cells undergoing absorption often develop neurofibrillary tangles derived from the protein Tau. Although Tau generally acts as a regulator for the system's transport circulation, in diseased regions, Tau decays essentially incapacitating the system of nutrient transport. Lacking essential supplies, these cells weaken and eventually dissolve (Figure 15). This causes regions of the brain tissue to shrink while ventricles containing cerebrospinal fluid become engorged.
3.2 STAGES OF ALZHEIMER’S DISEASE

As this process occurs, individuals begin to lose short-term and working memory. Stored knowledge of task-related skills decline and contextual recognition such as place recognition, personal narrative and interpersonal connections decreases drastically. Patients experiencing these symptoms experience elevated pain levels, disorientation, anxiety and can often become ‘locked in’ and socially isolated. Eventually, patients may be unable to maintain self-care activities such as eating, speaking, hygiene practices and bodily functions. As the support of caregivers and clinicians increase throughout the progression of the disease, affected individuals can lose dignity in painful and dehumanizing circumstances.

The official stages of Alzheimer’s disease are based on Dr. Barry Reisberg from New York University. Numerous organizations including the Alzheimer’s Association as well as medical care facilities have adopted this 7 stage framework as a standardized measurement for disease progression.
Stage 1: No Impairment

The first stage of Alzheimer's disease features no clinical symptoms of the condition, it is sometimes referred to as pre-Alzheimer's disease. There may be a buildup of beta-amyloid plaques, and neurofibrillary tangles, although this does not determine future prognosis as older adults without pre-Alzheimer's disease may have similar amounts of plaque.

Stage 2: Very Mild Decline

During this second phase one will begin to recognize early signs of mild cognitive impairment. These minor concerns include misplacing items or some difficulty recalling familiar names. This stage is not unlike regular aging and may not be distinguishable on standard memory tests or to family members. It is likely that the MCPT (Multisensory Cognition Proficiency Test) test would reveal sensory changes indicative of early-stage cognitive decline. Researchers suspect that the peanut butter test may be able to detect probable Alzheimer's disease at this stage. The peanut butter test is an olfactory study which revealed individuals with early-stage Alzheimer’s have difficulty identifying even stronger smells such as peanut butter (Roberts, 2015).
Stage 3: Mild Decline

The third stage of Alzheimer’s disease will likely interfere with the patient’s lifestyle. Memory deficits will become noticeable and the patient will likely underperform on function tests. Words in conversations, names of new acquaintances and organizational skills will begin to prove challenging.

Stage 4: Moderate Decline

Both contextual and autobiographical memory will be greatly affected at this stage. Performing life tasks requiring higher cognitive functions such as bills and financial organization becomes a greater challenge.

Stage 5: Moderately Severe Decline

For elderly individuals aging in place, independent living will likely be reassessed in favor of an in-home carer or a facility. Independent tasks become more challenging and remembering mundane but necessary tasks a feat. These patients will likely still be able to recognize their loved ones both by face and name but may forget to take medications or prepare meals. Both semantic and episodic memory will be greatly affected.
Stage 6: Severe Decline

Patients during this phase will likely have lost all ability to perform tasks required for daily living. As confusion and memory loss increases greatly, patients will often be unable to recognize any of their loved ones. Anxiety also accompanies this stage as does confusion which often leads to restlessness and wandering. It is not uncommon for patients in this phase to experience hallucinations and psychotic episodes.

Stage 7: Very Severe Decline

This stage is considered to be the final stage of disease progression. Patients in this stage will often be admitted into hospice care. Sometimes patients are referred to as ‘locked in’ due to their inability to interact with, respond or react to the environment around them. Although some patients in this phase may still be verbal, their words will likely be echolalia and unrelated to any occurring event or context. While in earlier stages, individuals with Alzheimer’s may feel frustrated by their cognitive decline, patients in the final stage have little awareness about their condition. Almost all bodily functions (including the ability to swallow) present difficulty.
3.3 INNOVATIVE ALZHEIMER'S STUDIES

Although cures are still in process through long-term studies, effective solutions are not currently near. There are however specific interventions which target deficits faced by individuals experiencing remarkably difficult circumstances. One of the most effective non-invasive strategies, is in the form of music. Although many studies reveal the benefit of music (Fig 18) in dementia and Alzheimer's, the effects despite being notable, hold little long-term benefit. Previous approaches to aging and Alzheimer's disease have ranged drastically.

3.3.1 Multimodal Aerobic Alzheimer's Study

In a recent 2017 study published in the *International Journal of Physiotherapy* by Kampragkou et al., researchers created an aerobic exercise program combined with core motor-neural exercises which included memory and music therapy over a period of 12 weeks. In addition participants were given tests to access their functional and cognitive ability. “The subject group included 30 Alzheimer’s patients, men and women with middle type of Alzheimer's disease.” These participants were patients from the *Chronic Disease Center* and were placed into control and intervention groups. Alzheimer's disease incorporates various deficits, both in terms of cognitive function and motor-based capacities. Although many approach Alzheimer's through targeting cognitive processing, this intervention
sought to affect change through movement. Over the 12-week span, participants in the study group performed the following, 3 days out of the week: 30 minutes of exercise followed by 10 minutes of memory music therapy games. Evaluation was determined by: 1) Mini Mental State Examination (MMSE), 2) the “Alzheimer's disease Assessment Scale Cognitive test” (ADAS) measuring ability, 3) “Katz Index Independence in Activities of Daily Living” (ADL), 4) “Get up and Go test” as well as the 5) “One leg standing balance test” (OLST) for functionality. The study group had an improvement in The Mini Mental State Examination while the control group revealed further deterioration. This trend continued throughout the various tests with the exception of the ADL where both groups showed no change. In sum, this study reveals that a multimodal aerobic intervention offers improvement to both cognition and function in patients with Alzheimer’s but may not be enough to increase indolence for daily living (Katz Index). The functional theory concludes that by manually re-including no-longer enacted tasks and exercises, related synaptic connections can be supported, thereby deferring and preventing Alzheimer’s related deterioration.

3.3.2 Counterclockwise Aging Study

In 1979, Ellen Langer, a Harvard psychologist sought to explore whether conditions related to aging may be artifacts of our society. In the study, 8 men in
their 70’s were brought to live in a simulated 1950’s environment for 1 week. This was conducted through a multisensory intervention. Every sensory modality was shifted “back in time” in order to create the illusion of an earlier period (Langer, 1979). Chefs prepared recipes common to their youth reflecting on the post war commercial food industry. The location in a secluded and rural region in New Hampshire in a period appropriate home. The remote region was shielded from many of the modern noise pollution one would typically encounter. Beyond the stillness, sounds experienced were various varieties of birds. Within the house, analog radios played music, broadcasts and advertisements popular during the 1950’s period. As all participants left their clothes and products behind, these items were replaced by period specific brands. Every item from creams to colognes had period appropriate scents evoking olfactory memories, common to their youths. Visually, residents were stimulated by period clothes, 1950 television shows and decor. After the study commenced, every participant reported feeling younger thereafter and 60% had higher IQ and memory test scores.

### 3.4 Alzheimer’s and Music Research

#### 3.4.1 Anxiety Attenuation

A study conducted by H. B. Svansdottir et al. in 2006 at Landspitali University Hospital in Reykjavik, Iceland revealed music therapy has the capability to reduce
anxiety in patients with moderate and severe dementia in a case–control study. Patients (N=38) diagnosed with moderate or severe Alzheimer's disease were randomly assigned to participate in either the control or therapy group. Interactive music singing and listening sessions in the therapy group revealed “a significant reduction in activity disturbances in the music therapy group during a 6-week period measured with the Behavior Pathology in Alzheimer's disease Rating Scale (BEHAVE-AD). There was also a significant reduction in the sum of scores of activity disturbances, aggressiveness and anxiety.” Although results were encouraging, the longitudinal examination revealed the positive results to remain for only four weeks following the end of music therapy. This aspect indicates that music interventions for these patients are effective but need to be implemented on an ongoing basis.

3.4.2 MEMORY RECALL

In a study performed by Nicholas R. Simmons-Sterna et al. at Boston University in 2010 compared levels of memory recall in conditions including songs versus non-music listening conditions. Participants diagnosed with Alzheimer’s were encouraged to recall both personal memories and lyrical memories in conversation with researchers. Patients in this condition experienced staggered and halted speech and struggled to recall basic wordings. However, in conditions
where music was included in the interaction, participants experienced greater recall of lyric and personal memories. According to Simmons-Sterna, “the results confirmed our hypothesis that patients with AD performed better on a task of recognition memory for the lyrics of songs when those lyrics were accompanied at encoding by a sung recording than when they were accompanied by a spoken recording.”

3.4.3 SOCIAL INTERACTION

According to Ayelet Dassa’s and Dorit Amir’s 2014 study, “the role of singing familiar songs encouraged conversation among people with middle to late-stage Alzheimer’s disease.” Researchers exposed a group of patients with late-stage Alzheimer’s to group-music therapy sessions over the course of a month. Patients participating in the sessions who listened to favorite songs from their younger years experienced increased inter-social engagement with both fellow patients, family members and caregivers. Dr. Amir stated, “content analysis revealed that songs from the participants’ past elicited memories, especially songs related to their social and national identity. Analyses also indicated that conversation related to the singing was extensive and the act of group singing encouraged spontaneous responses. After singing, group members expressed positive feelings, a sense of accomplishment, and belonging.”
3.4.4 COGNITIVE PROCESS OF MUSIC INTERVENTION IN ALZHEIMER’S

Music impacts the cognitive process in patients with dementia on a multidimensional level. According to a study performed by Simmons-Stern et al., “Music processing encompasses a complex neural network that recruits from all areas of the brain, including subcortical areas such as the basal ganglia, nucleus accumbens, ventral tegmental area, hypothalamus, and cerebellum (Grahn, 2009; Levitin and Tirovolas, 2009; Limb, 2006) and cortical areas such as the medial prefrontal cortex (Janata, 2009) and orbitofrontal cortex (Limb, 2006) that are affected at a slower rate in AD compared to the areas of the brain typically associated with memory (Thompson et al., 2003). Thus, stimuli accompanied by
music and a sung recording may create a more robust association at encoding than do stimuli accompanied by only a spoken recording in patients with AD.”

3.5 REVIEW OF SHORTCOMINGS IN PREVIOUS ALZHEIMER STUDIES

Previous studies for Alzheimer's have not proven successful or adaptable in clinical settings due to a number of outlying factors:

Unimodal: some of the previous studies have suffered from the fact that they are approaching a multimodal disease (Alzheimer's) with a unimodal approach. Even current medicine has a good understanding of the multifaceted concerns relating to this disease. When treating Alzheimer's disease, it is common to treat symptoms as they arise. Therefore a patient will be prescribed various medications ranging from sleeping interventions (for circadian rhythm support), anti-hallucinogenic supplements (as patients often experience visions, disembodied sounds and hallucinations), antidepressant medication to aid in mood stability, as well as drugs to support neuropathy and nerve-related sensations. Every individual experience with Alzheimer's is dictated by the extent and regional orientation of damage to the brain. As the disease progresses, more regions are affected. Therefore, when developing a treatment, it is vital to explore one that can affect a widespread change. In mouse model studies conducted as part of the aging brain initiative (Tsai, Boyden 2016) mice who were exposed to
the 40Hz gamma light frequencies experienced reduction of beta-amyloid plaques specifically in the visual cortex regions whereas mice receiving multimodal stimuli had more widespread plaque removal.

**Imbalanced Approach:** Although the link between Alzheimer’s and music has been exemplified in various studies, researchers approaching this work usually stem from neuroscience or cognitive studies. Although this is beneficial for other areas of research, it lacks musicological knowledge vital to identifying specific sonic factors responsible for neural changes. When this form of research is approached purely from a music studies/ethnomusicology scope, it can lack aspects allowing it to cross over into the clinical domain.

**Failure to Cross Clinical Threshold:** Ellen Langer’s (Harvard University) 1979 study had incredible results in every single participant with 60% of the participants having significant improvement in memory and IQ scores, even weeks following the initial intervention. Unfortunately, this study lacked specific scientific formatting that would allow for repetition or identification of the specific components which factored into the remarkable changes. This fascinating experiment would be worth repeating with structural analysis in place.

Learning from previous studies, I have been inspired in my research to make strides at this unique intersection of research. Given my multidisciplinary background and expertise in rarely explored realms of sensory studies, health
and music cognition, I view this master's work as part of bridging these vastly different worlds in my collaborating with the Aging Brain Initiative. These contributions will support the foundation of broader understandings of the role of music in the context of medicine.

3.6 DESIGNING NOVEL TESTS FOR LATE-STAGE ALZHEIMER’S

Current clinical behavioral tests for Alzheimer’s are geared towards diagnostics and detection during earlier stages. The tests prove non-applicable for assessing later stages of Alzheimer’s and tracking subtle changes of disease progression or reversal. In undertaking this research where Alzheimer’s reversal seems a probable concept, having a test which may access areas of possible improvement would be essential. Finally, as many tests are geared towards earlier stages, they overlook the crucial opportunity to provide clinical baselines and reference points in later and non-verbal stages. The results of the newly adapted tests are not compared to a specific standard but rather an individual’s own baseline score to determine cognitive health. The MSE (Mental Status Examination) is one of the tests that influenced the design of the LSAE (Late-stage Alzheimer’s Examination). The MSE has several sections including those that focus on observations over inquiry - beneficial for individuals who are not verbally expressive.
MSE Observation Components

Appearance (observed)

Behavior (observed)

Attitude (observed)

Level of Consciousness (observed)

Orientation (inquired)

Speech and Language (observed)

Mood (inquired)

Affect (observed)

Thought Process/Form (observed/inquired)

Thought Content (observed/inquired)

Suicidality and Homicidality (inquired)

Insight and Judgment (observed/inquired)

Attention Span (observed/inquired)

Memory (observed/inquired)

Intellectual Functioning (observed/inquired)

By combining observed aspects of the MSE (Mental Status Examination) test in addition to specific gestural observations NVB (Non Verbal Baseline) I created a
new testing modality to examine participants or patients who are non-verbal (see appendix). Throughout this work, my restructured form of this test is referred to as the NVBMSE (Non Verbal Baseline Mental Status Examination). Prior to my creation of NVBMSE, there were no non-verbal tests for patients with Alzheimer’s. Usually, once a patient reaches the later stages of Alzheimer’s where a patient is no longer able to verbally communicate, the medical team does not closely monitor cognitive changes relating to intellectual aptitude. However, my research reveals that subtle sensory indicators are ideal barometers to identify subtle but marked changes in patients receiving gamma therapy.

3.7 ANECDOTAL GAMMA APPROACHES

The Tsai, Boyden et al. study is groundbreaking, especially since subsequent to the publishing of their research, independent researchers and musicologists have taken notice and have been conducting preliminary tests with this 40 Hz frequency. These results have both been anecdotally reported to the Aging Brain Initiative as well as documented through open source postings and blogs. Trends noted throughout these studies reveal that Gamma treatment seems to help loved ones become more engaged and active. The Aging Brain Initiative has received reports that loved ones have been setting up rudimentary gamma light systems for their ill relative. Some of these individuals who have created their own DIY
gamma rigs have been in close contact with the Aging Brain Initiative team and have shared various documentation to demonstrate notable milestones in cases where their loved one regained speech or greater range of physical expression following 40Hz exposure. Although these tests are not conducted in controlled environments, they provide interesting recounted testimonies of a growing movement of cognitive hacking and generally positive outcomes. In 2016 a study was conducted at the University of Toronto where Alzheimer’s patients received 6 sessions which involved vibroacoustic therapeutic chairs with built-in speakers set at 40 hertz. Subsequent to this their cognition is noted to have greatly improved. In a 2017, a month after the publishing of the NATURE study, a company by the name of TheraNova conducted a small scale trial with an elderly pair in San Francisco. The wife was diagnosed with Alzheimer’s and experienced an improvement upon exposure to the Gamma lights on a consistent basis for 1 month. “She rarely remembers events from earlier in the day, even something memorable, like a visit from one of their six children”. The study reported that, “within days of beginning the trial at TheraNova, Peg’s memory improved. She began to remember events from the day before, not always, but far more often. Their children remarked on it. Peg also seemed mildly euphoric after the sessions.” Due to the experimental nature of the treatment, the trial was abruptly discontinued, the once positive benefits witnessed by Peg’s husband and family quickly diminished. He shared his frustration in a letter: "Peg has declined. When she entered the study she was seen as stage three of seven, she stayed in 3 for
the whole trial until August. At the end of trials she immediately regressed to 4 in my opinion.” This raises concerns regarding potential variance in patient treatment response and length of therapy as 6 sessions may not be enough to trigger long-term plaque removal.

4.0 DESIGNING FOR ALZHEIMER’S AND THE AGING BRAIN

4.1 CLAIMS AND HYPOTHESIS ON AD AND SENSORY PERCEPTION

As AD affects various brain regions, there are a variety of sensory changes that can occur. Although one could argue that sensory changes are solely due to brain damage in specific regions, my work establishes a new theory based on this overarching question: How much of our active sensing is based on previous memory? It is easily assumed that we are perceiving the world in real time. However, it is likely that our perception of a current experience is only a sensory trigger for an entrained perceptual response recorded at an earlier biographical point. A 2009 study titled, “The influence of memory on perception: It’s not what things look like, it’s what you call them” revealed that “prior knowledge influences how we perceive the world.” In the study, Dutch and German participants arranged various color cards from a yellow-to-orange continuum. According to the study, this research was conducted “on stimuli that were prototypically orange or
yellow and that were also associated with these color labels. Both groups gave more “yellow” responses if an ambiguous hue occurred on a prototypically yellow stimulus. The language groups were also tested on a stimulus (traffic light) that is associated with the label orange in Dutch and with the label yellow in German, even though the objective color is the same for both populations. Dutch observers categorized this stimulus as orange more often than German observers, in line with the assumption that declarative knowledge mediates the influence of world knowledge on color categorization (Mitterer, 2009).” Another example of this is our well-established understanding of various scents. Our olfactory regions are mediated by memory connections which delineate the sweet scent of soap from the sweet smell of a cookie. One will recognize a cookie as inherently edible and the other as inedible, in spite of the fact that both elicit a sweet odor. A toddler smelling the bar of soap will likely take a bite, while an older child or adult will refrain from doing so, having previously made the association that certain scents are not related to the ability to safely consume an item. Is most of perception association? As most associations are learned and rely upon memory, it is no great leap to state that most perception is memory based. My hypothesis explains why people with AD experience a severe disconnect from their environment. For a person with AD, the world without context becomes surreal. Shadows appear to be entities, dark floor tiles seems to be holes in the ground and one’s own feet can become unfamiliar scurrying phantasms. Studies have long documented the fact that our visual perception of color is modulated by the
names we learn to call various hues. For example, indigenous Inuit populations have several hundred variations of white and while in the English language, we have only a few. Furthermore, the few words for variants of the color white usually aren’t transferable across individuals i.e. the difference between pearl white, ivory white and off-white. If one forgets learned and cultural associations, does one also forget how to sense the world? Are individuals with Alzheimer’s sensing the world in its purest form, unaided by previous assumptions or cultural influence? If you have no reference to relate something to, then something isn’t anything. We learn to base our perception on the experiences we have formed, a color is muted or bright usually in relation to another. We are the product of our associations which is why in forgetting these associations, one loses oneself. According to Marvin Minsky the idea of ‘consciousness’ is a “suitcase word.” In drafting his book ‘The Emotion Machine’ he examines the concept of consciousness from various perspectives, “Thinker 1: Consciousness is what unifies our present, past, and future together, by making sense of all our experience. Thinker 2: Consciousness makes us 'aware' of ourselves, and gives us our sense of identity; it is what animates our minds and gives us our sense of being alive. Thinker 3: Consciousness is what gives things meanings to us; without it, we would not even know we had feelings” (Minsky, 2005). Minsky reveals that these myriad perspectives show, “that "consciousness" does not refer to any single idea or thing, but that we use it as a suitcase-word for a great many different activities” (Minsky, 2005). In unpacking this, I hypothesize that ‘consciousness' is
the cumulation of recalled multisensory associations. As music connects various sensory regions, the memory-restoring effect so often seen in patients listening to songs of their youth, is justifiable.

4.2 PERCEPTION CHANGES IN ALZHEIMER’S AND AGING

4.2.1 AUDITORY/SOUND PROCESSING AND MUSIC

Various studies have documented music’s ability to provide a successful conduit to facilitate text comprehension in individuals with Alzheimer’s (Raglio, 2009). However, in the non-Alzheimer’s population, there was no significant difference in trials with and without music. The remarkable elevation in the test scores of individuals with Alzheimer’s is attributed to the fact that parts of the brain which process music are more widespread. Therefore, more surface area is likely to be preserved allowing music to be a conduit to a wider processing range, compared to dwindling regions of the brain that usually process speech or text. There is however, a slight variation in musicians. A study conducted in 2016 (Baird, 2016) examined musicians in aging populations with Alzheimer’s disease as well as healthy elderly individuals. Comprehension and memory testing was performed at two delay intervals including 30 minutes and 24 hours. Results of this study were overall congruent with previous studies revealing that individuals with Alzheimer’s have significantly better recall when words are sung instead of spoken.
Furthermore, this study revealed musicians with Alzheimer’s showed further improved memory of sung text over non-musician participants with Alzheimer’s. This indicates that musical training facilitates memory functions in people with Alzheimer’s.

4.2.2 VISUAL PROCESSING

E. Salobrar-Garcia (2017) performed an assessment of the visual acuity, contrast sensitivity, color vision and visual integration in the Alzheimer's disease progression according to the scale GDS. This study was conducted with 38 patients with mild to moderate Alzheimer's disease as well as a control base. Patients with mild Alzheimer’s revealed a drastic decrease in visual acuity, spatial based contrast sensitivity (“the higher the spatial frequency, the greater the loss of CS perception”) and lowered ability to see blue-toned colors. Although patients with moderate Alzheimer’s exhibited far greater cognitive decline, their performance on the named tests was congruent to the participants with mild Alzheimer’s. According to this study (Garcia, 2017) “a significant increase of the total number of errors in the color test (p < 0.05)” was recorded in all instances. No notable differences were noted between the mild and moderate groups for visual acuity, contrast sensitivity. Results reveal that visual tests are a good early marker for Alzheimer’s. This is because, in identifying Alzheimer's disease
progression, some of the most significant changes occur in color vision. The article states that this is likely linked to the fact that, “AD patients, show alterations in the M, P, and K visual pathways. Psychophysical tests could be useful tools to diagnose support and follow-up in mild AD.” Another study exploring color vision in Alzheimer’s patients, tests a patient’s ability to perceive illusory (optical illusion) colors. Certain optical illusions are able to invoke colors in healthy brains. This study revealed similar findings of color perception decline in individuals with Alzheimer’s. The study employed the Fechner Color Theory as a method to explore perceptual changes in patients with Alzheimer’s. The Fechner color effect is demonstrated by viewing a moving black-and-white disk with patterns. When one views the moving patterns, illusory colors appear sometimes known as pattern induced flicker colors (PIFCs). This perceptual quirk was initially noted by Gustav Fechner (Figure 17).

Color receptors resonate with different wavelengths and may be responsible for the various tones individuals perceive. According to (von Campenhausen & Schramme, 1995), the effect is induced by latencies of color-specific ganglion cells originating from retinal neural activity and amplitude changes in the primary visual cortex which aid in the process or pattern recognition. As a result of this, when the black and white wheel is spinning, a range of colors appear. In

Figure 17: Fechner Color Wheel
Kaubrys’s 2016 study *Perception of Fechner Illusory Colors in Alzheimer Disease Patients*, 40 Individuals with Alzheimer’s were recruited alongside 40 normal controls. A speed-controlled rotation device turned an achromatic Benham’s disk. Variables of variant speeds and directions were presented to illicit illusory colors. Results revealed that subjects in the Alzheimer’s group experienced a narrower bandwidth of colors. For example, for one patient, out of the 8 arcs of color, only 3 appeared strongly. The most significant difference between the control and Alzheimer’s study groups was in the color blue (“$\chi^2=26.87$, $p<0.001$ clockwise, $\chi^2=22.75$, $p<0.001$ counter-clockwise”) which was nearly imperceptible for the patients with Alzheimer’s. Researchers surmise this shift is likely due to visual cortical impairment. A study conducted by N. A. Arnaoutoglou revealed that “color perception differentiates Alzheimer's disease (AD) from Vascular Dementia (VaD) patients”. Although both conditions present with a similar effect, the affected regions of the brain vary. According to the study, “The Ishihara color blindness test has a sensitivity of 80.6% and a specificity of 87.5% to discriminate AD and VaD patients when an optimal (32.5) cut-off value of performance is used.”
4.2.3 DESIGN FEEDBACK TESTS

Most digital interfaces and applications despite accessibility features and accommodative settings are difficult for elderly individuals to use, especially those with Alzheimer’s or dementia. In a feedback session at the elderly care home Youville (Figure 18), over 20 elderly individuals participants joined in a music technology design feedback session. Music is beneficial for individuals with Alzheimer’s especially when performed. In places such as patient rooms or elder care apartments where traditional instruments are impractical, digital instruments are good options. Participants trying an iPad music interface (Figure 19) reported various difficulties in using the system. Although a few were able to use the interface to make music, most found it difficult. The top 3 concerns were: tactile interface, multi-touch and icon placement. The screens used in many of the digital interfaces require a certain amount of hand moisture, moisture that is usually lacking in older skin (Kalisch, 2017). Therefore, elderly individuals often resort to using i-pens in order to interact with the device, removing much of the innate aspects of music making. Secondly, there was no interface that functioned purely as an instrument without additional features. Ordinarily, additional features can be welcome, however, when
hands movements are more imprecise, additional unwanted windows can pop up or the whole app can shut down distracting from the overall experience due to frustration. Finally, navigating the applications with icons without words for non-self explanatory instruments proved challenging.

4.3 MULTISENSORY TESTING

4.3.1 OLFATORY TESTS

The peanut butter test is one of the principle studies associated with sensory diagnostic criteria. Over 90 participants study conducted at the University of Florida to explore olfactory changes in Alzheimer’s. The study tested three subject
groups: neuro-cognitively healthy subjects, participants with Alzheimer’s in stages 1 through 3 and individuals with dementia. All participants were asked to identify peanut butter placed in increasingly nearer intervals to their nose. The only participants who struggled to smell the peanut butter were the participants with Alzheimer’s. Researchers noted that in these patients, their left nostrils seemed less able to identify the smell (Figure 20). In fact the sample of peanut butter needed to be moved 10 cm closer to the left than to the right before accurate identification took place. Another study which utilized the sense of smell as a diagnostic measure for Alzheimer’s was conducted by Mayo Clinic Researchers in Rochester, Minnesota. In their study, elderly participants who tested poorly on olfactory tests had a 2.2 times greater chance of exhibiting other symptoms of cognitive decline. The results also revealed that participants who reported memory difficulties during the initial assessment and therefore had low test scores had a greater tendency to develop Alzheimer’s (Roberts, 2015).

A three and a half year longitudinal olfactory study published in JAMA Neurology included the collective data of 1400 individuals. The average age group was 79. All participants were healthy and near cognitively normal exhibiting no measurable symptoms of memory dysfunction or deficit. All participants underwent smell tests with 12 items including food and non-food scents. Over the 3 1/2 years, 64 participants were diagnosed with early-stage dementia and 250 participants developed minor memory problems. Results revealed that as
olfactory capabilities decreased, their likelihood of Alzheimer's and memory loss increased. Researcher Rosebud Roberts stated that “the findings suggest that doing a smell test may help identify elderly, mentally normal people who are likely to progress to develop memory problems or, if they have these problems, to progress to Alzheimer’s or dementia” (Roberts, 2015).

4.3.2 VISUAL TESTS

A clinical study tracked “Visual dysfunction and its correlation with retinal changes in patients with Alzheimer’s disease” (Vilades, 2016). Twenty-four patients with Alzheimer’s disease and 24 controls underwent multiple vision tests: “visual acuity (VA), color vision (using the Farnsworth and L’Anthony desaturated (D) 15 color tests), and contrast sensitivity vision (CSV; using the Pelli-Robson chart and CSV-1000E test) to measure visual dysfunction.” In addition to this, spectral domain-optical coherence tomography was used in imaging measurements of the retinal nerve fiber layer and macular thickness.

Structural measurements of the Retinal Nerve Fiber Layer (RNFL) and macular thickness were obtained using Spectral Domain-Optical Coherence Tomography (SD-OCT). Alzheimer’s patients showed significantly poorer performance in the contrast sensitivity vision, color vision tests. Furthermore, macular thinning was noted across every sector tested with exception of the fovea and the RNFL. These
results are consistent with the fact that color vision is correlated with macular volume. The study concluded that patients with AD had visual dysfunction that correlated with structural changes evaluated by SD-OCT. Macular measurements may be reliable indicators of visual impairment in AD patients.

4.3.3 TACTILE TESTS

Cognitively healthy individuals employ haptic or tactile analysis countless times in daily life. In tests, these individuals can accurately identify both common and uncommon objects, merely by touch, without error. According to Lederman, “Haptic perception is a process mediated by cutaneous and kinesthetic afferent subsystems” (Lederman, 2018). A large number of mechanoreceptors and thermoreceptors embedded in the skin as well as mechanoreceptors in muscles, tendons, and articulated joints provide the information necessary for the active exploration of objects and surface properties (Kalisch, 2016) Although other sensory mechanisms in Alzheimer’s have been more widely tested, tactile based diagnostic measures for this disease are uncommon. Tobias Kalisch’s research entitled “Cognitive and Tactile Factors Affecting Human Haptic Performance in Later Life” offers good insight into haptic-
based cognitive processes in 81 older adults. The study investigated the haptic capabilities of older adults through object recognition testing (Figure 21). Principle findings include age correlated performance decline. Humans frequently rely on vision to provide information about the world around, however, haptic signals can provide similar cues that interact with both tactile and visual regions of the brain. Our tactile sense is one of the most sensitive and discerning of all our senses. A study conducted by researchers at the Royal Institute of Technology in Sweden researched human tactile perception through double-blind tactile tests. Participants were able to feel ridges only nanometers in size. It as previously believed that humans are able to feel a feature about .2mm. However, with dynamic touch, humans are able to feel features as small as 13 nanometers. Mark Rutland, Professor of Surface Chemistry at the institute stated, “This means that, if your finger was the size of the Earth, you could feel the difference between houses from cars.” Touch recognition is highly linked to various cognitive processes. The way one moves the hand over a surface, for example, is a sequence of highly strategic tactile hand placements to provide information capable of reconstructing an identifiable concept of an unidentifiable object. Furthermore, coordination with visual memory is another factor which relates to recognition ability. Finally, other aspects of recognition such as object weight, surface texture, and density provide multimodal clues towards identification. This study reveals the importance of a touch-based examination. This would provide further insight into Alzheimer's disease progression or recession.
4.3.4 AUDITORY TESTS

Many studies indicate that music upon listening to music the brains of Alzheimer’s patients process these sounds differently than brains unaffected by a euro-cognitive disease. Although music boosts progress in memory exercises far more in the Alzheimer’s population than the general population, it is not currently known if part of this effect could be due to the altered sound processing occurring in this disease. A 2016 mouse model study (Otama, 2016) revealed that amyloid plaque accumulation extends beyond the brain into cochlear hair. These plaque cells contribute to auditory distortions especially for higher frequency ranges (>32 kHz), intrinsically changing sound conduction and ultimately its perception. Past studies have revealed a correlation between hearing loss and Alzheimer’s. However, this finding reveals possible biological channels through which this could occur. In humans, this has been studied through the application of the Montreal Battery for amusia evaluation (Campanelli 2016). In this study, 30 patients with Alzheimer’s disease and 30 healthy controls were given the Montreal Battery of Evaluation of Amusia (MBEA). According to researchers, “This battery evaluates melodic (scale, contour, and interval) and temporal (rhythm and meter) perception of music and musical memory.” Researchers were surprised to note that while there was evidence of altered music processing in the Alzheimer’s group, many music-related abilities were spared. According to the study, “AD subjects show partially spared abilities
for temporal organization of music, though not for melodic perception and musical memory.” This indicates that temporal lobe regions responsible for timing, tend to be preserved.

A study last year also explored Alzheimer’s and music perception but through an emotional lens. The study “recognition of emotions from voice in mild cognitive impairment and Alzheimer's disease dementia” (Amlerová, 2017) 89 patients with Alzheimer’s participated in a multiple choice listening exercise. Subjects with documented ranges of disease severity listened to 25 sentences with various emotional prosody including happiness, sadness, fear, disgust, or anger. “Amygdala, temporal pole (TP) and superior temporal sulcus (STS) were measured by volumetry (1.5T MRI, FreeSurfer 5.3.). Kruskal-Wallis H test with post-doc Mann-Whitney U tests corrected for multiple comparisons using the Holm-Bonferroni correction were used to evaluate between-group differences in emotional prosody” (Amlerová, 2017). Difficulty in identifying emotional affect correlated directly with disease progression. Future studies could examine whether spoken prosody scores could be increased through sung stimuli.

A study performed by Laura Maria Araújode Carvalho revealed that individuals with Alzheimer’s also have difficulty with speech processing in general (Carvalho, 2017). The cocktail party effect is often referred to in sound perception as being
able to differentiate background noise from foreground, directed speaking. The study explored a variety of factors that affect perceptual performance of understanding speech. The sample pool consisted of 25 elderly individuals with a range of Alzheimer's stages. There was a statistically significant correlation between poor scores on the Alzheimer's disease Assessment scale and hearing ability. Furthermore, psychiatric testing revealed a correlation between lack of hearing in Alzheimer's and increased rates of depression and a predictor for increased progression.

In light of the sensory changes occurring in Alzheimer's, I created the MCPT (Multisensory Cognition Proficiency Test). The MCPT (see appendix) is the first and truly multisensory test for Alzheimer's disease. The MCPT is an examination to determine baseline sensory cognition proficiency and establish precise markers for sensory changes at various intervals in patient care settings or a longitudinal experiment. Unlike traditional memory or IQ tests, this exam explores cognitive health and aptitude through distinct sensorial measurements (visual, olfactory, auditory and tactile) which in sum, present the detailed cognitive-behavioral profile of a patient or study participant. Present scores can be compared with past scores to identify improvement or regression. Another Alzheimer’s test engaging many of the senses is the CogNotes system for early detection designed by Adam Boulanger. According to the Alzheimer’s Review website, “CogNotes is actually a first cognitive diagnostic tool to perform daily
assessments, or at least with enough frequency that an individual can flag initial signs of Alzheimer’s disease soon enough to start effective treatment.” According to Boulanger, the system can be summed up as, “Alzheimer’s Disease assessment embedded in the creative act of music composition” (Boulanger, 2014). This groundbreaking approach was a major departure from standard memory question and answer tests, incorporating rewarding creative aspects. For the test, participants are instructed to compose on the Hyperscore software, following this, they hear a 1.5 second long clips from their song and view the song-fragment on the screen. Participants are prompted to place the sample into the correct location of their overall composition. There are various levels of testing novel pairings based on the original composition. Counterintuitively, individuals with musical background do not have any advantage in this test. The multisensory aspect of combining music listening, visual associative sound representations and memory, actively engages various cognitive regions and thereby more closely assesses several aspects of cognition ranging from working memory to auditory acuity. The MCPT is likely complimentary to the CogNotes system as it does not focus on aspects of memory to examine cognitive decline. Instead, the MCPT tests sensory function to create a personal point of reference in evaluating cognitive health. the MCPT includes additional sensory implications such as smell, color and tactile identification, senses that are usually not included holistically in other Alzheimer’s tests or in the computer-based CogNotes system. In fact for testing purposes, color, smell, color and tactile identification must have
physical or tangible manifestations. According to the head of University of Newcastle’s Tetrachromacy Project, Dr. Gabriele Jordan, even when testing for color vision in optometry or tetrachromacy tests, medical practitioners prefer not to use computers partly due to monitor, bandwidth and frequency variance.

4.4 ALZHEIMER’S IN THE ARTS

In taking a multimodal and multisensory approach to the treatment and study of Alzheimer’s disease it is important to consider the role of Alzheimer’s in art. The

Figure 22: William Utermohlen Paintings
most known case of an artist with Alzheimer’s is painter William Utermohlen. When diagnosed with Alzheimer’s, Utermohlen began to track his illness and the toll it took on his perception and his self-image through portraiture. Every year for a sum of eight years, Utermohlen painted himself. In Figure 22, some of his portraits are displayed and dated. One can see how he painted prior to his disease in 1967. The painting the year of his diagnosis, 1996 shows Utermohlen intensely gazing at the viewer, one eyebrow slightly lifted perhaps indicating confusion in the face of resignation. During the early phase of diagnosis, it is common for individuals to feel frustrated at their increased confusion and memory loss. Often, individuals struggle to grasp for words, search for misplaced items. For these individuals, discerning their whereabouts and connections to relatives becomes increasingly challenging. In 1997 (Figure 22), the painting uses sullen colors which seem to capture this stark moment. He also appears to be looking down with his head slightly tilted forward as though he was on a precipice, looming precariously over the edge, about to fall over. Although the color variance does not appear upon first glance, upon analysis, each point and tone is subtle but carefully chosen to construct a slight reddening of the face and features; a careful and skilled use of tonality. Perhaps most notable is the fine quality of each stroke. Even upon magnifying the photograph, it never falls apart in the way an impressionistic renderings might. Instead, details seem more apparent, pores rush to the field of vision and stray hairs appear almost photorealistic. In the year labeled 1998, we are moved by an onslaught of four
colors. In this portrait, his face is almost all yellow save for shading using orange. The painting seems to be painted either from a mirror with molding or through a window. Dashes of blue and red line the structure on the side. A bold use of color once again to define features. His face sags beneath an almost comically pinched mouth and jagged eyebrows frame eyes that seem simultaneously widened yet narrowed. Depicted as year 1999, the strokes become less defined and the style merges further from photorealism. In this year although he includes more color, he hardly distinguishes the facial color from the background color with one bleeding into the other, only to be defined by a thick almost crayon-like line. The artist's mouth is agape and the eyes are blurry and unfocused. It is difficult to distinguish if this is due to the challenging nature of capturing light scattering and directionality with a human eye on paper or whether he was simply honoring a reality of his condition at the moment. As further paintings progress, the strokes become increasingly thick, losing detail and increasing pigment to the face so that it becomes increasingly mottled distorted. The pigment becomes placed without attention to shading and seems carelessly applied without any feature-defining qualities. By the last portrait, a face is barely distinguishable and what remains seems skeletal and distorted.
4.5 SENSORY CHANGES SUMMARY

The previous studies placed within this multisensory taxonomy of perceptual changes in Alzheimer’s creates a structure for a new type of diagnostic testing. In treatment, many protocols center around occupational therapy. As Alzheimer’s affects the brain widely, it may be more valuable to implement therapeutic interventions through the various sensory stimuli in order to evoke brain higher-functioning rhythms such as gamma while supporting certain synaptic pathways. It is vital that this approach is multisensory as so many senses are impaired in Alzheimer’s, by exerting these regions through sensory stimulation, it is likely that various brain regions can be re-stimulated.

5.0 MULTISENSORY APPROACH

5.1 MULTISENSORY RESEARCH BACKGROUND

My background experience prior to commencing my studies at M.I.T. allowed me to specialize in multisensory research. I chose this enigmatic scope of research when studying the brain and its various mechanisms as I noted early in my academic career that aspects of our brain can be tested, defined, researched and treated through the exploration of the senses (Figure 23). My capstone thesis at Stanford University, where I received my bachelor’s degree, encompassed the
studying of multisensory perception through the lens of synesthesia, a neurological quirk of sensory cross-modal associations. Based on my research, I created computer-aided tools to evaluate cultural and neurological sound associations through a battery hosted on a self-created web platform capable of providing unique windows into cognition, neurology and music. While studying at Oxford University, I examined the role of sound as weapon of war. At Dartmouth, my master’s thesis, examined the neural pathways, plasticities and interconnectivity of the brain through multisensory perception. This was explored through the studying of “Cultural Synesthesia”.

5.2 MULTISENSORY PERCEPTION IN HUMANS

“Cultural Synesthesia” does not fall under the scientific category of true synesthesia but stands as a statement to sonic environment and tone associations. Neurological synesthesia stems from the Greek words syn: meaning
“with” or “joined” and a second word, aisthesis translated to mean “feeling” or "senses.” This etymology accurately describes the condition. The neurological quirk Synesthesia creates an effect in individuals allowing them to perceive stimulus through several senses. A leading theory attributes this to an interconnectivity of the somatosensory pathways. This is a fascinating condition where in effect, the brain's pathways are “cross wired”. (Cytowic) When one of the senses are stimulated it evokes distinct, involuntary, sensory/cognitive reactions in another pathway. Although nonsynesthetic people may not experience powerful cross modal effect, all brains function through multimodal aspects. During my studies, I also worked as a scanning assistant with Prof. Michel Casey at Bregman Media Labs, on a temporal lobe study to identify whether imagined/hallucinated music pitch orientation can be recovered via fMRI (Casey, 2017). This study was replicated in the Brain and Cognitive Science department at Dartmouth by recovering the same pitch and tonal data but from visual cortex regions of the brain. In helping to spearhead the MusicMindHealth initiative alongside Dr. Joe O’Donnell at Geisel’s School of Medicine, further research revealed the importance of integrating music-based and multisensory studies in the
medical field. Human beings rely upon associative layers (Figure 24) to underlie and define perception. These layers include: learned, cultural, universal, synesthetic, (epi)genetic, environmental, and learned associations.

**Learned Associations**

The fact that we are able to read and write is based on associating abstract shapes (letters) with vocal sounds (letter names) and stringing these together to form words with meanings which we combine to express specific sentiments in the form of sentences. Learned associations reach beyond this and even include aspects of our information processing and academic knowledge acquisition.

**Cultural Association**

This relates to the fact that our perception is largely shaped by our culture. For example, the colors we know are not standard universal colors, but a product of our environment and cultural affordance. Some cultures such as the Candoshi-Shapra people of Peru have different color naming and groupings (Kay, 2009). Studies have shown that on color difference tests, people from this tribe do not distinguish some of the colors we would separate as vastly different such as
yellow and red. Another example of cultural association could lie in associating types of music as happy or sad.

**Universal Associations**

Some associations are universal as they are based on our human cognitive structures. Although particular neuro-diversities may add variance to these “universal associations”, neurotypical individuals share particular associative features across the globe. For example, Köhler’s (1929) linguistic “Kiki, Boulba” study, demonstrates associations in non-synesthetes, supporting the hypothesis that general listeners engage cross-sensorial connections. The Kiki, Boulba experiment (Köhler) in linguistics reveals a phenomenon of name-to-shape association among a general (non-Synesthetic) subject base. Even in recent repetitions of this experiment, over 90 percent of all subjects identify the spiked shape with the name Kiki, and the rounder shape as Boulba. This principle has been further explored on an international level study at Dartmouth (Sievers et al., 2011). The Bouba/Kiki effect (Kohler) denotes a cultural synesthesia found in non-specified mappings between objects and sounds. For the purposes of this experiment, subjects are presented

*Figure 25: Köhler 1929, Kiki (R) and Bouba (L) Stimuli*
with two distinct shapes (Figure 25): one spiked, the other cloud-like. When asked to select which shape was “Bouba” and which was “Kiki”, subjects unanimously named the spiked shape to be “Kiki” and the rounder shape “Bouba.” This associative process is indicative of an innate differentiation between the active conscious part of the brain and the passive. These shapes and sounds mimic the way in which neurons in the brain are arranged. My explorations in the multisensory field revealed how our cognition is rooted multi-modally and that the ‘suitcase word’ consciousness lies within the array of sensory associations. Based on this past research, I have established that humans are able to accurately detect specific visual shapes within sounds, even in repetition trials.

**Environmental Associations**

Some universal associations rely upon environmental factors such as human beings on planet earth. For example, important road signal lines around the world are yellow reminiscent of the sun. The color red for example universally seems to represent danger to the point where stop signs are red in all countries around the world. Prior to 1954 stop signs were yellow until the traffic influx increased the need for a more impactful color: namely red. Researchers at Dartmouth College created an experiment to explore our relationship with the color red. The subjects in this experiment were non-human, macaque rhesus monkey primates. These
monkeys were ideal subjects as their eyesight and color vision is very similar to that of a human being. After a monkey was placed in an individual room, three handlers with bananas, entered the room together: one wearing blue, one in green and the other in red. No matter who entered the room first or which handler wore the red outfit, any handler in red would be unanimously be avoided by the monkeys. Although the handler in red also held out a banana, all monkeys seemed to feel it was not worth the risk and ate the other handlers bananas. Results of the experiment despite being concise were not conclusive as to the reason red is such an offensive color. It is clearly a trait that relates to the beginning of humanity (Dobson, 2011).

(Epi)Genetic Association

The scientific community is in the earlier phases of discovering epigenetic associations. Trans-generational epigenetic inheritance is a type of genetic memory that can pass from parent to child. Certain fears or associative contexts can be preserved to the extent, that future generations will display the same fear response. According to the mouse model study “Parental olfactory experience influences behavior and neural structure in subsequent generations” conducted by Brian Dias, exposing a mouse to the odor of acetophenone while receiving an electrical shock, caused additional olfactory neuron to developed in the noses and
brains of these mice. Subsequently, the pups of the mice and even the following pup generation all exhibited the same startle response when smelling the acetophenone odor despite never having prior exposure to the odor or any interaction with their parents or grandparents (Dias, 2013). A *C. elegans* nematode (roundworms) model study has also revealed that this epigenetic effect can be seen over 14 generations later (Huang, 2017). Other genetic factors influence the associations we form as well and can construct certain biases towards our preferences. For example, some individuals associate the flavor of cilantro with that of soap and thereby highly dislike the flavor. Researchers exploring 23andMe participant profiles identified that the taste variation in cilantro may be a variant in olfactory receptor genes. The gene OR6A2 has been identified and is thought to bind aldehydes of the herb’s scent, making the herb seem extraordinarily “soapy” to these individuals. Other genetic factors influencing color vision or even height can greatly affect perception of the world. In fact, individuals who have a variant of the gene apolipoprotein E (APOE) on chromosome 19 have an increased risk for Alzheimer’s.

**Synesthetic Association**

While the aforementioned associative layers are inherent to all, biologically founded synesthetic associations apply to individuals with this perceptual
variance. The condition of Synesthesia affects approximately 1 in 200 people. The neurobiological cause of synesthesia, is thought to be the result of genetically informed differences during the process of synaptic pruning. This results in aspects like colored hearing, musical tasting and grapheme-conceptual differences (Cytowic, 2009)

**Sensory Layers of Association**

These sensory associative layers comprise the way in which we perceive and are furthermore interwoven with our memory, perception and cognitive health. Not only are our senses and sensory associations windows to deeper regions of our brains, they are also outwardly expressed pathways, that allow us to tweak synaptic connections inside the brain.

### 6.0 FOUNDATIONAL MULTISENSORY THESIS PROJECTS

#### 6.1 FOUNDATIONAL PROJECTS

During my master’s studies at MIT, I conducted various multisensory projects to explore the brain's relationship to multisensory processing. These projects range from ‘Chronosonogy’ (Figures 26, 27) which extended current neuroscience
research to alter human perception of time, (presented at Member's week in the spring of 2017), to the exploration of the hormonal changes instilled by lullabies (published in NIME GPS and supported by colleague Rebecca Kleinberger, MIT Media Lab).

**Chronosonogy**

This project was created through extending the neuroscience research of Teki et al., which reveals "Distinct Neural Substrates of Duration-Based and Beat-Based Auditory Timing" and the work from Fassnidge et al. examining "Visual Interference of Auditory Signal Detection." Our perception of time is impacted by combining factors of visual-auditory override and imaginary notes sensations. Chronosonogy is both an experience and a newly discovered time-shifting phenomenon that activates a neurological quirk audio/visual quirk. Our understanding of time can be modulated by our perception. When humans listen to melodically sparse music, it is perceived as slower. When listening to music with a higher density of notes, it will invariably feel as though the song is shorter.
When comparing songs of equal lengths but different note densities, humans will typically assume that the sparser songs are longer as confirmed in the study by Teki et al. Other multisensory studies reveal another cognitive quirk. It has been long established that humans associate visual objects with sounds (Kohler, 1929). Further studies have also revealed that we attribute congruent sounds to visual, moving objects (Sievers et al., 2011). A study conducted by Fassnidge et al. revealed that flashes of animated, shapes, colors and light can be perceived to have a tone. In designing my Chronosonogony project (MIT Media Lab 2017), these studies were combined to further explore our audio/visual cognitive capabilities. Three screens presented different lengths of animated musical clips. Despite differences in length, all musical clips featured the same note density. The longest musical clip featured a denser animation sequence while the shortest clip featured a sparse animation sequence. This project was displayed to over 50 individuals who were asked to vote on which clip they perceived to be the longest. Instead of increasing note density to make the longest clip seem shorter, this effect was attained by increasing the visuals which added auditory hallucinations to the melody. This in turn made the longest clip seem sonically denser and thereby shorter. Results revealed that over 90 percent mistakenly perceived the longer clip to be the shortest. This is in line with the initial hypothesis and opens possibilities of cognitive principles to strategically shift human time perception.
Further creative projects I created towards the completion of my master’s degree at MIT Media Labs, include the ‘Multimodal Music Modules’ (M3), which gave sensory physicality to some of the most common song associations, in the form factor of an interactive modular experience. The M3 (Figures 28, 29) is a glimpse into a future where our media is designed for more than two senses at a time. Our brains are vastly interconnected and experience the world through multiple modalities simultaneously; the M3 brings this to the foreground. Electronic elements within the sensory modular components create an interactive experience allowing one to feel music tactilely, sense it olfactorily and explore a 3D visual representation. Based on my cognitive behavioral studies, The Multimodal Music Modules highlight associative layers of our sensory perception translating a song into music for the senses.
Objects in our lives are usually either digital or not; mostly a wall is just a wall. The Sonic Murals Project (Figures 30, 31) another multi sensory device I created at MIT Media Labs, explores what happens when we blur those lines. Implementing touch capacitance and conductive pigments in an innovative way, my design made it so that any surface can become a sensor, a tool for data collection, or a musical instrument, as exhibited in this project. When interacting with touch or proximity sensors on a sonic mural, one can experience spacial exploration and sound creation on a multi-sensory level. ‘Sonic Murals’ employ the most colorful array of conductive mural paints available (which I fabricated), as well as touch and proximity sensors to allow users to experience spacial exploration and sound creation on a multi-sensory level. The concept for Sonic Murals was created in response to a challenge by City of Boston. Our group was
encouraged to conceptualize projects that could bring together diverse regions of the city through innovative and meaningful exchanges. Learning more about Boston, it became clear that there were many regions such as the T (Boston’s subway) where diverse crowds gather yet do not interact. I sought to build on this preexisting infrastructure of gathering spaces where connectedness could be of most value. A commonality between common spaces are always the walls which house them. In designing a project, I also wanted to create something that would be uniquely suited to Boston. My experiences in the city was underscored by the vibrant murals stretching from freedom trail to the “Roxbury Love” (Mandela) mural by Richard “Deme5” Gomez and Thomas “Kwest” Burns, 2014 on Warren Street. Journalists Tony Matthews and Deanna Grant-Smith recently published an article entitled, "How Murals Helped Turn a Declining Community Around" highlighting the importance of this form of public art (Matthews, 2017). On visiting murals throughout the city, I was struck by the eyes of the portraits seemingly watching over the street like wise guardians. I conceptualized the question, “if murals could talk, what stories they would tell.” In wanting to give murals a voice, I in turn sought to give agency and a platform for the voices of community members. Every wall has the potential to hold a Sonic Mural that can be painted by the community who can in turn record their songs, voices and stories onto their artistic contribution. When IDEO placed pressure sensors on a public staircase in 2011, behavior change was noted. Since then, studies, such as Tsekleves et al. have shown how this musical intervention encouraged
connectedness, playfulness and camaraderie in the same place strangers would pass without greeting one another. Following installations of musical stairs, people tend to reroute their path to climb the musical stairs as less people frequented the escalators. Tsekleves et al. focused on this in the work, "The Role of Playfulness and Sensory Experiences in Design for Public Health and for Ageing (sic) Well." It is my hope that Sonic Murals could find a similar role within cities within a more accessible context without the barrier of stairs. Instead of being a completed project that an outside organization brings to a particular community, Sonic Murals can be created by the very people who pass through the public spaces on their daily commutes.

**Calculating Connectedness: The MIT Community Challenge**

As depression is another condition linked to gamma abnormalities in the brain. I collaborated with Prof. Rosalind Picard and MIT’s MindHandHeart on Calculating Connectedness: The MIT Community Challenge a study on tangible aspects that address depression through means of external and internal relationships. These spots were enacted through stimulating both intrinsic and extrinsic reward responses via the digital platform.
Motif

In the multisensory Alzheimer’s research realm, I collaborated with students in ML professor Pattie Maes’ class on my original idea for a sonic memory recall device to help alleviate Alzheimer’s symptoms. Seeking to design an aid to support individuals with Alzheimer’s both prior and during treatment Motif is a wearable device to support members of our society who need it most. Motif is an aesthetically pleasing, auditory cueing system for individuals at risk or suffering from dementia or Alzheimer’s. By playing songs in response to particular people, places and situations, Motif is able to trigger memories and provide context. Via the RFID technology, a relative or carer with an RFID pendant or card (Figures 32 - 34) encountering a loved one with Alzheimer’s, automatically triggers their musical “theme” or “leitmotif” to provide greater context when autobiographical memories are musically invoked. Patients at risk for Alzheimer’s or individuals struggling with memory concerns can greatly benefit from this wearable musical intervention, to improve their wellbeing and quality of life.

Figure 32 +33 + 34: Motif Sonic Memory Trigger
6.2 COGNITARIUM

Introduction

Cognitarium is a dynamic experiential preview of early groundbreaking research in multimodal music cognition. Distilled elements from innovative experiments, meld to create an in-room planetarium for the mind—underscored with gamma sounds defined by Professor Tod Machover and, at a specific showing, performed live by Professor Tod Machover on the Cello (and during a premiering Member’s Week Cognitarium opening, cutting-edge double bassist Emilio Guarino).

![Figure 35: Cognitarium Design](image)

Design Concept

When first interfacing with the raw, visual Gamma stimuli within the mouse model lab setting, the visual gamma frequencies proved to be overtly intense. Similarly, the auditory square-wave gamma ‘clicks’ were challenging and grating to the ears. Although several aspects of the original experimental design were vital to
the overall experiment, some alterations were required to make a gamma space more habitat and comfortable for humans. As it would be necessary for humans to spend lengthy times in the gamma environment, we sought to implement components necessary for entrainment while situating it in an appealing context. In the design process, I posed the following questions: Where are humans likely to observe lights and fixate on them? Which dark environments are pleasant and produce a feeling of meditative awe (Figure 36)? The answer to these questions led us to construct a planetarium-like environment. In a planetarium, darkness is welcome and one enters the space to gaze at bright, flickering lights (stars). Sonically, music and deep rumbling sounds are anticipated as they are associated with outer space. Furthermore, when lights flicker at the gamma frequency, it occurs so quickly that it almost appears as though the lights are shimmering - like stars.

**Cognitarium Componentes**

The Cognitarium is composed of four various components (Figure 37): gamma light, darkness, gamma sound and projection. The interactions of these elemental
components combine to shape the overall experience. When participants or visitors enter the Cognitarium, the enveloping darkness provides contrast to both the bright outside world as well as the internal 40HZ lights and sounds. Once inside, the colorful “gamma planets” - 40Hz programmable bulbs mounted to the ceiling at various height intervals surround the visitor in the space. The colorful orbs floating in the darkness are complimented by cascading projected gamma stars. There are three different projectors employed in the original cognitarium design that compose the total experience. Two of the projectors feature fields of rendered, animated starlight. The stars appear to be slowly drifting through space yet take turns flickering individually and in specific groupings at 40 Hz spectrums. They glimmer gently across the face of two of the room’s walls adding a meditative aspect to the entrainment experience. The third projector fills the void across the ceiling with a backdrop of projected floating lights composing a rendering of the Milky Way. As the intense frequency can be grating, the projected stars provide visual relief.
Further Cognitarium Formats and Applications

In collaboration with Professor Tod Machover and Ben Bloomberg and architectural guidance from Nicole L’Huillier, the Cognitarium extended beyond a project (Figures 38, 39). The Gamma Cognitarium Solarium is a bulb-based gamma environment system installed in the home of an early gamma therapy adopter with Alzheimer’s. According to Oxford English Dictionary, the word solarium dating back to mid 19th century Latin refers to “A room fitted with extensive areas of glass to admit sunlight.” In the Med History journal article, “What Tuberculosis did for Modernism: The Influence of a Curative Environment on Modernist Design and Architecture” by Margaret Campbell, researchers note that the solarium space is historically connected to the medical field. Architects in the early 1900s, applied components of Greek vernacular house designs to
tuberculosis treatment facilities. The exposure to light during the daytime helped to increase vitamin D levels and normalize circadian rhythm patterns often distorted after long hospital stays in darkened rooms. Inspired by this history, the Gamma Solarium features colorful gamma lights rotating in various color cycles depending on the time of day. Furthermore, as Solarium also was the name of a constellation between the constellations of Horologium, Dorado and Hydrus, it pays homage to the original Cognitarium.

**Cognitarium Future and Evaluation**

The Cognitarium in the current form is constructed inside of a workspace within our lab with light-blocking curtains. The Cognitarium is on a rotational schedule with the workspace and is frequently deconstructed to reconvert to a general space. This arrangement doesn’t allow for the depth of experimentation that could require permanent installation. With the current setup, certain limitations arise. In the future, it would be beneficial to expand the current vision of the Cognitarium to deepen the experience by increasing sensory interactions with vibration, olfactory stimulation and a starrier, domed expanse of the 40Hz flickering. The current edition of the Cognitarium serves not only to share aspects of gamma therapy with potential collaborators, but also a place to run pilot experiments. Furthermore, the space has been our lab’s test area for the in-home
gamma installation. Before making network or lighting changes to the official installation, we are able to test run our gamma setup on our personal servers while seeing the illumination effects within a space. Not only is the Cognitarium an experientially rich project, it also gives insight regarding future installations.

7. GAMMA INSTALLATION

7.1 INSTALLATION BACKGROUND

Case studies or interventions at earlier research stages are atypical to the standard study process. However, in exceptional circumstances researchers have the opportunity to collaborate with early adopters who are seeking experimental treatment under medical supervision as a last resort tactic. This is the case with the wife of an Aging Brain Initiative supporter diagnosed with late-stage Alzheimer’s. Our team was challenged to create an innovative in-home installation

Figure 40 + 41: Bulbs Replaced With Gamma Firmware for 40Hz Flicker

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using the principles of gamma. This was to be part art in-home exhibit as well as a chance to make initial observations about the way in which gamma exposure can have beneficial effects in humans. For the installation, I partnered with MIT Ph.D. doctoral candidate Ben Bloomberg a colleague in my lab, my PI Prof. Tod Machover as well as the patient, who we will call (S.P. for protection) S.P.’s care team.

### 7.2 CASE MEDICAL HISTORY

In introducing S.P., it is important to note that the name has been obscured for privacy reasons. S.P. was diagnosed with Alzheimer’s over a decade ago, however, displayed atypical symptoms including complications from 3 fall-related TBI’s (Traumatic Brain Injuries). Early fMRI scans revealed unilateral damage consistent with injury. Notable symptoms included speech complications, word forgetfulness, and early-stage aphasia. Various speech therapies were actively included although a fitting treatment for the pathology was not identified. As aphasia increased, follow up fMRI scans revealed progressively bilateral brain atrophy, more consistent with Alzheimer’s. Despite a more complex history, TBI’s are not uncommon among this population, due to age related instability and fall risk. The following reports consist of PET Scans and CT Scans to aid in the
diagnostic evaluation given the clinical symptoms of dementia observed. The imaging was conducted at different hospitals as noted below:

1/9/13 PET Scan

The first imaging occurred on 1/9/13 (Figure 42) where the patient presented in the ER for the nuclear scan of her cranium. At this time a PET scan as well as a CT were taken as is customary. These reports first suggest that the patient had perhaps suffered a left sided aneurysm.

9/9/13

Doctor reports now find that the decreased cortical uptake in the frontal temporal and parietal lobes (Figure 43). However, it was noted that the sensorimotor cortex and uptake in the deep gray matter structures appeared relatively preserved. The corresponding CT images reveal evidence
of a progressive brain disease involving central atrophic and the CSF space and the ventricles are of increased sizes. These images present a consistent impression of severe Alzheimer’s dementia and cerebral atrophy.

2/22/18

Patient received a functioning imaging assessment for dementia. PET and CT scans were taken for the first time in nearly 5 years. The respective scans were concordant for visible signs of Alzheimer's disease (Figures 44, 45).

The diminished left cortical uptake from 2013, is now viewed bilaterally. The bilateral ventricles have increased in space and size, indicating brain tissue destruction. The physical progression in the pattern recognized in many Alzheimer’s patients that present with dementia.
Currently, although S.P. is low verbal, she does communicate her feelings through facial expressions and motions. Being extremely mobile and physically aerobic, when a particular situation becomes overstimulating or frustrating, S.P. leaves the space. If there is something which she perceives to be disorganized or out of place, she will attempt to move or clean it. If something is extremely pleasant for S.P. (such as photographs of babies), she will spend time, seemingly transfixed enjoying it. Knowing this we wanted to create an installation that could be readily modifiable to fit her aesthetic and comfort level.

7.3 INSTALLATION

When planning the installation, we collected information based on the locations in the house where S.P. spends her time (Figure 46). The initial concept of a gamma system was to create an in-home treatment space for gamma exposure. However, when learning that S.P. frequently walks throughout different spaces of her home, particularly her bedroom, tv area and kitchen, we began to develop a larger concept. Instead of having an isolating
or confining space, we oriented the design to make several spaces capable of transferring gamma light and sound. As is oft said, the best technology is invisible, disappearing seamlessly into the flow of our lives. In designing the installation system we took into account components already present within the spaces and iterated a system based on this. Lights in the spaces were replaced by programmable bulbs alongside an app capable of lighting in the gamma frequency. As multisensory gamma affects wider regions of the brain, a sound system was installed attached to the SONOS speaker system within the home. The system installed by Ben Bloomberg was a sub harmonic frequency boosting system: “The new system uses a set WiFi controlled lights which have the form factor of standard A19 incandescent bulbs in order to easily be used in any existing location in the house where there are currently lights installed. The WiFi lights can be controlled easily via a corresponding, custom-built phone app, which timestamps usage and treatment periods. A central server monitors the usage of the lights, and the app has presets for standard lighting, as well as custom fades and

![Gamma App Screenshots](image)
colors. Each bulb contains a hardware timer which permits a customizable degree of 40Hz flashing light to be added to the presets, allowing the balance between colors and the 40Hz signal to be carefully controlled so that the experience is both pleasurable and beneficial for any particular user at any specific time and context. On the back end, these lights speak the Art-Net lighting control protocol. This allows many different types of interfaces to be used to control the lights, including professional lighting consoles, and opens the possibility for enabling classical lighting design techniques to be applied in combination with the 40Hz signal. The clocks in the lights are currently synchronized using a power-up counter and a network-based heartbeat signal” (Ben Bloomberg, 2018). This system combined with the 40 Hz flickering is able to support the entrainment process. Sundowning refers to a stage in Alzheimer’s when the rhythm becomes vastly disrupted (Musiek, 2017). As certain kinds of lighting have been proven in studies to impact sleep hygiene (Choi, 2017), we created different color settings. The daytime setting features a cool blue-toned rotation while the nighttime setting cycles on warmer, more amber hues. An additional light setting cycles through a number of S.P.’s favorite colors. These colorful shades are ideal for accompanying dance or art therapy sessions as well as holding attention.
7.4 NVBMSE

Baseline results were collected through the NVBMSE (Non Verbal Baseline Mental Status Examination - see appendix) cognitive behavioral testing to establish cognitive performance in non or low verbal individuals with Alzheimer’s. Following the first few weeks of the installation, S.P. began to experience various positive changes. A log was set up so the care team of nurses, care workers and family members could document notable behaviors, interactions with the gamma system, as well as any changes over the period of installation. Caregivers reported S.P. spending more time looking in the direction of the lights and noted that she often seemed mesmerized by the color fades.

7.5 OBSERVATIONS

While visiting relatives recognized S.P.’s higher level of communication and interaction, videos were taken by caregivers at various intervals to reveal S.P.’s gradual changes in behavior and progression. The earliest videos of S.P. feature her performing extremely repetitive motions as often seen in Alzheimer’s patients. There are some moments however, such as during her music therapy session, where she begins to mimic the motions of a caregiver and sways to the music. Another early video shows S.P. leaning over a photo of a baby speaking in a soft voice and looking intently for many minutes. It is unclear to caregivers whether
she believes the baby to be real, but she seems dedicated to this allusion. In later videos and interactions, there are noted instances where she has an intermittent awareness of her situation. Her words become more coherent and she seems to search for the correct phrase. Although these instances pass quickly, they seem indicative of cognitive improvement in light of the fact that being conscious of memory challenge is typically lost during later stage Alzheimer's. In most recent video recordings more notable findings come to light. One of the tapings shows S.P. remarking the fact that she feels tired and would like to go to sleep, after which she leans her head on her caregiver's shoulder and rests. Not only was she able to piece together the sentence, but she also made this remark in correlation with how she felt at the time, and what her intentions were. Furthermore, she carries out these intentions by resting and falls asleep. Further footage shows S.P. looking through book of paintings seeing colors and images she admires and expressing this both gesturally and verbally. This behavior is vastly different from earlier footage where she is viewing a photograph of a baby. Here she seems aware that she is looking at a book. She is also connecting with her art therapist and speaking with her about the shared subject matter.
7.6 INSTALLATION EVALUATION

The in-home gamma installation was a truly innovative pilot and the first of its kind. As with all early-stage projects, there are many beneficial understandings derived from evaluating the initial design. The key areas are the following: (1) spatialization, (2) accessibility, (3) baseline reports and (4) personalized gamma stimulation opportunities. (1) While the spatial dispersion of the gamma lights covered the most frequented regions of the home, there are other frequently occupied spaces in her home where it could make sense to extend the lighting and sound system. Although the Sonos sound system has a wide reach, this could be extended as well to ensure a multisensory interaction throughout the space. (2) Creating the installation in an active care setting was illuminating as we quickly learned how intertwined the experience of the care team is with the individual who has Alzheimer's. Although in-home nurses and staff are dedicated to the patient’s care, schedules and routines are usually rigid. Therefore, any addition to the care-schedule must be easily accessible and intuitive. We created an app to navigate the gamma installation system easily. The app was uploaded to the mobile devices of visiting healthcare staff as well as a central iPad to control both the Sonos and gamma lights. Despite the fact that the app is self-explanatory, the extra step of adjusting the various settings to convert the lights to their gamma mode was a barrier. Due to this, several bluetooth switches were developed and will be installed. (3) For research and health purposes, a baseline
is important to determine current cognitive health before the application of any therapies, medical or artistic. Although the NVBMSE (Non Verbal Baseline Mental Status Examination) assessment was performed, S.P.’s most recent PET scan was in 2013. As the installation was requested immediately however, the gamma setup was implemented and the PET Scan was received months later. Although this will still serve as a form of baseline when comparing findings to future PET scans, future installations should perhaps be dependent on a recent or initial PET scan or Beta-amyloid assessment at the outset. (4) Spending time with S.P. and watching videos through the online log uploaded by head caregiver C.D., it is clear that there are certain activities to which S.P. is drawn. For future directions of the installation process, it would be fascinating to create some interest-oriented gamma devices. For example, S.P. has a life-size robotic cat plush toy that she enjoys petting and observing. Studies have shown that cats purr within a frequency range of 25-150 Hz, including 40 Hz gamma frequencies. An example of a personalized gamma stimulation design is to design the beloved plush toy so that it is able to purr (both audibly and haptically) continually in the gamma frequency range. As we learn more about specific comfort mechanisms and interests of individual struggling with Alzheimer’s or memory loss, a broader range of designs can be fabricated.
8. GAMMA INSTRUMENT

The gamma instrument (Figure 50) has components of the Cognitarium and Solarium; however, it is a mobile smaller scale instrument and extremely interactive.

In healthy individuals, gamma brainwave activity is thought to occur at times of higher cognitive function. During times of composition or music listening, this effect is greatly strengthened. Increasing gamma entrainment in individuals who are lacking this frequency can likely be achieved by embedding gamma in an appropriate cognitive context. Although passive listening experiences can still induce the entrainment effect, it is likely that one would be able to retrain gamma patterning and have better cognitive outcome by combining it with higher function tasks. A study by Bhattacharya and Petsche (2001) entitled “Musicians and the Gamma Band: A Secret Affair?” reveals that “a significantly high degree of phase synchrony in the gamma frequency range globally distributed over the brain was found in subjects with musical training (musicians) compared with subjects with no such training (non-musicians)” (Bhattacharya, Petsche, 2001).
remarkable difference was only noted in the gamma band. A spoken neutral text control showed no variance revealing this effect is only linked to music. Furthermore, the study revealed that gamma band oscillations were more significant at times of improvisation or composition. The study concludes that, “The high degree of synchronization in musicians could be due to their high ability to retrieve musical patterns from their acoustic memory, which is a cogent condition for both listening to and anticipating musical sounds.” Although years of musical training cannot be delivered within a brief interaction with the gamma instrument, giving the agency of composition and music performance can help to assert cognitive patterns associated with musical synchrony and acoustic recall to boost the gamma signal. No significant differences were found in other EEG
frequency bands. Listening to neutral text did not produce any significant differences in the degree of synchronization between these two groups. For musicians, left-hemispheric dominance was found during listening to music. The right hemisphere was found to be dominant for non-musicians in text listening.

6.4.1 GAMMA INSTRUMENT HARDWARE

The first edition of the Gamma Instrument was an auditory-tactile interface. This appeared in the format of a black box (Fig 52) with various raised capacitive textures. Through user interaction, it was noted that the hard surface offered little haptic feedback. To incorporate pressure-based capacitive variation, other interface textures were explored (Fig 53). The surfaces explored were no longer opaque as the importance of a light-following effect became increasingly important for gamma delivery. When conducting tactile
preference tests with elderly individuals, softer and smooth surfaces were preferred. In light of the target demographic as well as the goal to capture more defined touch-feedback, fabric was exchanged for the hard-surface model. The highly reflective fabric usually used in photography, was an effective solution as the synthetic base holds up to sanitization in medical conditions and the reflective components help to diffuse and scatter the gamma light. The black-box touch interface limited testers to specific “nodes” when playing the instrument. Therefore, the design shifted to a broader surface-approach with more capacitive components, allowing a greater range of freedom, while still providing for visual guides for note playing. Using one Arduino and another Arduino-like board, the code allows users to play the instrument simultaneously as it notes interruptions in the surface output through each separate input. The final Gamma Instrument features slight tactile ridges as well as colorful gamma hand-following lights and
gamma audio. Future editions could engage further senses within the vibrational or olfactory domains.

**Gamma Instrument Design Evaluation**

Currently the Gamma Instrument is located inside of the Cognitarium. Future editions of the Gamma Instrument could feature a more interactive component within the Cognitarium. This would provide the flexibility to test subtle differences between spatial and personal gamma devices. As we learn more about the gamma frequency and its impact on the brain, these findings can be applied to future editions of the Gamma Instrument. Other facets of the Gamma instrument can be adjusted as well. An example of this is color. Currently, the Gamma Instrument cycles through an array of hues and color spectrums. My future explorations will likely clarify understandings about how specific colors can augment the playing experience and amplify gamma entrainment. When these findings are established, the identified hues can be highlighted on the instrument’s surface. The device itself is innately programmable; beneficial for future tests and modifications. Although the instrument has an obvious use and design for medical settings and care facilities, it will be beneficial to experiment further with the Gamma Instrument to learn about ways in which individuals can integrate it within their daily lives. Could a table or countertop feature a Gamma
Instrument component? Would the Gamma Instrument be suited to a piano or acoustic shape given the design familiarity? Could this instrument be used in a live concert setting? Several testers of the Gamma Instrument have also posed the following challenge for the future, “what if it were larger?” Although the personal size is beneficial for laptop or table use, it is valid to experiment with other sizes. A larger scale could broaden the touch surface including more notes for musical flexibility and increase the number of users who can interact with the instrument. Finally, in tandem with the Cognitarium, I plan to explore the possibility of engaging other sensory features such as vibration and olfactory components. The sensory information delivered through the olfactory and proprio-vibration receptors have the potential to remove a wider section of amyloid plaques from the corresponding areas of the brain; and may help with memory and movement (fine motor skills).

Figure 55: Evaluation Graphic Image
9. EVALUATION

9.1 INSTALLATION/CASE STUDY

The pilot test with the in-home installation was an important factor in understanding aspects of designing for an in-home setting as well as for a specific case of Alzheimer’s. This pilot case aided in the establishment of a pattern of identifying a patient’s routine and embedding the gamma creatively and seamlessly within a patient’s environment and lifestyle to best boost compliance. Communication with the team was impactful in evaluating aspects of the installation, the process of participant cognitive assessment and evaluative tracking during the duration of study or installation.

9.2 PILOT STUDY

In a gamma pilot study I conducted, 10 healthy participants between the ages of 19 and 55 were presented with 35 minutes of an audio-visual experience. Half of the participants listened to a selection of instrumental and vocal music across various genres ranging from classical to jazz. Subjects were in gamma and non-gamma, experiment and control groups. All subjects were instructed to observe the lights, the experimental focal point. The non-gamma group listened the the
provided music while watching an LED color array (built for the study) the other half of participants listened to the same set of music yet with embedded gamma tones. The experiment group was directed to look at colorful 40 Hz flashing gamma lightbulbs. Each subject was given a baseline MCPT test as well as two intermittent activities to manage alertness during the course of the experiment. Following the audio-visual stimuli session, participants retook the MCPT test. In the non-gamma test group, only 1/5 of subjects presented with improved scores which could be attributed to general music listening or outlier status. Each of the gamma participants had improved scores in 3 or more sensory areas with an increase of improvement being in auditory and color matching components. Despite the fact that this is early evidence, it is significant that these two particular areas revealed the most improvement as the gamma stimulation
targeted these senses. In a further format of this pilot study it would be important to retest these scores a week following, to further evaluate longer-term effects as well as various sensory combinations of the gamma and non-gamma stimuli. Furthermore, an additional group will receive gamma through only one modality to explore precise differences between multisensory and unimodal stimulation. Finally, it will be interesting to explore the difference in results between active and passive gamma treatment experiences. The conducted evaluative pilot, shows initial evidence of the benefit of gamma stimulation for multisensory cognitive enhancement in neuro-cognitively healthy individuals. Although the increase in individual MCPT scores improved by an average of 30% across three or more sensory areas, it is likely that with more interaction, longer and more frequent stimuli exposure time, scores could likely improve further.

9.3 ENGAGEMENT

Both conferences and community engagements such as a workshop at the Youville House Assisted Living program in Cambridge, underscored various phases of the thesis process. I participated in the The 2017 International Symposium on Wearable Computers conference on wearable technology that challenged participants to explore the dynamic capacity of wearable materials to perform a role in assistive technology. Engaging with community members
through technology-based tests greatly informed both design factors and provided a platform to troubleshoot various technological interventions with memory patients. As part of this process, I also met with older individuals to discuss form-factor related perspectives. On a broader scale, I had the chance to document feedback from many members during members weeks during fall and spring on the current design installment of the cognitarium and gamma instrument. This feedback both shaped the continued design-thinking process and simultaneously the evaluation.

9.4 USER EXPERIENCES

From the time of its completion to the submission of this thesis, nearly 70 distinct individuals of varied ages and different musical backgrounds (musician and non-musician) have played the gamma instrument alone. Both verbal responses, as well as behavioral user interactions were noted and documented. The form factor of the gamma instrument is selected to approach the following goals: increasing cognitive interaction, creating a comfortable experience, supporting natural brainwave gamma state, and leveraging the underlying neurological principal of signal transduction.
Increasing Cognitive Interaction

Initial mouse-model findings seem to reveal that gamma plaque removal occurs in regions of the brain where sensory engagement occurs. Therefore it is likely that in humans, any engagement that boosts gamma brainwaves could further support this metabolic cognitive process.

Creating a Comfortable Experience

As the raw auditory stimuli of the gamma frequency is incredibly grating, it needed to be sculpted into a form factor that would be a tolerable and comfortable treatment option. This should be taken in consideration in particular for patients who could benefit from gamma therapy. The current suggested protocol for Alzheimer’s patients suggests the employment of gamma stimuli for at least an hour daily. Therefore the delivery needs to be an engaging form factor that could encourage patient compliance with the gamma treatment.

Figure 58: Efficacy + Entrainment
Supporting Natural Gamma Brainwave State

Findings reveal that musicians when composing or improvising, experience higher-than-average amounts and levels of gamma brainwaves (Bhattacharya, 2001). When artificially introducing gamma stimuli, it is likely that by introducing this in conjunction with a gamma-oriented activity, entrainment would occur more quickly. Furthermore, in patients with Alzheimer’s this could be a useful modality to retrain the brain to shift to this brainwave stage naturally.

The Role of the Thalamus in Entrainment

The thalamus is the part of the brain that responds to the external sensory signals. It is responsible for aspects of visual entrainment through direct activation of the optic nerve and the resulting stimulation of the thalamus. The thalamus can also generate entrainment of gamma pulses through process of music memory, auditory hallucination or meditation. It appears that once the thalamus commences entrainment the entire brain follows suit. This reaction has been long observed using EEG monitors as described in the quote below from Michael Hutchison in his book, The Mega Brain. “The great neuroscientist W. Gray Walter carried out a series of experiments in the late forties and fifties in which he used an electronic stroboscopic device in combination with EEG equipment to send rhythmic light flashes into the eyes of the subjects at frequencies ranging from ten to twenty five flashes per second.” According to Hutchinson, “He was
startled to find that the flickering seemed to alter the brain-wave activity of the whole cortex instead of just the areas associated with vision. Wrote Walter, “The rhythmic series of flashes appear to be breaking down some of the physiologic barriers between different regions of the brain. This means the stimulus of flicker received by the visual projection area of the cortex was breaking bounds— its ripples were overflowing into other areas.” (Hutchinson, 1996) In a more recent study by McCormick et al. researchers found that the thalamic and cortical activity has a direct correlation to the sensory motor processing capacity of the brain (McCormick, 2015). Consequently, when sensory motor processing in the brain is in good function, entrainment can occur at a faster rate, even when applying meditation techniques.

9.5 USER INTERACTIONS

Concerns

The foremost evaluative point that comes to the forefront with user interactions for non-musicians is their concern about whether they will be able to naturally shift into the gamma brainwave state through composing or improvising. This concern is valid as musicians generally must have years of experience before being able to fluidly compose or improvise on traditional instruments. Therefore, the gamma instrument is designed to accommodate all skill levels. Accomplished
musicians familiar with the instrument will be able to play full musical pieces while non-musicians can still play abstractly selected notes through capacitive contact and create euphonious, pleasant sounds.

Reported Experiences

Many playing the instrument (Figure 59) whether or not they are aware of further cognitive implications, experience an immediate transformative feeling. Testers remark a range of feelings while playing the gamma instrument. Many comment that they experience a major time-shift and feel that they can sense time contracting and expanding at different rates. Many report feelings of flight or floating. Some have also reported colors seeming brighter and more intense after
playing the instrument. The majority of the individuals testing the instrument remark that it is mesmerizing, saying that they could “play it for hours” with many returning to play it again.

**Interaction Styles**

As the Gamma instrument is designed to be played by a wide range of individuals with various music or non-music backgrounds, individuals take many different approaches to playing the instrument. Testers receive very little instruction on how to play the instrument as it is vital to assess the intuitive nature of the design. Some individuals play the instrument by selecting particular notes in sequence, while others use broad strokes or sweeping motions combining notes into multi-tonal chord progressions. Some also experiment with spacial shapes shifting from triangular motions to circular movements seemingly “drawing” (Figure 60) with light and music. In interactions with several playing the instrument simultaneously, people alternate between taking turns, to playing the instrument together (Figure 61). A kind of unusual collaborative
improvisational process occurs creating an unusual musical as well as social dynamic. Most instruments are not designed for multi-person composition or improvisation, whereas the Gamma Instrument is suited to facilitate these interactions. Socially, individuals experiment with aspects of adjusting their hands in space to touching each other’s hands to experiment with capacitive sensors. This aspect of human tactile contact is interesting to consider especially in light of research on human contact in Alzheimer’s disease (Loi, 2018). The aspect of collaborative sound creation was inspired by my work on the C.I.S.T (Control Interface Sculptural “Thing”) which was developed with colleagues during a seminar led by my PI, Professor Tod Machover. The room-scale instrument (Figure 62) was created with the goal of facilitating communication and connectedness through music. Many activities often have a distinct leader and follower, however,
the dynamics are vastly different in the gamma instrument as both seem to equally share the task of creating sounds. Furthermore, it is interesting to note the way in which two people playing simultaneously will watch and listen to the musical decisions of their co-performer and spontaneously respond musically. These aspects of the design specifically accomplish components originally intended during the initial planning phases of the instrument.

9.6 DESIGNING FOR ELDERS WORKSHOP

In design feedback workshops at centers for the elderly, certain interfaces were notably difficult to use. This complication can be summed up in the phrase, “when we design, we rarely design for our future selves.” Instead, we design for our current selves. Our current concept of intuitive design is rarely inclusive. Often, that which is intuitive for some will seem confusing and unfamiliar to others. In user tests, various components became apparent as important factors when designing devices for elderly individuals and those with memory concerns such as Alzheimer’s. One user test in particular, was conducted with 25 elderly

![Figure 62: Collaborating on CIST (L. Whaley)](image)
individuals ranging from healthy to memory care patients. All residents in attendance were over the age of 70.

**Tactile Interface**

During this testing workshop, it was noted that touch screen based technologies (Figure 63) posed a difficulty for individuals attempting to interact with them. Various music-based apps and sites were tested for the assessment. Many of the elderly users rated the iPad as an interface as a negative experience. This unpleasant experience often centered around the process of attempting to control certain aspects with their fingers found many found difficult and frustrating as the screen would be unresponsive. This resulted in a lower task completion rate. According to Andrew Hsu, Ph.D., a pioneer in touchscreen tech at Synaptics, “In an ideal situation, you barely touch the surface of the screen and the sensor is able to detect the presence of your finger.” In some cases, however, that finger confounds the technology, it’s a problem we’ve been wrestling with for 20 years now,” says Hsu. “It’s a very delicate balance. We
spend a lot of time essentially trying to determine whether a user has touched the surface or not.” As touchscreens generate a small electrical field, they rely on the human finger to create a disturbance in this field to register a specific command. It was noted that interfaces that use resistive based technologies or a higher capacitive touch threshold would be vital for older populations.

**Information Overload**

Some individuals suffered from information overload. This was caused both by stray touches on the flat surface that closed or shifted the current app to the home screen, as well as other icons which added to confusion.

**Unfamiliar Format**

In user surveys, participants noted that many of the interfaces felt alien and unfamiliar. Patients were given drawing supplies to show their ideal interfaces. Several mentions resembled boxy formats when associated with music, perhaps reminiscent of FM radios, turntables or cassette players, something which influenced the final design of the gamma instrument.
Survey

Each participant filled out a survey after the session to share thoughts on the interfaces. The final exercise encouraged every participant to write/draw their ideal interface (Figure 64). Responses during the session as well as the collected surveys after helped to influence interactive gamma designs.

10. GAMMA IN CONTEXT

10.1 GAMMA AND THE SENSES

Future explorations for the Ph.D. portion of my research will include the integration of various imaging techniques and sensory testing modalities. Further studies will examine other sensory methods to deliver gamma or heighten the level of entrainment. Past research has revealed that humans make multimodal leaps. During studies at Dartmouth I “investigated the perception of music and sound in a psycho-musicology study examining non-Synaesthetic associations to sound i.e. the propensity for listeners to recruit quasi synaesthesia (Nikolic,
2014) in everyday hearing. Köhler (1929) first described the linguistic “Kiki, Boulba Effect” which revealed a sound-to-pictorial/shape association among general (non-Synaesthetic) subjects. In more recent replication studies of the Kiki-Boulba experiment, over 90 percent of all subjects identified the spiked shape with the name Kiki, and the rounder shape as Boulba (Köhler, 1929). These experiments support a hypothesis that non-synaesthetic individuals employ universal cross-sensory associations. The Kiki-Boulba experiment has not been verified using musical stimuli. However, music composition practice and some behavioral studies support a hypothesis of broadly congruent musical cross-sensory associations in general listeners. For example, sound-scores in films are composed with the goal of eliciting specific emotional responses in listeners (Leeds, 2001). Such soundtracks are designed to augment the visual experience, by reinforcing immersion amongst a majority of the audience. A majority effect indicates a norm of sound and music-based associations, whether culturally learned or innate proclivities. Synaesthetes and non-synaesthetes are generally believed to have opposing neurological patterns. However, findings such as those described above, reveal a possible “synaesthetic spectrum.” Although the cross-modal wiring is far more apparent in synaesthetes (Cytowic, 2002) music fMRI studies have shown that sound elicits strong associative responses in multiple areas of the brain in non-synaesthetes as well” (Rieger, 2016). Through this understanding it is likely that humans could even associate certain colors, textures, tastes or smells with this frequency.
10.2 GAMMA RESEARCH TRAJECTORY

As the context of this work includes transitioning gamma research to the human scale, it is vital to mention that this master’s thesis addresses initial and developmental stages in undertaking this within the context of a larger Ph.D. project. While the master’s thesis focuses on designing stimuli experiences experiments and a case study, the Ph.D. work approaches the gamma treatment within the context of multimodal cognitive interventions. The Ph.D. portion will include a series of studies and trials beginning with a normal participant pool and closing with individuals at various stages of Alzheimer’s. The estimated timeline below reveals the various phases of research that will commence during the Ph.D. portion of this work.

- **Initial Phase:** Often conducted on non-human mouse populations to evaluate efficacy.

- **YEAR 1: Phase IA - between 20 and 80 student subjects - No Pathology:** Researchers test treatment in a small group of people for the first time to evaluate its safety, determine effective "dosage range", and identify side effects.
• **YEAR 2: Phase IB - between 20 and 80 subjects with Alzheimer’s:** Researchers test new treatment in a small group of people for the first time to evaluate its safety, determine effective "dosage range", and identify side effects.

• **YEAR 3-4: Phase II - 100-300 subjects with Alzheimer’s - incl. Control Standard:** The treatment is given to a larger group of people to see if it is effective and to further evaluate its safety and long-term benefits.

• **YEAR 5: Phase III - 1,000-3,000 subjects - incl. Control Standard:** The treatment is given to large groups of people to confirm its efficacy, monitor side effects, compare it to commonly used treatments, and collect information that will allow the drug or treatment to be used safely.

• **Phase IV (Treatment already on market):** Studies are done after treatment has been marketed to gather information on the drug’s effect in various populations and any side effects or benefits associated with long-term use.

### 10.3 THE FUTURE OF GAMMA

Further studies may reveal the benefits of including gamma as an early preventative Alzheimer’s treatment in addition to plaque maintenance and reversal in individuals with later stage Alzheimer’s. In light of this, it is valuable to
examine ways in which to interconnect gamma more seamlessly into general purpose use. For example, it is suspected that current car engine sounds could perhaps be harmful, therefore overlaying 40 Hz in a ubiquitous way could be a useful solution (Figure 65). Just as individuals go to physical therapists and chiropractors for physical health maintenance, a future with gamma treatment centers can be imagined. Gamma systems could become a form of cognitive maintenance or “mental floss.” Furthermore, a deeper integration into music via radio or player settings could bring broader access to gamma through multiple channels. It is fascinating to be on the precipice of a field that could provide countless noninvasive approaches to healing and reversing neuro-cognitive conditions such as Alzheimer’s as well as perhaps other low-gamma related conditions such as schizophrenia or depression.

**Figure 65: Multisensory Gamma**

**NOVEL CONTRIBUTIONS**

- Transition mouse-model study to human centered research
- Explorations supporting greater understanding of multisensory Gamma brain entrainment
- Multimodal Medical Instrument For Delivery Of GAMMA Stimulation For Individuals With Alzheimer’s

**Figure 66: Thesis Contributions Summary**
Our senses are not only barometers for the human body and mind, but also portals of communicating with various regions of the brain and biological processes. It is enlightening to know that the treatments that can cure us, are likely within our reach and within our hearts. For millennia we have known of impactful aspects of multisensory music experiences, how wonderful to be able to quantify particular aspects that can change our brains and heal the world.
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APPENDIX

LIST OF ACRONYMS

MCPT: Multisensory Cognition Proficiency Test

ASAS: Alzheimer's disease Assessment Scale cognitive test

MMSE: Mini Mental State Examination

MSE: Mental State Examination

NVB: Non Verbal Baseline

NVBMSE: Non Verbal Baseline Mental State Examination

ADL: Katz Index Independence in Activities of Daily Living

OLST: One Leg Standing Balance Test

CIST: Control Interface Sculptural Thing
Non Verbal Baseline Mental Status

Nonverbal communication (NVC), also known as nonlinguistic communication, is described as communicating ‘without words’ spoken or written (Nelson, 2010). Nelson (2010). Based upon this, this form assesses nonverbal communication.

Initials/Code

Short answer text

Proxemic (spatial relationships with partner)

☐ Body Positioning/Changing

☐ Leaning In

☐ Leaning Out

☐ Other

Kinesic Emblems (meaning gestures)

☐ Head Shakes (yes)

☐ Head Shakes (no)

☐ Shrug (maybe)

☐ Palm outward (stop)

☐ Shaking finger/Hand (no)
Illustrators (these gestures are often paired with a verbal message)

- Illustrating Size
- Illustrating Shape
- Indicating Space
- Gesturally referencing something not present
- Indicating Distance
- Indicating Colour/Tone
- Other...

Affective Displays - body and facial gestures that portray affect such as happiness or sadness that may vary in intensity and frequency depending on culture and other personal factors.

- Meaningful Smiles
- Meaningful Frowns
- Meaningful Confusion
- Meaningful Tactile Interaction
- Other
Regulators signs that regulate conversational turn-taking,

- Eye Contact
- Pauses
- Nodding
- Leaning in/Forward
- Squinting
- Behavior mimicking
- Other...

Adaptors (movements made with low awareness by the sender)

- casually twisting one's hair to relieve tension and stress.
- body positioning and changing,
- biting on one's nails
- Fidgeting
- Other...
MULTISENSORY COGNITION PROFICIENCY TEST

DATE ________________  PARTICIPANT ID# ________________

ABOUT THE MCPT:

The MCPT (Multisensory Cognition Proficiency Test) is an examination to determine baseline sensory cognition proficiency and establish precise markers for sensory changes at various intervals in patient care settings or a longitudinal experiment. Unlike traditional memory or IQ tests, this exam explores cognitive health and aptitude through distinct sensorial measurements (visual, olfactory, auditory and tactile) which in sum, present the detailed cognitive–behavioral profile of a patient or study participant. Present scores can be compared with past scores to identify improvement or regression.
COLOR ARRANGEMENT TASK

Present participant with physical or digital colour sorting placards (Farnsworth-Munsell) in following order. Each correct placement receives 10 points. Score ranges to 560.

TIME _______________  SCORE _______________
AUDITORY ATTENTION TASK

A) Present participant with two recorded two minute stories. Play sound files simultaneously. Ask participant to pay attention to a particular story. After 5 minute interval, request subject to recall the correct story.

RECALL PERCENTAGE ________________  SCORE ________________

B) Present participant with two new recorded two minute stories. Play sound files simultaneously. Ask participant to pay attention to both stories. After 5 minute interval, request subject to recall both stories.

#1 RECALL PERCENTAGE ________________  SCORE ________________

#2 RECALL PERCENTAGE ________________  SCORE ________________
PITCH MATCHING TASK

Play participant 20 distinct pitches followed by a pause beep and thereafter a matching or nearly matching pitch. The participant must answer after each “match” is presented whether it is a match or a mismatch.

RECALL PERCENTAGE #1 ________________________________

RECALL PERCENTAGE #2 ________________________________

TOTAL MATCHES: ________________________________
OLFACTORY SCENT PAIRING TASK

Present participant with two sets of 10 distinct yet similar scents. Participant is asked to pair sets of scents together within a given period. Each correct pair is 10 points.

TIME ________________  SCORE _______________

OLFACTORY SCENT IDENTIFICATION

Present participant with 10 distinct odors. Place each 10 inches from the nose. As participant guesses, move the scent object 1 in towards nose with every incorrect guess. When a correct guess is made, note the number of inches away. Each number is added together to create a final score. Top score is 10.

FINAL SCORE ________________
HAPTIC OBJECT IDENTIFICATION

Have 20 objects available out of sight from participant. Participant must be either blindfolded or place their hands inside of a visually obscuring box. The participant is given precisely 30 seconds to identify the object after which they must give a verbal identification. Each guess is awarded between 0–10 points with the scores of 0, 5 and 10. Guesses that are close to the item but not exact are given the core of five.

TOTAL SCORE: __________________________
INFORMATION

BASELINE SCORE:  
TEST NUMBER:  

TEST 1:  
TEST 2:  
TEST 3:  

NOTES:

MCPT