Rikke Kjølberg

Inducing Gamma Oscillations in Healthy Individuals

A pilot study that examines non-invasive treatment for Alzheimer´s disease

Master's thesis in Psychology

May 2019

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Acknowledgements

Beside my psychology studies, I have been working on a nursing home for demented patients. For over five years I have been working with people suffering from various types of dementia. I have observed and been around families and dependents who have lost their loved one day by day and little by little. In my opinion, dementia is some of the worst diseases I can imagine. Much of what I have witnessed is for me an unworthy way of living and leaving life.

When the question of which subject I was going to write about in the master thesis arose, there was little doubt. I have since the beginning of this job had a desire to do something for this patient group. My experience is that the patient group are often forgotten, and it seems like most people think that dementia is a natural part of ageing.

If only this small thesis could contribute a little, or at least possibly inspire other students to examine the field of Alzheimer´s disease I am appreciative.

First and foremost, I want to give a big thank to my supervisor Stig Hollup for great enthusiasm and for believing in me and my idea for this project. Thank you for putting so much of your time in guidance, and thanks for all you have taught me this year.

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Rikke Kjølberg
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Abstract

Objective: The aim of the current study was to examine if two different gamma inducing conditions could lead to higher gamma levels in a healthy population of psychology students. Specifically, the study aimed to examine 1) whether it is possible to induce gamma oscillations using either photic stimulation or neurofeedback training in healthy individuals, 2) whether photic stimulation or gamma inducing neurofeedback can lead to lasting changes in the EEG of healthy individuals, and 3) whether one of the two interventions is more effective and can be recommended for future studies. *Method:* 20 volunteer students were assigned into two groups with 10 participants in each group. Group 1 received photic stimulation and group 2 received neurofeedback training as gamma inducer. The sessions lasted in 20 minutes each and all participants received five sessions in total. A resting EEG was recorded before and after the intervention working as a pre and post-test. *Results:* The data showed no significant higher gamma levels after intervention in either of the two conditions, and no significant difference between the two groups. *Conclusion:* The present results indicate that photic stimulation and neurofeedback is not an effective gamma inducer after five sessions, with 20 minutes of exposure. It is necessary with a longer period of exposure to the conditions to show significant improvements in the gamma band for both frequency (Hz) and amplitude (μV). Due to these results, the interventions cannot be recommended for treatment for Alzheimer patients, but it can be recommended to further investigate the effect of gamma inducing protocols in a longer period of time. Optionally, it can be recommended to examine the effect of exposing subjects to several sensory stimuli at the same time.

Keywords: Photic stimulation, EEG, Neurofeedback, Oscillations, Gamma, Alzheimer, Dementia

Sammendrag

Mål: Hensikten med studien var å undersøke om to ulike gamma-induserende protokoller kunne føre til høyere gamma-nivå i en frisk populasjon av psykologi studenter. Studien hadde som mål å undersøke 1) om det er mulig å indusere gamma oscillasjoner ved å bruke enten lysstimulering eller nevrofeedback trening i friske individer, 2) om lysstimulering eller gamma-induserende nevrofeedback kan føre til varige forandringer i EEG hos friske individer og 3) undersøke om en av intervensjonene var mer effektiv enn den andre, og om de kan anbefales for fremtidige studier. *Metode:* 20 frivillige studenter ble tilfeldig delt inn i to grupper med ti deltakere i hver gruppe. Gruppe 1 mottok lysstimulering i form av blinkende lys og gruppe 2 mottok nevrofeedback trening som intervensjon. Intervensjonsøktene varte i ca. 20 minutter hver og alle deltakerne mottok fem økter totalt. En hvilende EEG måling ble tatt opp før og etter intervensjonene og fungerte som en pre og post-test. *Resultater:* Dataene viste ingen signifikante forhøyede gamma nivåer etter intervensjon i hverken gruppe en eller gruppe to. Det var heller ingen signifikant forskjell mellom de to intervensjonene. *Konklusjon:* Resultatene fra studien indikerer at lysstimulering og nevrofeedback ikke er en effektiv gamma induser etter fem økter med 20 minutter eksponering. Det er nødvendig med lengre perioder med eksponering for at intervensjonen skal vise signifikante forbedringer i gamma båndet målt både i frekvens (Hz) og i amplitude (μV). På grunnlag av disse resultatene kan en ikke anbefale intervensjonen som behandling for Alzheimers pasienter. Derimot, kan det anbefales å videre forske på effekten av gamma induserende protokoller i en lengre tidsperiode. I tillegg anbefales det å undersøke muligheten for å eksponere utvalget for flere ulike sensoriske stimuli på en gang.

Nøkkelord: Demens, Alzheimers, EEG, Oscillasjoner, lysstimulering, Nevrofeedback, Gamma

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Introduction

"Though those with Alzheimer´s might forget us, we as a society must remember them."

- *Scott Kirschenbaum*

Alzheimer's disease (AD) is a brain disorder characterized by progressive dementia that occurs in middle or late life. The illness causes damage to the neurons that cannot be reversed. AD is the most common form of dementia and is characterized by the progressive loss of cognition, for which there are currently limited treatment options (Verret et al., 2012). According to the World Alzheimer Report (2018), one person in the world develops dementia every 3rd second, and by 2050 125 million people will have developed some form of dementia. Considering the disease´s high prevalence and substantial socioeconomic costs for society at large, AD is regarded as an important public health problem. In fact, statistics indicate that it may constitute the "pandemic of the 21st century", making it a high priority for medical research today (Folch et al., 2018).

The motivation behind this current study is to try to examine the use of a non-invasive intervention procedure which could be relevant in the treatment of Alzheimer´s disease in the future. The current treatment given to those that suffer from the disorder today is often psychotropic drugs which has severe side effects and which only slightly eases symptoms. Given the importance of AD for public health, development of treatments and studies understanding the pathophysiological mechanisms of this disease is necessary. Evidence by Belleville et al. (2011) as cited in Boggio et al. (2011) has suggested that subjects at risk of developing AD have relatively plastic brains. Therefore, interventions promoting plasticity in specific neural networks are desirable in AD and may further result in reducing the behavioural consequences of the disease.

Neuronal oscillations are believed to organize information processing and communication between brain structures. Mapping of brain oscillations, using EEG or MEG demonstrated that oscillations are ubiquitous throughout the brain, which means that particular oscillatory patterns are associated with specific cognitive functions and that those patterns can be disturbed in various states of the disease (Bergmann, Karabnov, Hartwigsen, Thielscher & Siebner, 2016). For a long time, many neuroscientists believed that everything they needed to know could be observed in the anatomy of neurons, synapses, circuits, and regions. Brain rhythms and oscillations were seen as incidental. Today, evidence shows that brain rhythms

have a causal role in brain function. Methods for manipulating, modulation and changing our brainwaves are possible and can be performed in multiple ways. Sensory stimulation has shown to be a method to manipulate and modulate brainwaves and appear to induce a reorganization of the ongoing oscillations into stimulus-specific configurations, but the functional significance of the endogenous oscillations has remained poorly understood (Linkenkaer-Hansen, Nijulin, Palva, Kaila & Ilmoneiemi, 2004).

The current study is largely inspired by the work done by the Picower Institute of Learning and Memory underlying the Massachusetts Institute of Technology (MIT). Specifically, their head director Li-Huei Tsai and colleagues, have found new ways of non-invasively changing brain rhythms that might benefit patients with different cognitive and attentional deficits, like Alzheimer´s disease. By exposing mice to flickering light, MIT neuroscientists have shown that they can improve cognitive and memory impairments similar to those seen in AD patients, which is a significant contribution in AD research. Besides, it provides new approaches and ideas to similar studies which can support and shed light on the critical findings and the need for non-invasive studies for diseases such as Alzheimer´s disease.

This pilot study aims to investigate the effectiveness of a non-invasive intervention on a healthy population of students. The current study will examine if it is possible to manipulate brain waves, more specifically gamma oscillations, in the brains of healthy subjects using two different gamma inducing protocols. The current study is a randomized experimental study with a prospective design. Firstly, the thesis will present relevant theory and research which is central to the understanding of Alzheimer´s disease. Secondly, this current study will investigate the effectiveness of the intervention and further evaluate if it could be recommended for future studies. Finally, the thesis aims to shed light on the need for non-invasive treatments and the possible beneficial effects of inducing gamma oscillations in the brains of AD patients.

Dementia

Dementia is a clinical syndrome caused by neurodegeneration and characterized by an inexorably progressive deterioration in cognitive ability including memory, thinking, behaviour and capacity for independent living (Prince et al., 2013). Although dementia mainly affects older people, it is not a normal part of ageing. Worldwide, approximately 50 million people have developed dementia, and there are nearly 10 million new cases every year (World Health Organization, 2017).

Dementia is usually chronic or progressive, causing deterioration in cognitive function beyond what is expected from normal ageing. Dementia is often used as a common term for several diseases which results in different kinds of cognitive impairment associated with loss of brain function. Dementia includes a variety of diseases, such as vascular dementia, dementia with Lewy bodies, frontotemporal dementia, and other types. Nevertheless, Alzheimer´s disease is the most common (Nasjonalforeningen for folkehelse, 2018).

The condition develops slowly, often over several years. As written above, the condition is progressive, and to this date, there is no cure for any dementia. One estimates that if the patient does not die of any other reason, he or she will die of the illness during 10 years after debut. The disease involves both cognitive, psychological and motor symptoms in which the most common involves deterioration in memory, thinking, orientation, behaviour, comprehension, calculation, learning capacity, language, and judgement among others (Nasjonalforeningen for folkehelse, 2018).

In the early stages of dementia, most people continue to live a quite normal life. Although, the patient still experiences problems of forgetfulness, finding the right words in a conversation, losing track of time, and becoming lost in familiar places. These daily challenges can cause many to withdraw from social events and avoid contact with the outside world, which further can result in reduced quality of life. Additionally, these symptoms often lead to social isolation, mood swings, stress, unrest, and irritation. The vast majority of the patients in the early stage will often be aware of their symptoms with memory loss and may also express this through uncertainty and shame. Comorbid diagnoses like depression and anxiety are also prevalent.

The World Health Organization recognize dementia as a public health priority. This statement means that in May 2017, the World Health Assembly endorsed “the Global Action Plan” on the public health response to dementia. The plan provides a comprehensive blueprint for action which includes increasing awareness of dementia, reducing the risk for dementia,

research and innovation, and support for dementia caregivers (World health organization, 2017).

Today's principal goals for dementia care according to the World Health Organization (2017) are *a)* early diagnosis in order to promote early and optimal management; *b)* optimizing physical health, cognition, activity, and well-being; *c)* identifying and treating accompanying physical illness; *d)* detecting and treating challenging behavioural and psychological symptoms, and *e)* providing information and long-term support to careers.

Alzheimer's Disease

Alzheimer´s disease (AD) is the most frequent cause of dementia among older men and women. The most common early symptom is a gradually worsening and difficulties with remembering newly learned information. These symptoms occur because the first neurons to be damaged and destroyed are usually in brain regions involved in forming new memories. Alzheimer´s disease is named after a German psychiatrist and neuropathologist named Alois Alzheimer. In 1906 Dr. Alzheimer found changes in the brain tissue of a woman who had died of an unusual mental illness. Her symptoms were memory loss, language problems, and behaviour deficits. After her death, Dr. Alois Alzheimer examined her brain and found abnormal clumps, now called amyloid plaques, and tangled bundles of fibres now called neurofibrillary tangles. These brain abnormalities would become identifiers of what later became known as "Alzheimer´s disease (Cole & Kramer, 2016).

Despite the major scientific and clinical advances made concerning AD research during the last 30 years, there is currently no treatment available to cure Alzheimer´s dementia or to alter its progressive course. The currently available treatments are all symptomatic, which means, they lessen the symptoms of the disease by acting on different levels of the neuropathological process. Although they can improve the patient's quality of life, none of them is genuinely able to slow down the rapid, fatal progression of the disease (Folch et al., 2018). Numerous treatments are being investigated in various stages of clinical trials. Since 1998, over one hundred drugs have been tested, and only four have been authorized for use. Moreover, these medications can only help or manage some of the symptoms of dementia, but the effects differ among individuals (Patterson, 2018).

Today, various psychotropic drugs against behaviour and psychiatric symptoms, such as sedative medications, antidepressants, and antipsychotic medications are being used as a treatment for the disease. At present, only four currently available drugs have been approved for treating Alzheimer´s disease. They belong in two groups: *a)* the acetylcholinesterase

inhibitors (AChEI), and; *b)* antagonists of the N-Methyl-D-aspartate receptors (NMDAR). Due to the reduced ability of AD patients to transmit neurotransmitters, the action mechanism of AChEI drugs is to increase cholinergic transmission through inhibiting acetylcholinesterase in the synaptic cleft. Memantine is an NMDAR antagonist, which means that it reduces excitotoxicity by blocking the receptor. This is beneficial due to the fact that levels of the excitatory neurotransmitter glutamate are pathologically high in AD patients. Both drug groups are indicated as a treatment for patients in moderate stages of AD. Nevertheless, it has been shown that none of these approved drugs has a real curative effect, which further indicates that they provide only a palliative measure, and their effectiveness decreases over time (Folch et al., 2018).

It is evident through both media and the literature that a lot of elderly and those affected by the illness becomes over- and incorrectly medicated. In the absence of better alternatives, doctors and health professionals choose to medicate the psychological symptoms, such as depression, anxiety, hallucination, and unrest. Nevertheless, the side effects of especially psychotropic drugs are severe, and it is an increasing problem because one often needs supplementary drugs to treat the new side effects, and so it continues.

The Amyloid Cascade Hypothesis (ACH). A healthy adult brain has about 100 billion neurons. Neurons can form connections with other individual neurons through long branching extensions. These extensions are called synapses, and the brain contains about 100 trillion of them. The synapses allow signals to travel rapidly through the brain´s neuronal circuits, creating the cellular basis of memories, thoughts, sensations, emotions, movements, and skills (Alzheimer´s Association, 2017).

From as early as the late 1800s, the presence of amyloid plaques (then described as "miliary foci") was documented in the brain of elderly patients suffering from dementia. In 1906 Dr. Alois Alzheimer, as mentioned above, reported the presence of an odd substance in the brain of his patients. In the late 1960s, the pathological accumulation of proteinaceous deposits of β-sheet-containing (amyloid) fibrils were described in the context of various clinical conditions, including systemic forms of amyloidosis, Downs syndrome, and Alzheimer´s disease. Since 1992, the Amyloid Cascade Hypothesis (ACH) has played a prominent role in explaining the etiology and pathogenesis of Alzheimer´s disease (Reitz, 2012). The ACH is one of the most influential models of the pathogenesis, and some researchers believe that it is the best hypothesis to explain the cause of AD. The Amyloid Cascade Hypothesis proposes that neuroinflammation is a major driving force behind

Alzheimer´s disease pathogenesis. The hypothesis proposes that the deposition and accumulation of β -amyloid (Aβ) is the initial pathological event in AD, leading to the formation of extracellular senile plaques, tau-immunoreactivity neurofibrillary tangles, neuronal loss, and finally, clinical dementia.

Most scientist now seems to agree that there are two proteins in the brain that are heavily involved in causing Alzheimer´s disease. The first protein is the beta-amyloid or β -amyloid (Aβ), which reaches abnormal levels in the brain of a person with AD and forms plaques (called beta-amyloid plaques). These plaques are believed to contribute to cell death by interfering with neuron-to-neuron communication at synapses. The other protein, which is called tau, does also reach abnormal levels. The tau protein forms neurofibrillary tangles inside the neurons and further block the neuron´s transport system of nutrients and different essential molecules inside (Patterson, 2018).

Ever since the formulation of the Amyloid Cascade Hypothesis, there have been questions regarding whether it completely describes the AD pathogenesis. The overall validity of the hypothesis has been argued by some to be strengthened by the initial failure of some therapeutic compounds that target amyloid precursor protein metabolism or Aβ itself in clinical trials in dementia due to AD. Even though, one crucial aspect to consider is the timing of treatment and the progression profile of the disease. In fact, Aβ accumulation in the brains of AD patients often precedes clinical symptoms by several decades, during a period known as “preclinical AD.” By the time people are diagnosed with dementia due to AD, Aβ accumulation in the brain has already been evolving for an extended period, often around 20 years or so, and the tau phase of the disease is already taking over (Huynh & Holtzman, 2018). Besides, the amyloid-betas that accumulate in plaques occurs in normal aging as well. There are also observations that senile plaques and neurofibrillary tangles develop independently and may be the products rather than the cause of neurodegeneration in Alzheimer´s (Armstrong, Cairns & Lantos, 2002). These observations suggest that the ACH may not provide a complete explanation of AD pathogenesis. There is doubt regarding the primary role of Aβ, whether it leads to tau formation, and whether the form of senile plaques and neurofibrillary tangles are directly related to clinical dementia. According to Armstrong (2014), there are two possible directions for future research. Firstly, to attempt a further understanding of the mechanisms of Aβ-mediated neuronal loss, and secondly, to modify the ACH itself. Modification to the ACH is proposed which may better explain the pathogenesis of AD, especially in late-onset cases of the disease (Armstrong, 2014).

Electroencephalogram (EEG)

An electroencephalogram (EEG), is a measurement that records the electrical signals of the brain, or more specifically, the oscillations in our brain. It was first demonstrated by Hans Berger in the 1920s to measure brain activity (Berger, 1929). Berger observed two types of rhythms. One of the rhythms displayed high amplitude and low frequency and appeared when the subject had their eyes closed and relaxed (later called the alpha wave). The second rhythm exhibited low amplitude and higher frequency and appeared when the subject had their eyes opened and focused on the task (later called beta wave).

The EEG registers electric impulses and patterns that come from the surface of the scalp and enables us to glimpse the generalized activity of the cerebral cortex. The EEG-device amplifies and filters the signals, and the activity is called neural oscillations or "brainwaves."

The recording of an EEG is relatively simple. The method is non-invasive and pain-free. During the recordings, small sensors or electrodes are attached to the scalp to record the electrical signals produced from the neurons of the brain. The signal produces when brain cells are "communicating" with each other. Small voltage fluctuations, usually a few tens of microvolts (μV) in amplitude, are measured between selected pairs of electrodes (Bear, 2016, p. 647). The electrical impulses in an EEG look like wavy lines with peaks and valleys, and the lines can be observed to look for abnormalities in the patterns.

For the most part, an EEG measures the voltage generated by the current results of excitatory (EPSP) and inhibitory (IPSP) postsynaptic potentials. These potentials flow during synaptic excitation and inhibition of the dendrites of many neurons in the cerebral cortex. The cortex lies right under the skull and makes up most of the brain´s mass. The electrical contribution of any single cortical neuron is exceedingly small, and the signal must penetrate several layers of non-neural tissue, including the meninges, fluid, bones of the skull, and skin to reach the electrodes. Therefore, it takes the synchronized activity of many thousands of neurons to generate an EEG signal large enough to be measured (Bear, 2016, p. 647).

The observation of electrical signals from the nervous system goes back as early as 1848. These early studies revealed that peripheral nerve conduction involved changes in electrical fields and led to the findings of brain wave activity in monkeys and rabbits. Through the later years, the EEG became an object of much interest in the realm of psychiatric and neurological sciences, and when the digital computer technology developed in the 1960s and 1970s, the EEG became more accessible to analysis (Evans & Abarbanel, 1999).

The human EEG, on the other hand, was discovered in 1924 by a clinical psychiatrist named Hans Berger. Berger´s article in 1929 was the first to describe a pattern of oscillating electrical activity recorded from the human scalp. Berger (1929) was also one of the first to speculate that the technique could be used to measure and define biological markers corresponding to human behaviours. Further, Berger understood that such a technique could prove to be useful diagnostically and therapeutically as well. After the discovery, an extension of its use in clinical diagnosis and research followed, both in psychiatric and neurological sciences.

While analysis of EEG cannot tell us *what* a person is thinking an EEG can, however, help us examine *if* a person is thinking. In general, high frequency, low-amplitude rhythms are associated with alertness and waking, or the dreaming stages of sleep. Low-frequency, high-amplitude rhythms are associated with non-dreaming sleep states, certain drugged states, or the pathological conditions of coma (Bear, 2016, p. 653).

Today the clinical application of electroencephalography (EEG) is universally accepted and the technique it widely and globally used. In fact, the EEG remains among the most widely used test of neural function and activity. The measurement is inexpensive, and it is extensively used as a differential diagnostic tool, particularly for the diagnosis of epilepsy, which can be performed at hospitals or even at the bedside.

The EEG has high sensitivity and specificity in the diagnosis and management of, e.g. epilepsies and seizures. The bedside or portable EEG recordings can be extremely helpful in systemic conditions, especially for critically ill patients. The technology allows the patients to get fast and effective help, without having to move or travel long distances (Quinonez, 1998).

Among others, the EEG is an inexpensive and non-invasive examination of functional brain activity that is one of the few clinically available measures capable of detecting changes in, e.g. delirium. Delirium is an acute confusional state that causes disturbances in attention, consciousness, and cognition. In EEG, characteristics of delirium include slowing or drop out of the posterior dominant rhythm, generalized theta or delta slow-wave activity, poor organization of the background rhythm, and loss of reactivity of the EEG to eye opening and closing (Jacobson & Jerrier, 2000).

In sum, the EEG is a classic non-invasive method for measuring a person´s brainwaves. In addition, it can be used for detecting abnormal brainwaves and as an effective diagnostic test.

Oscillations in the Brain

Our brains have evolved a variety of systems for rhythmic control. Sleeping and waking state are the most striking periodic behaviour, but some rhythms controlled by the brain have more prolonged and shorter periods, as the oscillatory rhythms of the cerebral cortex. The functions of some rhythms are obvious, while others are obscure, and some rhythms indicate pathology (Bear, 2016, p 646).

When a single neuron fires in the brain, it sends an electrochemical pulse down its axon. However, vast networks of neurons can also fire together, creating regular cycles of neuronal activity. Formally, these are called neural oscillations, and more colloquially, they constitute brainwave patterns. Oscillatory activity is a hallmark of neuronal network function in various brain regions, including the olfactory bulb, thalamus, hippocampus and neocortex (Bartos, Vida & Jonas, 2007). If one single neuron regularly fires action potentials, the rhythmic activation of postsynaptic target cells will make a fluctuation. If several neurons fire action potentials, both regularly and synchronously, this fluctuating output signal is amplified, defining temporal windows of increased and reduced excitability in a larger population of target cells. At the same time, the rhythmic synaptic activation pattern results in a fluctuating field potential signal, which can easily be measured using extracellular recording electrodes (Bartos et al., 2007).

When we are measuring and analysing oscillations, we divide them into several factors: frequency, distribution, source, waveform/shape, and reactivity. The results of these analyses are usually measures of the amount of energy distributed in the frequency bands of the waveform. These waves are classified by how frequently the population of neurons fire in a single second. If we observe 1 to 4 waves per second, it is called a delta wave, which usually occurs during deep sleep. If they fire 12 to 30 times, that is a beta wave, which is typical of normal wakefulness. Moreover, if they fire 30 to 90 times, that is a gamma wave.

Gamma waves. Within this spectrum of oscillations on the brain, gamma oscillations have received particular attention, regarding their relationship to higher brain functions. Neural oscillations in the low-gamma range (30-50Hz) have been implicated in neuronal synchrony, computation, behaviour, and cognition.

Abnormal low-gamma activity, hypothesized to reflect impaired synchronization, has been documented in several brain disorders. Thus, understanding the relations between gamma oscillations, neural synchrony and behaviour is a major research challenge (Engelhard, Ozeri, Israel, Bergman & Vaadia, 2013).

Gamma oscillations have been proposed to represent higher mental abilities, like reference signals for temporal encoding, attention and memory, sensory binding of features into a coherent percept/perception, and storage and recall of information (Bartos et al., 2007). Although gamma oscillations occur in all cortical areas, they are particularly studied in the hippocampus. A lot of the research is also conducted using implanted electrodes in the hippocampus. The reasons are that the power of extracellularly recorded gamma oscillations is higher in the hippocampus area than in other regions of the brain and they easily get evoked in specific behavioural conditions. This allows the researchers to analyse the relationship between network oscillations in the hippocampus area and behaviour (Bartos et al., 2007).

In contrast to cortical regions, where sensory stimulation includes gamma waves, the conditions that give rise to the persistent hippocampal gamma oscillations are not fully understood (Csicsvari, Jamieson, Wise & Buzsaki, 2003). Studies have already demonstrated disrupted gamma rhythms in various neurological diseases and psychiatric disorders, however, the interplay between the pathology and the emergent neuronal circuit properties has not been fully determined. It is found abnormal gamma range activity in schizophrenic patients (Green et al., 2003), in patients with seizures/epilepsy (Medvedev, Muroo & Meador, 2011), in patients with autism (Brown, Gruber, Boucher, Rippon & Brock, 2005), ADHD (Lenz et al., 2008), and also in patients with Alzheimer´s disease (Verret et al., 2012). Some hypothesize that such abnormalities may reflect impairment in neural synchrony that causes cognitive deficits. In several of these neurological and psychiatric diseases that may lead to cognitive impairment, network activities supporting cognition are altered even during preclinical stages. That means even before the patient notices symptoms or neurocognitive exams can detect them (Palop & Mucke, 2016). In patients with Alzheimer´s disease, decreased low-gamma EEG synchronization is found in the resting state (Koenig et al., 2005).

These results suggest that modulation of neural synchrony is a controlled method, which means that gamma oscillation could ameliorate some of the deficits caused by various pathological conditions. In addition, it could advance our understanding of the relationship between these neurophysiological parameters and behaviour (Engelhard et al., 2013). Recent studies have begun to show a causal link between gamma oscillations and Alzheimer´s pathology, suggesting that gamma oscillations may even offer a plausible future therapeutic target (Nakazono, Jun, Blurton-Jones, Green & Igarashi, 2018). However, in Alzheimer´s disease, changes in synaptic activity are also shown to alter molecular pathology. Studies have shown that increases in synaptic activity, in living animals, will increase levels of amyloid beta ($A\beta$) whose congestion is thought to lead to neurotoxic events including

neuroinflammation, synaptic and neuronal loss, and tau-associated pathology (Iaccarino et al., 2018).

Gamma oscillations, in contrast to for example theta oscillations, are local activity derived from the transmembrane current of a population of periodically synchronized neurons. In healthy rodents and humans, the hippocampus and the entorhinal cortex exhibit prominent gamma oscillations that emerge at specific phases of theta oscillations (Nakazono et al., 2018). Accumulating evidence suggests that the entorhinal-hippocampal circuit is severely affected during the progression of Alzheimer´s disease. Several transgenic mouse models of AD have been developed and used to examine the impact of AD pathology on entorhinal-hippocampal circuitry (Nakazono et al., 2018). In general, molecular and cellular pathology is thought to alter synaptic activity. However, at least in one disorder, Alzheimer´s disease, changes in synaptic activity seems to affect the molecular pathology.

More recently, hippocampal gamma oscillations in AD models have gained increasing attention. In a study published in 2013, Goutagny and colleagues found that theta-gamma cross-frequency coupling is impaired in isolated hippocampus preparation from 1-month old mouse models of AD, which is prior to plaque debut. These mice first develop amyloid deposits at three months of age (Goutagny et al., 2013).

Changing Neuronal Oscillations

The brain is composed of more than 100 billion nerve cells. For many years, neurologists, psychotherapists, and researchers have studied the brain, and for a long time, it was thought that brain activity such as brain waves and secretion of brain chemicals were beyond conscious control. Nevertheless, current research has proven that it is possible to interfere with them (Zhuang, Zhao & Tang, 2009).

Entrainment is the process whereby two interacting oscillating systems assume the same period, which has different periods when they function independently. In other words, entrainment is the synchronization of biological rhythm and an environmental stimulus (Zhuang et al., 2009). Brainwave entrainment refers to the brain´s oscillatory response to rhythmic sensory stimulation, such as pulses of sound or light. When the brain is provided with stimuli, for example through the eyes, ears or other senses, it emits an electrical charge in response, called a Cortical Evoked Response (CER). These electrical responses travel throughout the brain and become what one see and hear (Zhuang et al., 2009). A lot of research is done investigating the benefits one can get from brainwave entrainment. Among others, there is research on entrainment related to increased focus and concentration

(Cruceanu & Rotarescu, 2013), increased memory performance (Hanslmayr, Matuschek & Fellner, 2014), increased creativity and problem solving (Tracy, Ahmed, Khan & Sperling, 2007) and enhanced sleep and ease of getting to sleep (Abeln, Kleinert, Strüder & Schneider, 2013).

There are different tools and methods to manipulate and influence brainwaves. However, the following two methods are relevant for this current study.

Sensory stimulation using light. Sensory stimulation refers to different techniques used to stimulate the senses to increase alertness and activation of one or more of the senses such as taste, smell, vision, hearing, and touch. Sensory stimulation therapy has been used on persons with dementia to trigger emotions and memories, and mainly, the method has been used to evoke positive feelings (Wegerer, 2017). The therapy has become widely used to treat other conditions as well, including Alzheimer´s (Clements-Cortes, Ahonen, Evans, Freedman & Bartel, 2016), autism (Edelson, 1984), brain injuries (Johansson, Widner, Wiklund & Johansson, 1993), chronic pain (Dyrehag, Widerstrøm-Noga, Carlsson & Andersson, 1997) and other forms of dementia (Spaull, Leach & Frampton, 1998). The main goal of this form of sensory stimulation has been to improve the patient's mood, self-esteem, and well-being (Wegerer, 2017). Photic stimulation, in specific, has been used in for example migraine (Subasi, Ahmed, Alickovic & Hassan, 2019) and depression (Sun et al., 2015).

However, sensory stimulation used to manipulate or influence brainwaves has been less studied. Brain oscillatory activity is assumed to be critical for normal cognitive function and is altered in Alzheimer's disease patients (Goutagny et al., 2013). Recent research, more specifically, researchers at the Massachusetts Institute of Technology (MIT) might have indications as to how therapy concerning brainwaves and entrainment work. The earlier focus on the Amyloid Cascade Hypothesis, as described earlier in the thesis, is now viewed in a new light. The oscillations or the brainwaves in the human brain are according to the researchers at MIT, much more critical when it comes to neurodegenerative diseases than earlier anticipated. The research team at MIT have been using photic stimulation to induce gamma oscillations in the brains of AD mice. The researchers first used a technique known as optogenetics, which allowed them to control the activity of genetically modified neurons by exposing them to flickering light. Using this approach, the researchers stimulated specific brain cells known as interneurons, which then synchronized the gamma activity of excitatory neurons (Boyden, 2015).

Subsequent, the researchers wanted to examine if they could use an even less invasive technique to achieve the same effect. They then came up with the idea of using external light to drive gamma oscillations in the brain.

Professor Li-Huei Tsai from the Picower Institute for Learning and Memory, have in collaboration with MIT professors Boyden and Brown found that it is possible to stimulate gamma waves in the brains of mice with Alzheimer´s disease by exposing them to flickering light at a particular frequency. Using the light device, the researchers found that an hour of exposure to the light flickering at 40 Hz enhanced gamma oscillations and reduced beta-amyloid levels by half in the visual cortex of mice (Iaccarino et al., 2016). The light signal activated the brain and trained neurons to fire at gamma frequencies.

The results indicate that it is possible to clear amyloid plaque from parts of the brain with a flickering light. The strobe was designed to manipulate the rodent's brainwaves, triggering a host of biological effects that eliminated the plaque-forming proteins. After one hour of exposure to the light, the beta-amyloid were almost cut in half. Repeated exposure, an hour a day for a week, produced reductions in amyloid levels and the sticky amyloid plaques. In addition, the flickering light and the resultant gamma waves reactivated sluggish microglia, the brain´s immune cells. The microglia became more extensive and started scavenging amyloid peptides. Restoring gamma waves also appeared to help keep neurons from dying, which also prevents brain shrinkage. The brain´s vasculature started to expand, which in addition to reducing amyloid production, also may help clear amyloid from the brain.

As described above, gamma oscillations that occur within the entorhinal cortex-hippocampal circuitry play essential roles in the formation and retrieval of memory in healthy brains. Since the discovery of amyloid beta (Aβ) aggregates in the brains of AD patients, hundreds of studies have examined the production and clearance mechanisms of these peptides, based on the theory that their accumulation initiates a series of neurotoxic events in Alzheimer's disease (Singer et al., 2018).

These observations all together indicate that entraining gamma oscillations may provide a broad spectrum of systemic effects in the brain, including in non-neuronal cells, to attenuate AD-related pathology (Iaccarino et al., 2016).

Although promising findings in mouse models of Alzheimer´s disease, it has been notoriously difficult to replicate the process in humans (Thomson, 2018). A group of researchers in Denmark has tried to replicate the Iaccarino et al. (2016) study using human AD patients. The researchers used a light emitting diode (LED) with a 40 Hz flicker. Six of the AD patients received ten days of light therapy, with two hours of daily exposure. After ten

days of exposure, the results showed no significant decrease in cortical amyloid load for any of the patients. The researchers concluded that future studies need to investigate if extended duration would have beneficial effects, and also that the subjects need to look directly in the light source and not only be exposed to a flashing environment (Ismail et al., 2018).

Neurofeedback. The roots of modern neurofeedback can be traced back to Dr. Barry Sterman and his experimentation with cats in the 1960s. Sterman ran an experiment to examine if cats could increase their sensory motor rhythm (SMR) with repeated training. The cats received food when they did right, and soon the cats quickly learned how to control their brainwaves to get access to the food. Several years later Sterman was working for NASA. While working there, he experimented with exposing the same cats to toxic rocket fuels. In addition to some of the cats getting seizures of the fuel, Sterman noticed that a few of his cats were immune. Sterman noticed that the immune cats were the same cats he has used in the SMR brain training experiment some years ahead. Sterman later began experimenting with human subjects leading to massive discovery in the treatment for seizure disorders like epilepsy. The clinical practice of neurofeedback could never have progressed into what they are today without the work and this rare coincidence unveiled of Dr. Barry Sterman (Advanced Neurotheraphy, 2015).

The EEG biofeedback or neurofeedback, however, originated in the late 1960s and 1970s as a method for retraining brainwave patterns through operant conditioning. This means that by measuring current brain activity and rewarding it, it is possible to change into more appropriate patterns of activity. Neurofeedback is a psychophysiological procedure in which online feedback of neural activation is provided to the participant for the purpose of self-regulation (Sitaram et al., 2017).

During typical training, the researcher put a couple of electrodes on the patient's scalp, and then electronic equipment provides real-time, instantaneous audio, visual, tactile or a combination, feedback about the patient´s brainwave activity. The feedback-loop works as a rewarder which enable the patient to learn how to modify aspects of his/her brain activity (Hammond, 2011). The EEG signals detected by the electrodes are amplified and digitized by specialized hardware, then sent to a computer who map certain aspects of the signal to some form of feedback (Chapin & Russell-Chapin, 2014). Most common are graphs and digits, but also changes in colour, patterns or even animations that change as a direct result of variations in the participant´s EEG are possible (Yucca & Montgomery, 2008).

The main aim of the neurofeedback as a behaviour therapy technique is to teach or improve self-regulation of brain activity (Thibault, Lifshift, Birbaumer & Raz, 2015). This through the voluntary production and control of EEG signals to achieve a specific result. Ordinarily, a person cannot directly influence their brainwave patterns because they lack awareness of them. However, when a patient gets the ability to observe his/her brainwaves on the screen, it gives the patient the ability to influence and change them. This mechanism is what we call operant conditioning (Hammond, 2011). The use of neurofeedback as an operant conditioning paradigm has disclosed that participants are able to gain some control over particular aspects of their EEGs (Vernon et al., 2003).

According to Sherlin et al. (2011), certain principles must be followed for the neurofeedback training to be effective. To achieve desired effects one must ensure a discrete and uncomplicated setup of the equipment, and as much as possible of noise and artefact must be avoided. The feedback and reinforcement must be fast, and the signal or behaviour under training must be specific. Other reinforcement must be directly connected to the learning process and in order to ensure generalization of the neurofeedback training to real-life situations, one must include transfer trials (Sherlin et al., 2011).

With continuing feedback over time, including coaching and practice, the patient can retrain a normalization of better brainwave patterns. Neurofeedback is comparable to exercising or doing physical therapy; the difference lies in using the brain instead of the physical body. In practice, it enhances the cognitive flexibility and control over individual brainwaves, and therefore additionally, the general cognitive functions in the brain.

Since the origin of Neurofeedback in the 1960s, an amount of research has accumulated on the effectiveness of neurofeedback in the treatment of different disorders. Neurofeedback has been applied with various purposes, to different patient groups, on problems stemming from different learning disabilities and also on healthy individuals (Marzbani, Marateb & Mansourian, 2016). Examples of studies using neurofeedback includes patients with epilepsy (Sterman & Egner, 2006), ADD and ADHD (Thompson & Thompson, 2005; Arns, de Ridder, Strehl, Breteler & Coenen, 2009), anxiety (Mennella, Patron & Palomba, 2017) and also other cognitive and neurodegenerative disorders like Alzheimer´s disease and dementia (Luijmes, Pouwels & Boonman, 2016; Staufenbiel, Brouwer, Keizer & Wouwe, 2014). Studies further provide encouraging indications that neurofeedback offers a treatment alternative for use with stroke, depression, fibromyalgia, autism, insomnia, and tinnitus. Additional clinical applications include the use of slow wave alpha/theta feedback training as a complementary therapeutic tool in the treatment of substance abuse (Peniston &

Kulkosky, 1989; Gabrielsen, 2012). Neurofeedback is also being used increasingly to facilitate peak performance in "normal" individuals and especially in athletes, including Olympic athletes and national teams (Graczyk et al., 2014).

The term "brain plasticity" is usually used to denote the capacity of the brain to compensate for the effects of lesions through structural and functional changes that might occur after suitable rehabilitation. Many diseases and conditions have reported brain plasticity, examples are spinal cord injury, after amputation of a limb, after strokes or lesions in the brain, in Alzheimer´s disease or after other traumatic brain injuries (Otte, 2001).

Cognitive neuroscience reveals plasticity to the extent that was not expected on the basis of behavioural research. In this field, the term "plasticity" represents the potential for flexible recruitment of the neurons, reflecting structural and functional changes, sometimes as a response to learning and experiences. One mechanism that could contribute to plasticity is neurogenesis, the growth of new neurons (Gutchess, 2014).

Koralek, Jin, Long, Costa & Carmena (2012) found in their study using rodents that striatal neurons change their firing rates and build strong connections with motor cortex neurons. This result indicates that corticostriatial plasticity is the basis for learning, not only for abstract skill learning but also for learning intentional neuroprosthetic skills in the absence of movements.

Neurofeedback and Alzheimer´s disease. To my knowledge, not large amounts of research has been conducted examining the effect of neurofeedback on people with dementia or Alzheimer´s disease. A lot of research regarding neurofeedback, however, is conducted on younger patients, especially patients who have ADHD or ADD. As mentioned earlier, it is also sufficient studies regarding people who have suffered strokes, people who suffer from epilepsy and brain trauma in relation to neurofeedback therapy.

The thesis will further summarize some of some of the literature concerning neurofeedback and Alzheimer´s disease or dementia.

A 2009 study by Berman and Frederick described how neurofeedback was conducted on patients with dementia. The study tested whether using EEG biofeedback could improve measures of memory and executive function. All the participants in the study received treatment with neurofeedback. The study found that the memory of the patients was significantly improved following the training, and the researchers also observed that the neurofeedback training was more effective for patients at an early stage of dementia (Berman & Frederick, 2009).

In 2012 another study was conducted, examining the effect of neurofeedback on older adults judged at risk of developing dementia. The patients received 30 sessions of neurofeedback training lasting 30 minutes each. The results showed an improvement in their verbal comprehension and associated brainwave patterns (Becerra et al., 2012).

In 2015 Surmeli and colleagues conducted a study examined whether training with neurofeedback had an improving effect on patients with dementia (9 patients with Alzheimer´s disease and 11 with vascular dementia). The cognitive test used in the study was the Mini-Mental Status Examination (MMSE) designed to measure cognitive impairment and to screen for dementia. The results showed an increase in the scores in the MMSE for all subjects, regardless of the type of dementia. The average MMSE- score increased with 6 points, which was found to be significant. Faulty this was the first time the same modality was shown to be beneficial in both dementia group.

In 2016 Luijmes et al. examined whether training with neurofeedback had a positive effect on cognitive performance in patients with Alzheimer´s disease. Ten patients aged between 61 and 90 years with AD received neurofeedback training. The patients also underwent pre- and post-tests, specifically the CAMCOG-test designed to assess cognitive functioning. The results showed that patients who received neurofeedback treatment had stable cognitive functions. The researchers concluded that neurofeedback has a positive effect on the cognitive performance on patients with Alzheimer´s disease (Luijmes et al., 2016).

Hohenfeld et al. (2017) examined whether the cognitive decline in Alzheimer´s disease can be counteracted using real-time fMRI neurofeedback training. Sixteen healthy elderly subjects and ten patients with Alzheimer´s disease completed the experiment. The neuropsychological battery included the Montreal Cognitive Assessment test (MoCA), visual and verbal memory test (VVM), Wechsler memory scale (WMS) and the visual patterns test and trail making test (TMT). The results showed that healthy elderly and patients with prodromal AD showed improved visuospatial memory performance after neurofeedback training. The researchers concluded that these findings suggest that cognitive decline, either related to prodromal AD or healthy ageing could be counteracted using fMRI-based neurofeedback.

These findings summarized above all have in common that they have used neurofeedback training on patients with Alzheimer´s and other forms of dementia with significant results. The use of neurofeedback in this study will focus on the use of the tool as an inducer for gamma oscillations. Nonetheless, there is still a need for more research on neurofeedback as a treatment option for dementia and AD. As summarized above, several

studies have indicated positive results when using the method as a treatment for the current patient group.

The Present Study

A lot of research has been conducted on the field of Alzheimer´s and dementia in the recent years, but according to the World Alzheimer´s Report (2018), it has been 40 years since any significant breakthrough in the field.

The work accomplished by Professor Tsai at the Picower Institute at MIT and the research done by Iaccarino et al. (2016) has been essential to the construction of the present study. The design and idea behind the study were inspired by the work and study mentioned above.

The main goal of the present study is to examine if it is possible to induce gamma through two different conditions. The aim is to examine whether one of the two protocols will succeed in inducing a significant amount of gamma oscillations in the subject´s brains.
In addition, the study aims to shed light on the need for non-invasive treatment and research on dementia and Alzheimer´s disease. Based on earlier research done by the team at MIT, neurofeedback research, gamma theory and the overarching objective which is to examine the role of gamma in the human brains, and if we are able to enhance it, the following research questions are covered:

1. Is it possible to successfully induce gamma oscillations at 40 Hz using either photic stimulation or neurofeedback training in healthy individuals?
2. Does photic stimulation in 40 Hz or gamma related neurofeedback training lead to lasting changes in the EEG of healthy individuals?
3. Are one of the two protocols more effective and can both or one of them be recommended for future studies?

The following hypotheses were formulated to answer these research questions:

H0: The gamma-levels during intervention will equal the levels at normal state
Towards
H1: The gamma-levels during intervention will increase compared to normal state.

and

H0: The average gamma-levels (pre-test EEG) equals the average levels after the intervention (post-test EEG)
H2: The average gamma-levels before and after the intervention is different.

Methods

Selection Strategy and Subjects

A total sample of 20 psychology students from the Norwegian University of Science and Technology (NTNU) were recruited for participation in this prospective pre-post intervention study. The participants were recruited through a request for participation in a lab exercise linked to their course "Applied and clinical biology". All the students of the course received an e-mail with a request for participation and were asked to return an e-mail if they wanted to participate. The final sample consisted of 11 women and nine men. The mean age for the total sample was 22.8 (SD=2.28), with a range of 20 to 30 years.

Table 1

Overview of participants in the study

	Male	Female	Total
Photic stimulation	4	6	10
Neurofeedback training	5	5	10
Total	10	10	20

The selection was randomly assigned into two groups. One group received photic stimulation through goggles with a flickering light at 40 Hz, and the other group received neurofeedback training through a gamma inducing protocol as the intervention. The study format consisted of one pre-test (EEG), five sessions with gamma inducing intervention and one post-test (EEG). All the participants conducted the same pre and post-test but received two different interventions in the two different groups. All of the data were processed confidentially, and the project was approved by The Regional Committees for Medical and Health Research Ethics (REK). All the participants gave their written consent to partake the study (see Appendix 2).

The study is considered to be a pilot study and was designed as an exploring experiment to examine if it is possible to induce gamma oscillations in the brains of healthy individuals. The study was also exploratory in the form of wishing to investigate which of the two interventions were the most successful, if any. Further, to evaluate if the method could be used in future studies conducted in a clinical population, and maybe in the future serve as a non-invasive treatment option for people with Alzheimer´s disease. The sample used in this current study is too small to evaluate if it could be used as a treatment in the future, but the

results may provide indications of what level of effort would be needed to significantly increase 40 Hz gamma in a healthy population.

Measurement/Equipment

All the participants went through a pre and post-test where their resting EEG (eyes open condition) was recorded and analysed before and after the intervention. All of the EEG recordings and the intervention sessions were performed in the same lab.

EEG recordings. EEG recordings were recorded pre and post-intervention using a 19 channel digital MITSAR WinEEG amplifier (version 201; St. Petersburg, Russia). The electrode cap contained tin (Sn) electrodes (Electrocap International Inc.), filled with conductive gel, and placed on the scalp according to the 10-20 international standard montage with the reference electrodes on both ear lobes and the ground electrode on Fpz (Klem, Lüders, Jasper & Elger, 1999). The electrodes included Fz, Cz, Pz, Fp1/2, F3/4, F7/8, T3/4, T5/6, C3/4, P3/4 and O1/2 (see figure 1). The recording was carried out in a resting state, where the participant sat in a comfortable chair in a soundproofed room. The participants were instructed to relax and to avoid muscular movement while recording. The recordings lasted 10 minutes each. The EEG data were analysed offline in the WinEEG 2.81.25 Software (Mitsar, St. Petersburg, Russia).

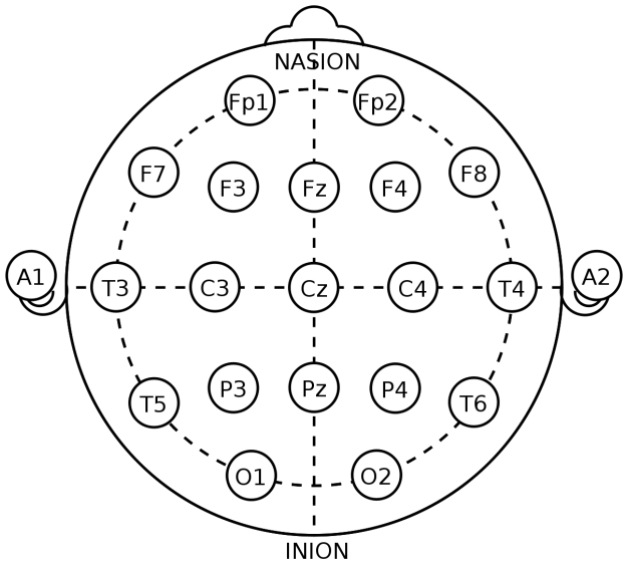

Figure 1. Electrode placement according to the 10-20 system.

Intervention procedure

The intervention consisted of five sessions for both groups after the pre-test EEG. The intervention took place two to three times a week from 4th of February 2019 to 6st of March 2019, included the pre and post EEG.

Group 1 Photic stimulation. Group 1 consisted of 10 participants which received photic stimuli through flickering goggles, with a gamma inducing protocol. They received the photic stimulation simultaneously with the 19 channel EEG equipment recording their brainwaves. This was performed to get access to their EEG while the stimulation was active and, specifically, to be able to investigate the gamma-oscillations from their visual cortex.

The goggles were protocolled to flicker for 1 minute in 40 Hz followed by a 30-second break with no stimuli. The protocol continued until the participant had been given a total of 15 minutes of photic stimuli.

The first sessions were initiated with a short conversation where the researcher asked the participants if they had any history with epilepsy or/either migraine. If not, the participant was informed about the protocol and asked if they had further questions. The sessions took place in a sound insulating room in a comfortable chair with arm and neck rest. The first sessions served as a test of the goggles, as well as a test to see if the participants tolerated the light stimulus. Therefore, the first session for group 1 was completed without the EEG-cap and the EEG recording.

The photic stimuli were pulsing light with flicker frequency of 40 Hz. The photic stimuli were presented to the subjects through a pair of goggles, which is an EEG accessory provided by MITSAR Brain Diagnostic Solutions. The light was protocolled to be red, and the goggles luminosity on a distance 2 cm of the light was 375+20% lx (with stimulation frequency at 40 Hz). The goggles are CE-certified for medical use (MITSAR Co Ltd, 2018).

After the first session, the following four sessions were performed with a 19 channel EEG-cap. This was the same cap as used on the pre and post-test EEG. The EEG recordings simultaneously with the intervention were perfomed to be able to investigate the gamma power during the session. The active time of photic stimuli lasted for 15 minutes, plus resting time in between the light intervals, which made the full time of intervention to approximately 22 minutes.

Group 2 Neurofeedback training. Group 2 which consisted of 10 participants received neurofeedback training (NFT) using BioTrace+ software (V2015B) and the Nexus 10 amplifier from Mind Media (Mindmedia BV, Heden, Netherlands). The protocol was presented as a gamma-inducing protocol with the main purpose to try to increase the gamma power band.

The sessions were normally initiated with a short conversation concerning the student´s overall form. Further, the participants were seated in front of a computer screen and had electrodes placed on the T3 and T4 sites of the scalp, in addition to reference electrodes placed on both mastoid bones. No specific instruction was given, only a brief explanation of what the main aim was, which was to increase the gamma power. In addition, the gamma power was symbolized as a white graph on the screen. The subjects were also instructed to keep the orange graph, which symbolized artefacts and muscle movements, as low as possible (see figure 2). Otherwise, the subjects were just told to relax and to try to find the most successful mental strategy that provided positive feedback.

During the NFT sessions, all of the participants were seated in a comfortable chair with a neck and armrest in a sound insulating room. The same room was used for the pre and post EEG recordings, as well as all the training sessions. The active training time lasted for approximately 25 minutes.

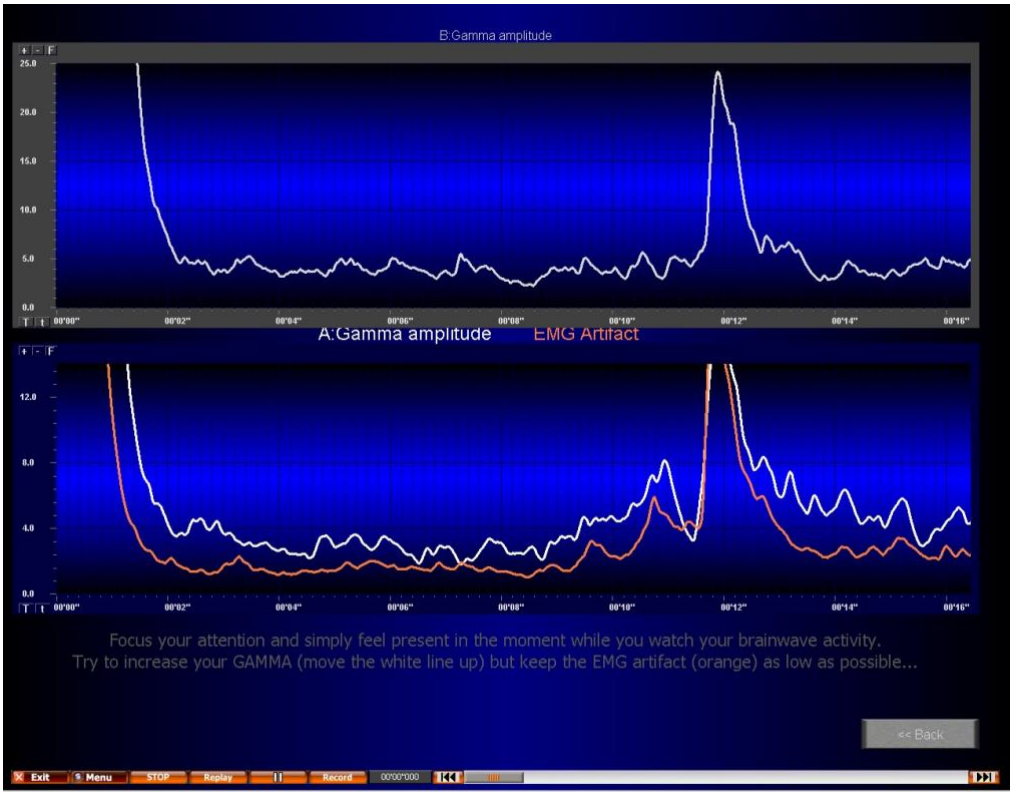

Figure 2. Gamma-inducing training protocol in Biotrace + software

Analysis and Artefact Correction

Pre-test and post-test EEG. For the total sample´s pre and post-test, the same analysis and artefact correction was conducted. Eye blink artefacts were isolated by applying ICA (Independent Component Analysis) to the raw EEG data. ICA is a computational method used to separate a multivariate signal into additive subcomponents based on the assumption that there is statistical independence between the components (Grin-Yatsenko, Baas, Ponomarev & Kropotov, 2010). The ICA method may identify unique spatiotemporal signals, like an eye blink or tension in the jaw, and provide a template for its morphology. This template is thereby subtracted manually from the raw EEG resulting in a relevant artefact removal. In addition, manual removal of large movements artefacts was also performed in the same Win EEG program. Finally, the recordings were converted to frequency spectra and a frequency table. For group 1 (photic stimulation) the mean gamma frequency (Hz) and amplitude (μV) for occipital area O1 and O2 were collected. This was performed because the stimuli were photic and expected to only have an effect in the visual processing centre of the brain (the occipital lobe). For group 2 (neurofeedback training) the mean gamma frequency (Hz) and amplitude (μV) for temporal area T3 and T4 were collected, as those were the sites the electrodes were placed for the neurofeedback recording.

Group 1. The intervention data for group one was analysed using the Win EEG software where 300 seconds of their recording was marked and further artefact corrected. Then, manual removal of large movement artefacts was performed. Finally, the recordings were converted to frequency spectra and a frequency table. For group 1 the mean gamma frequency (Hz) and amplitude in microvolts (μV) for the occipital area O1 and O2 was collected as the stimuli were photic and expected to have an effect only in the visual processing centre of the brain (the occipital lobe).

Group 2. For the second group, which received neurofeedback training, the data analysis was slightly different. This was based on the use of different software. All neurofeedback data from the participants in group 2 were analysed in the program Biotrace + by Mind Media. A Fourier transform analysis (FFT) was performed, and further, the data was transformed into a frequency table. The Biotrace+ analysis program only gave access to the amplitude in microvolt (μV); therefore, only mean amplitude data from mid temporal areas T3 and T4 were collected for group 2.

Statistical Analysis

The statistical software IBM SPSS 25.0 (SPSS Inc; Chicago, Illinois) was used for the statistical analysis. A visual inspection using a histogram in SPSS indicated that the data was not normally distributed. Based on this observation, a Shapiro-Wiik test was conducted to test for normality. The Shapiro-Wiik test was used as it is more appropriate for small sample sizes (<50) (Field, 2013). The results showed a non-significant Shapiro-Wiik test, which indicates that the data significantly deviated from a normal distribution. In addition, skewness and kurtosis values were calculated which also indicated non-normality. All of these findings concluded that the data derived from the study were non-normally distributed, which further lead to the decision to perform non-parametric tests as statistical analysis of the data.

Wilcoxon Signed-Ranks Test. Two Wilcoxon Signed-Ranks Tests was conducted to investigate and compare the pre and post-test gamma scores (frequency and amplitude) for the two intervention groups with a $p<0.05$ threshold for statistical significance. Prior to analysis, the data were checked for assumptions. The test was used to investigate whether there was a significant change in the two intervention groups before and after the interventions.

A calculation of Cohen´s effect size values for group 1 showed $d=0.72$ for frequency (Hz) and $d=0.05$ for amplitude (μV) which is considered to be moderate and very small effect sizes. For group 2 the same calculation showed $d=0.6$ for frequency (Hz) and $d=0.19$ for amplitude (μV). These calculations are considered to be moderate and small effect sizes considered by the following criteria: d= 0.2 small, d =0.6 is medium, and d= 0.8 is large (Cohen, 1988).

Mann-Whitney U Test. A Mann-Whitney U test was conducted to investigate the differences in the two independent gamma-induced protocol groups; the photic stimulation group (GR1) and the neurofeedback training group (GR2), which each consisted of 10 participants (N=20). The test was run with a $p<0.05$ threshold for statistical significance. Prior to analysis, the data were checked for assumptions.

Ethical Considerations

All of the participants in the study were informed about the background for the study, the main goals, implementation, potential effects and side effects, and the right to withdraw anytime without consequences (See Appendix 1). The participants signed an informed consent form prior to the study´s start (see Appendix 2). The study was presented for

Regional Committees for Medical and Health Research Ethics (REK) and received approval in January 2019.

Results

Table 2 summarizes demographic, mean and standard deviation values pre-intervention for the two groups. On the basis of a non-normally distribution of the data, two non-parametric tests were conducted to analyse the data. On average, none of the two intervention groups showed significantly increased gamma levels after the intervention compared to before the intervention (see table 3 and 4).

Demographic Characteristics

The two groups showed similar characteristics on the demographic variables. There was no statistically significant difference between the two groups at pre-test ($p > 0.05$), so the null hypothesis, which stated no difference before the intervention, was not rejected. The sample was not normally distributed; therefore, non-parametric tests were used. Demographic and pre-test data for the two groups are presented in table 2.

Table 2

Demographic and pre-test variables

	Photic stimulation (N=10)			Neurofeedback (N=10)		
	Cases (%)	Mean	SD	Cases (%)	Mean	SD
Gender						
Female	6 (60)			5 (50)		
Male	4 (40)			5 (50)		
Age (yrs.)		22	1.83		23.6	2.50
Hz		37.18	2.19		36.72	.97
μV		.39	.44		.72	.69

Note: Hz = /Frequency/Hertz; μV = Amplitude/microvolt; SD = standard deviation

Gamma Band Scores

The Wilcoxon Signed-Ranks test was conducted for each of the two intervention groups to compare the gamma band scores before the intervention (pre-test) and the gamma band scores after the intervention (post-test). Both frequency (Hz) and amplitude (μV) were investigated for the two groups. The mean gamma scores for area O1 and O2 were examined for group 1 and mean gamma scores for area T3 and T4 were examined for group 2.

Group 1 Photic stimulation. A Wilcoxon Signed- Ranks test was conducted to compare mean gamma band scores before and mean gamma band scores after the intervention for group 1. The test indicated that 3 participants presented a higher frequency (Hz) score pre-intervention than after the photic stimulation. However, 7 of the participants had higher frequency (Hz) score after the photic intervention. Regarding amplitude (μV), 4 participants had higher score before the intervention, and 6 participants got higher scores after the gamma-intervention.

The Wilcoxon signed-rank test showed that a 3-week intervention with 5 gamma-inducing sessions using photic stimulation did not elicit a statistically significant change in gamma scores in either frequency (Z= -1.478, p = .139), or amplitude (Z = 1.561, p = .575) in a healthy group of students (N=10). Results from the Wilcoxon test displaying changes in pre-intervention to post-intervention are presented in table 3.

Table 3

Change in gamma-band: frequency (Hz) and amplitude (μV)

Group 1		M	Change	SD	Min	Max	Sig $p<0.05$.
	Pre-test Hz	37.19	1.89	2.19	36.01	43.33	.139
	Post-test Hz	38.99		2.74	36.13	43.83	
	Pre-test μV	.39	0.02	.43	.06	1.43	.575
	Post-test μV	.41		.34	.05	1.16	

Regarding frequency (Hz), a change of 1.89 Hz was found, but the change was not significant. In the amplitude-band (μV) there were barely any change, hence not significant. However, the mean frequency for group 1 went from 37.19 Hz in the pre-test to 38.99 Hz in the post-test, which can indicate a plausible upcoming significant effect with more sessions over time.

Group 2 Neurofeedback training. A Wilcoxon Signed- Ranks test was conducted to compare mean gamma band scores before the intervention and the mean gamma band scores after the intervention for group 2. The test indicated that 3 participants had a higher frequency (Hz) score pre-intervention than after the neurofeedback training. However, 7 participants had a higher frequency (Hz) score after neurofeedback intervention. Regarding the amplitude (μV), 7 participants had higher scores before the intervention, and 3 participants represented higher scores after the intervention. The Wilcoxon signed-rank test showed that a 3 week, 5 in total gamma inducing sessions with neurofeedback training did not elicit a statistically significant change in gamma scores in neither frequency (Z= -.968, p = .333) nor amplitude (Z = -.764, p = .445) in a healthy group of students (N=10). Results from the Wilcoxon test showing changes in pre-intervention to post-intervention are presented in table 4.

Table 4

Change in gamma-band: frequency (Hz) and amplitude (μV)

Group 2		M	Change	SD	Min	Max	Sig $p<0.05$
	Pre-test Hz	36.72	1.25	.97	35.89	38.57	.333
	Post-test Hz	37.97		2.51	35.90	42.85	
	Pre-test μV	.72	0.13	.69	.10	1.86	.445
	Post-test μV	.59		.66	.09	1.87	

Regarding frequency (Hz), a change of 1.25 Hz was found but the change was not significant. In the amplitude-band, there were barely any change, hence not significant. However, the mean frequency went from 36.72 Hz for the pre-test to 37.97 Hz in the post-test, which can indicate a plausible upcoming significant effect with more sessions over time.

These results suggest that none of the two gamma-inducing interventions gave a significant effect on post-test EEG gamma levels. Specifically, the results suggest that five sessions with gamma inducing intervention are not enough to significantly change the production of gamma rhythms, neither in frequency (Hz) nor amplitude (μV).

Comparison of the Two Groups

The Mann-Whitney U test was conducted to investigate and compare the effectiveness of the two intervention groups. This was performed to try to address the research question that asked if one of the two groups were more successful than the other. The result indicated that there was no significant difference in the two groups in neither frequency (Hz) (U = 32.5, p = .186) nor amplitude (μV) (U = 47.5, p = .850) in the post-test scores, and thus the null hypothesis, which stated that the two groups are equal could not be rejected. This result indicates that we cannot state that one of the two gamma inducing intervention was significantly better than the other, nor can we state that one of the two gamma inducing interventions specifically should be recommended in future treatment.

Effect During Intervention

Group 1 Photic stimulation. During stimulation, all of the 10 participants in the photic stimulation group showed a consistently enhanced production of 40 Hz gamma, (see figure 3). As for the amplitude (μV) of gamma, you could clearly see an increase in power from pre-test to intervention 3, before the line falls and becomes stable at the post-test (see figure 4). This result indicates that the exposure to the flickering light of 40 Hz did have an effect on the participant's gamma oscillations while being currently exposed, however, the post-test results showed that the effect was not lasting.

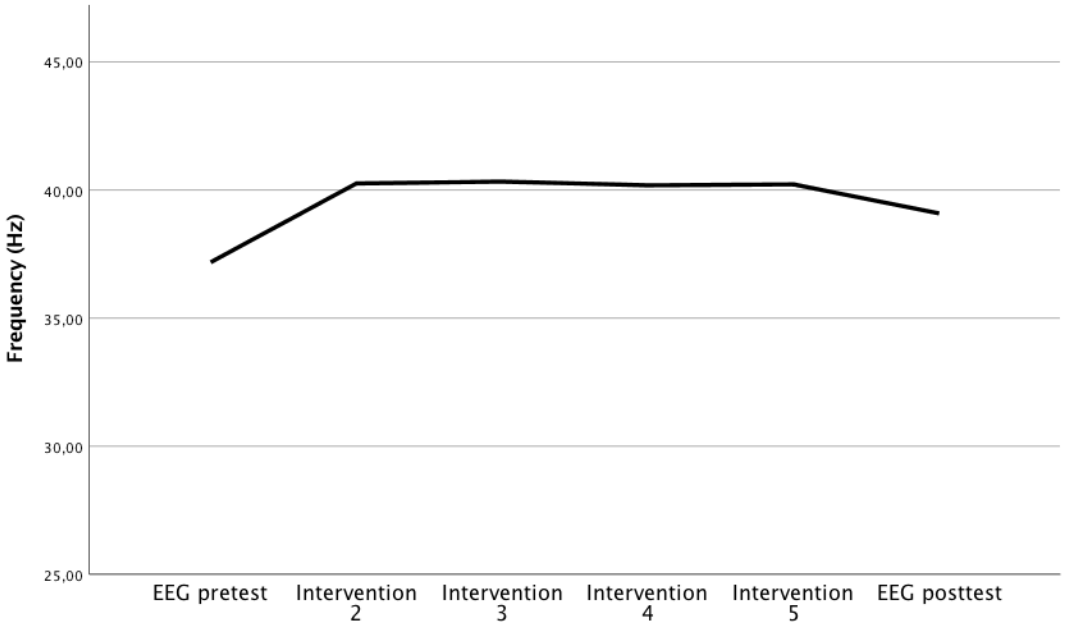

Figure 3. Line graph over Frequency (Hz) Pre-test, interventions and post-test**.**

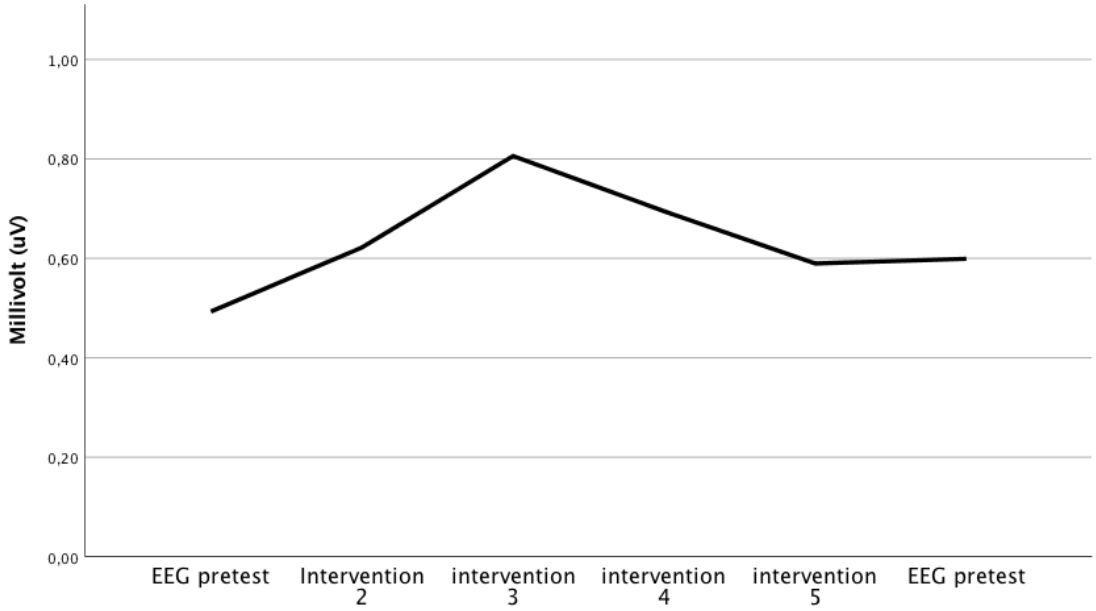

Figure 4. Line graph over Amplitude (μV) Pre-test, interventions and post-test.

Group 2 Neurofeedback training. Due to the software used in the neurofeedback group (Biotrace +), it was not possible to get access to the gamma frequency (Hz) data during actual training with neurofeedback. Only the training data for gamma power in amplitude (μV) was accessible. Therefore, gamma frequency (Hz) during actual training will not be reported for group 2. Only the actual training data for amplitude (μV) will be reported using a line graph. However, pre-test and post-test data are reported in frequency (Hz) using a line graph for group 2, showing changes from pre to post-intervention.

In the current state of neurofeedback training, several of the participants showed high amplitude (μV) levels in their gamma-band (M=11.88 μV). At pre-test (M= 0,73 μV) and post-test (M=0.60 μV), the difference was minor and much lower than at the current intervention data (See figure 5). According to the frequency measure, an enhancement from pre to post-test can be observed on the line graph (see figure 6).

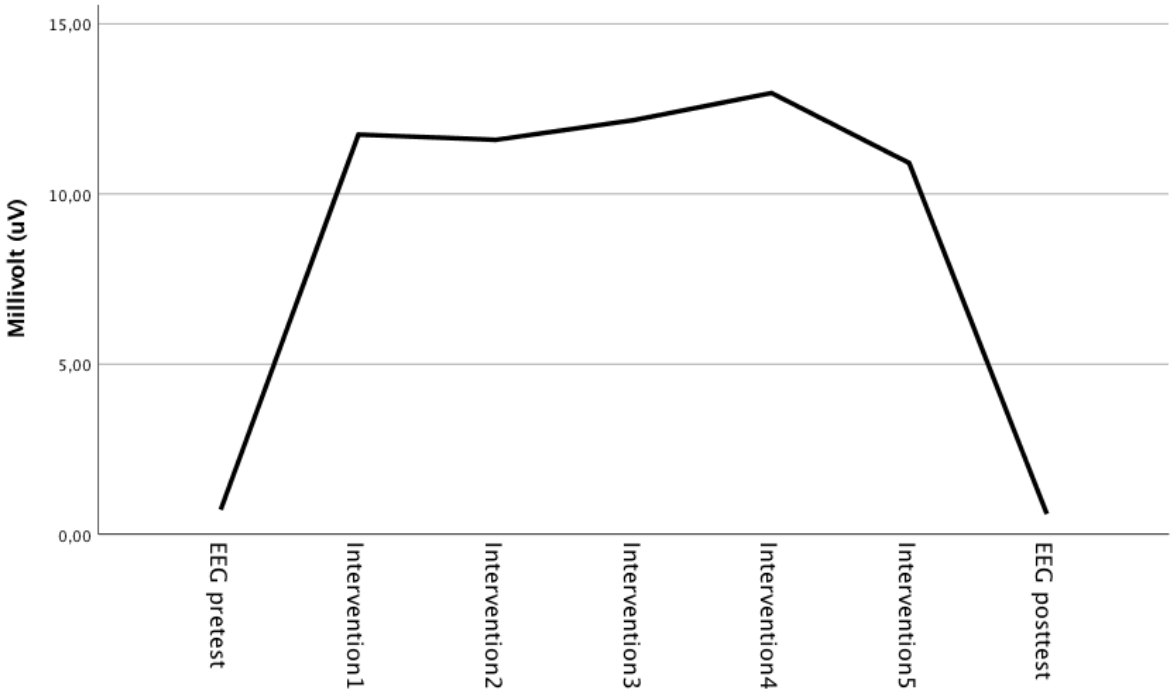

Figure 5. Line graph over Amplitude (μV) pre-test, interventions and post-test.

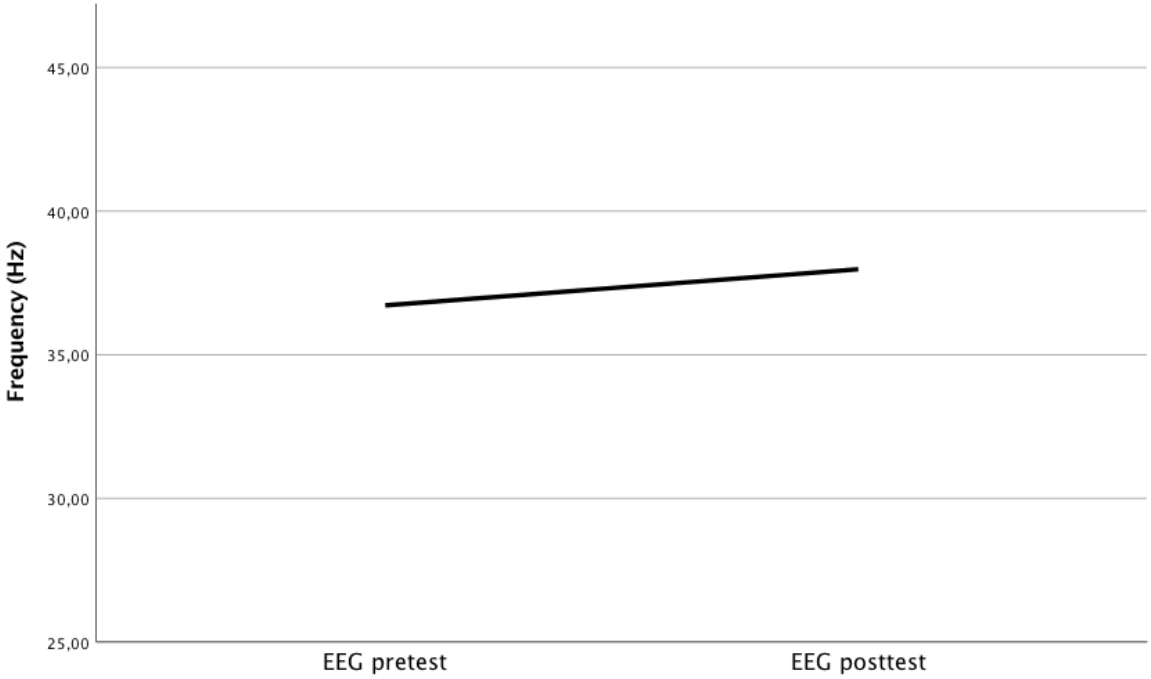

Figure 6. Line graph over Frequency (Hz) pre-test and post-test.

Discussion

The main aim of this current study was to examine whether it was possible to successfully change gamma oscillations in a healthy population of students. The study wished to examine whether this was possible with one of these two conditions; 1) photic stimulation or 2) neurofeedback training (NFT). In addition, the study was aiming to examine if it was possible to increase the existing gamma power using the two intervention protocols to create a lasting effect. Further, the study aimed to evaluate the efficacy of the two conditions, and if they could be recommended for use in future studies, specifically, studies concerning early-onset Alzheimer´s patients.

The research questions were investigated by exploring the effects of photic stimulation and neurofeedback training, using resting EEG recordings as a pre and post-test metric. The hypothesis was that both photic stimulation and neurofeedback training would lead to enhanced mean gamma levels measured in both frequency (Hz) and amplitude (μV) in the two groups. It was also hypothesized that the two groups would show a statistically significant increase from pre to post-test in both microvolt and hertz. It was further hypothesized that the increase would be in the area O1 and O2 for the photic group and the area T3 and T4 for the NFT group. This result would suggest that both groups would have had an effect of the intervention, and demonstrate that it is possible to induce and increase gamma levels in healthy individuals.

Summary and Interpretation of the Results

The final results indicated that none of the two intervention groups was successful in significantly increase gamma power in the post-test EEG in either frequency (Hz) or amplitude (μV). In addition, statistical analysis showed that there was no significant difference in the two groups when being compared. This result indicates that one cannot recommend one intervention over the other for future studies.

However, even if the study showed no significant increase in gamma levels in neither of the two groups in the post-test EEG, one of the protocols was very successful in manipulating the participant's oscillations during stimulation. In group 1 (GR1), the photic stimulation group, one could clearly observe that all the participants´ gamma oscillations were produced at 40 Hz when being stimulated by the light. This effect was durable and steady throughout all sessions, regardless of the participant´s initial gamma rhythm, which is the persons´ natural gamma in the absence of manipulation. This result may indicate that the study was successful in inducing gamma, but that there were not sufficient number of sessions

for a lasting effect. In other words, the result may indicate that it was too few training sessions to give a significant increase in the subjects' initial gamma rhythm at the post EEG. Specifically, these results suggest that it may be possible to manipulate healthy individuals to produce more gamma band activity through photic stimulation, which is important to know according to the possible beneficial abilities gamma has in relation to microglia's in the brain (Iaccarino et al., 2014).

In group 2 (GR2), the neurofeedback group, one could also observe an increase in the amplitude (μV) of the participants during the neurofeedback sessions. Nevertheless, the effect was not lasting and did not show any significant improvement during the post EEG recording. However, these results could be interpreted as if several sessions of neurofeedback training were provided, this could lead to lasting changes in the individual's EEG. This conclusion corresponds with earlier neurofeedback studies who have shown that a certain number of sessions is required before one could expect significant results (Marzbani et al., 2016). The downside is that it is both time consuming and resource consuming to arrange and facilitate such a large number of neurofeedback sessions over time. In addition, it will depend on a population that has both the time and the motivation to carry out such a large amount of training sessions.

The mean frequency for the total sample went from 36,9Hz in the pre-test to 38,5Hz in the post-test. This result may indicate and may be interpreted as a plausible change towards the desired 40 Hz rhythm, which could be significant with more sessions over time. Unfortunately, this current study was limited so that a sufficient number of sessions were not possible.

The effect size value GR1 (Hz, d= 0.72), (μV, d =0.05) and GR2 (Hz, d =0.6), (μV, d = 0.19) suggest moderate for frequency and a relatively small effect size for amplitude. This could be explained due to the fact that the participants only were given five training sessions each. This also points towards the encouraging possibility that a considerable amount of session of especially photic stimulation could or can lead to significant enhancement in the gamma band.

Findings in the Light of Relevant Literature

The possibility to successfully induce gamma in healthy individuals are in line with existing research from Iaccarino et al. (2014) and Singer et al. (2018), but the difference in this current research is that the effect was not lasting after the intervention ended.

Specifically, one could not observe a significant increase in gamma when the participant was not currently stimulated.

This current study's failure to get lasting results are in line with similar studies. Specifically, it is in line with the results from the Danish study which tried to replicate the Iaccarino et al. (2016) study on Alzheimer´s patients. The participants in the study from Denmark received light stimulation two hours daily for over ten days, but the group failed to find any significant results of the treatment. The researchers concluded that it is necessary with extended periods of stimulation along with a recommendation that the subjects should look directly in the light source (Ismail et al., 2018). This was actually done in this current study, using the goggles from MITSAR. The goggles enabled the participant to look directly in the source of the photic stimuli. Nevertheless, like the Danish study, there was not enough stimulation for significant lasting effects.

Some research is conducted concerning neurofeedback training and people with Alzheimer´s and dementia, but as far as I know, none of the research previously conducted used a protocol where the main goal was to induce gamma oscillations through the actual neurofeedback training. However, a lot of studies concerning neurofeedback as treatment have gotten significant results, in contrast to this current study. Several earlier neurofeedback protocols used on AD patients have had the main goal of examining neurofeedback as a method to increase the score on different cognitive measures. Otherwise, as previous studies have shown and recommended, a sufficient amount of training is required to be able to achieve significant results.

Consistent with other entrainment studies, this current study was partly successful in inducing gamma waves in healthy subjects. At least in the photic group, one could see on the analysed EEG data that all of the participants in the group produced a gamma rhythm of 40 Hz during the sessions. The problem was that this effect was not lasting, and the elevation of the gamma levels did not become significant on the post EEG. However, the studies at MIT using AD mice also showed that the effect diminished if the mice were not re-stimulated with the flickering light (Iaccarino et al., 2016).

Methodological Issues and Limitations

Sample. The students who participated in the study was psychology students. This may be a limitation because psychology students often have knowledge of psychological tests and instruments which may have had an effect on how they behaved and further, an impact on the results. Especially, in the neurofeedback group, one could clearly observe a desire in the participants to "succeed" and a clear frustration if they felt that they did not. One cannot rule out that this focus on performance overshadowed the main goal, and further influenced the results.

The appointments of the training varied for each participant at each session. The participants could decide for themselves when they wanted the session, according to their time and schedule. Sometimes the session took place early in the day, other times after lectures or after a long day at work. Due to this, factors such as stress, lack of motivation, sleepiness and lack of concentration could have affected the sessions as well as the pre and post-tests.

Finally, the current pilot study had a small selection (N=20), which offers very limited opportunities for generalization of the results. The small number of participants is due to restrictions in time and resources for the present study, which again was due to the total delay awaiting approval from the Regional Committee for Research Ethics (REK).

Design. The current study lacked a control group. Having a control group could have made it possible to compare the two intervention groups with a group with age-matched controls. There were two reasons for not having a control group, which was carefully considered. First, having a control group would have required a substantial amount of time to gather participants. This was unfortunately not possible due to time constraints of the master thesis covering only two semesters, and this current study was already delayed due to waiting for approval from REK. It was discussed to use already collected data from previous studies to make a control group, but it was important to have full control over the collected data to make sure the investigation was ethical and methodically similar. This was particularly important for reducing methodical limitation, which would not be possible if the study was going to use already collected data. The use of a control group could have significantly strengthened the study and will be recommended for similar studies in the future.

Software. Two different kinds of software were used in the two different gamma inducing conditions in this study. Group 1, which received photic stimulation, underwent their sessions with full EEG-cap and the use of the WinEEG software program from MITSAR. Group 2, which received gamma inducing neurofeedback training, underwent their sessions with the use of the Biotrace + software, with electrodes placed on the T3 and T4 sites of the scalp. The data collected during the intervention was not from the same software and may, therefore, be analysed and obtained on different terms. For example, factors such as noise and artefacts may differ. In addition, it was not possible to collect mean frequency (Hz) data from the neurofeedback group during training. One can thus, not rule out that using more equal tools with similar data collection and analysis could have led to different findings.

Number of sessions. Another important factor which probably plays a major role in the results of the interventions is the number of sessions and their length. The researchers from MIT exposed the AD mouse for one hour for seven days, and the study demonstrated a 50 % decline in amyloid load (Iaccarino et al., 2016) The research group from Denmark, who replicated the study in AD patients, instructed the participant´s caregivers to ensure that the participants received a continuous 60 minutes of stimulation twice daily (one-hour morning and one-hour evening) for ten consecutive days (Ismail et al., 2018). Even though the researchers could not control if the caregivers actually did as instructed, the patients received a sufficient amount of light therapy in contrast to the healthy subjects in this current study, which only received 15 minutes' x 5 times. However, it is important to mention that at least 20 sessions were planned in the original study plan, which could not be followed according to the delays due waiting for approval from REK.

Possible Side Effects of the Intervention

The side effect profile on light therapy is favourable in comparison with medications according to Terman and Terman (2005). To my knowledge, the worst side effects published in light therapy/photic stimulation literature is a mild headache and nausea for a short period of time after exposure. The participants in the light stimulation group in this current study did not report any severe side effects. However, some of the participants reported some discomfort under the current stimulation but none of the ten participants reported any discomfort in the time after the sessions.

According to Hammond & Kirk (2007), side effects and adverse reactions can occur in association with neurofeedback treatment. Lubar et al. (1981) as cited in Hammond and Kirk

(2007) demonstrated that people with problems with epilepsy could be made worse after neurofeedback if wrong training was conducted. Likewise, Lubar and Shouse (1976, 1977) as cited in Hammond and Kirk (2007) documented that both ADD and ADHD symptoms could be worsened if inappropriate neurofeedback was performed. In the article, they point out mild side effects, like tiredness and headache, but also severe side effects, like worsening depression, manic episodes, mood swings, seizures, and cognitive dysfunction. However, the authors point out that these side effects are only relevant if the protocols are used incorrectly (Hammond & Kirk, 2007). However, the claims published by Hammond and Kirk (2007) is not based on published data, and should, therefore, be considered with caution.

None of the participants in the neurofeedback group did report any side effects during this current study. However, several of the participants reported that they felt tired during training or that they became tired during the session. Absence of effect from the study could possibly be due to this tiredness, which may have led to challenges in concentrating during the sessions, and further to the lack of positive results. All the participants in the study were encouraged to report back if they experienced any discomfort or side effects after their sessions. However, one cannot rule out that some of the participants in this current study experienced mild side effects that were not reported or was overlooked.

Implications for Future Research

While working on this current study, a new study was published by the researchers at the Massachusetts Institute of Technology (MIT) in the journal Cell. In the new study, the researchers did not only use flickering light at 40 Hz but also investigated the use of auditory stimuli as 40 clicks per second. The team found that 40 Hz clicks, which was provided from speakers, produced the same brain changes in the auditory cortex as the light did in the occipital lobe. The mice also showed better performance in a navigating maze and in object recognition after the intervention (Martorell et al., 2019). In the latter study from 2016, the improvements by flickering light were limited to the visual cortex (Iccaranio et al., 2016). Now, when the researchers combined the light with the audio stimuli the researchers were able to reach other brain regions such as the auditory cortex and further the nearby hippocampus. On the basis of this new research and previous research done in the field, an implication for future studies is to examine the effects of combining different sensory modalities in gamma inducing protocols. This should be examined in healthy individuals, but additionally in subjects at risk of developing AD as people with minor cognitive impairment (MCI). In addition, it should indeed be examined in patients that currently suffer from AD.

The researchers at MIT have found that the effect is not lasting and that the treatment must be given continuously to maintain the benefits. An implication for future studies will be according to this fact, to try to examine how one could get a more lasting effect from the intervention. Further, it is important to investigate why the specific frequency in 40 Hz have such a profound impact. An implication for further research would be to investigate the molecular mechanisms underlying the current phenomenon.

In addition, another implication for future research is to make an even better neurofeedback protocol to induce and enhance gamma oscillations. The one used in this current study was very plain and uncomplicated, but perhaps too much of the participant's focus were directed towards how the protocol "worked". Conceivably, another feedback protocol could have evoked a more relaxed and focused state in the participant.

According to the understanding of Alzheimer´s disease pathology, it is still required several exploratory and more "out of the box" studies when it comes to other alternatives for treatment. In my opinion, non-invasive treatments are needed and must still be in focus of future research. The Amyloid Cascade Hypothesis is still one of the most influential models of pathogenesis and should be examined further in the future. This should definitely be at more interest at molecular levels.

The oscillations in our brain are a hallmark of several neuronal network function. The specific role of gamma waves is still not fully understood and extended awareness is needed in this current research context in the future. Not only in Alzheimer disease but also additional diseases and disorders which could be linked to abnormal impairment of neuronal synchrony in the brain. It is also relevant to not simply focus on the gamma waves itself, but consider the relation gamma waves have linked to other oscillations in the brain as well.

It is still a prominent question why the effects are so exceptional and relatively permanent in mouse models of AD, but not in humans. However, mice are not men. What provides results in a mouse model, does not necessarily work in human beings. However, the research team at MIT is currently working on projects using both human subjects and AD patients. In addition, they have a lot of resources and the capacity to create large enough projects, as it turns out is necessary to get sufficient results.

Conclusion

The current pilot study aimed to investigate the effect of two gamma inducing interventions on a healthy population of students. The present study found no significant evidence that photic stimulation or neurofeedback training could be efficient in changing gamma band power in the EEGs of healthy individuals. Statistical analysis was used to analyse the data. Based on previous research, it was assumed that both or one of the two gamma inducing interventions would lead to changes (enhancement) of the subject's gamma band, represented on the post-test EEG. The final analysis indicated no effect in any of the two condition groups.

Despite the failed findings, some implications in the results may indicate that with sufficient stimulation and with longer period of intervention, the study may have succeeded in fulfilling its main goals. Further, one of the aims of the study, which was to examine if it is even possible to induce gamma through the use of photic stimulation, showed that this was indeed possible with reliable and stable results. Despite the many limitations of the study, it is possible to claim sufficient levels of successfulness in the manner of elucidating what can be done in future studies and also which improvements can be done to extend this current study.

Nevertheless, a better understanding of Alzheimer's disease, dementia and the role of oscillations and specifically gamma oscillations in the human brain is essential for the development of the field. In addition, it is important to continue research, provide better quality studies, and to ultimately provide help or treatment that actually work for those who face the terrible disease and their caregivers. Furthermore, the use of assessment tools such as EEG, neurofeedback, photic or phonic stimulation may be beneficial in better understanding of how oscillations operate in the condition of Alzheimer´s disease.

Future investigations and studies with adequate samples, more time and resources, as well as improved economic support are highly needed. It is also crucial to look more into the long-lasting effects of neurofeedback and combinations of sensory stimulation when it comes to changing and manipulating oscillations. This is important in both healthy subjects, people at risk of AD but least and foremost it is crucial in patients with Alzheimer´s disease.

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Appendices

Appendix 1

Forespørsel om deltakelse i forskningsprosjekt

Dette er et spørsmål til deg om å delta i et forskningsprosjekt hvor formålet er å undersøke om vi kan indusere gammaoscillasjoner i friske mennesker. I dette skrivet gir jeg deg informasjon om målene for prosjektet samt hva deltakelse vil innebære for deg.

Bakgrunn og formål:

I Norge har over 77 000 mennesker demens og trolig vil antallet dobles frem mot 2040. Mange tror demens kun rammer eldre, men også yngre personer kan få sykdommen. Tilstanden utvikler seg langsomt, gjerne gjennom flere år. Til dags dato finnes ingen effektiv behandlingstilnærming for sykdommen.

Forskning gjort ved det Teknologiske Instituttet i Massachusetts (MIT) har vist at personer med demens og Alzheimer mangler gammaoscillasjoner i hjernen. Dette fører til celledød, hjernekrymping samt oppbygging av plakk som er hovedkomponenten i den biologiske markøren for Alzheimer. Gjennom å indusere gamma i musemodeller av Alzheimer, viste resultatene at de cellulære symptomene forsvant drastisk. Mengde plakk ble halvert og musene kunne lære igjen, i tillegg viste kognitive tester viste at hukommelsen var forbedret. I mus viser det seg at gjennom behandling med gammaindusering blir hjernen friskere og den begynner å jobbe mot Alzheimer assosiert patologi.

Formålet med denne studien er å undersøke om vi får til å indusere gammaoscillasjoner i hjernen til friske individer med enten lysterapi eller nevrofeedback. Vi ønsker å se hvilke av de to intervensjonene som gir mest gamma og eventuelt hvem som kan brukes i fremtidig behandling eller utprøvning på en klinisk populasjon.

Vi inviterer deg til å delta i dette studiet på bakgrunn av din tilknytting til faget ”Anvendt og klinisk biologi”, da dette prosjektet vil være en del av valgfri obligatorisk lab-øvelse i faget. Det understrekes at deltakelse er valgfritt.

Hva innebærer prosjektet?

Jeg, Rikke Kjølberg er masterstudent i psykologi ved NTNU og skal i forbindelse med min masteroppgave drive et prosjekt i samarbeid med førsteamanuensis Stig Arvid Hollup. Prosjektet går ut på å undersøke om vi kan indusere gammaoscillasjoner hos en frisk populasjon med deltakere. Vi ønsker å undersøke om det er mulig å øke gammaproduksjonen gjennom en enkel ikke-invasiv intervensjon. Ikke-invasiv betyr at vi ikke vil bruke metoder som trenger inn gjennom hud eller andre vev. Forhåpentligvis kan prosjektet bidra med ny kunnskap på området og kanskje også bidra til alternativ fremtidig behandling for pasienter med Alzheimers sykdom.

Ved deltakelse i studien vil vi først utføre en pretest EEG for å se hvordan dine hjernebølger er i hvilemodus. Den første pretesten vil ta ca. 45 minutter og vil innebære en hette på hodet med elektroder. EEG vil gjøres en gang før intervensjonen settes i gang, altså som en pretest, deretter vil vi gjøre en ny EEG som en posttest når du er ferdig med intervensjons-testene. Dette for å undersøke om det har skjedd endringer i ditt hjernebølgemønster etter å ha mottatt intervensjon.

Du vil tilfeldig plasseres i en av to grupper. En gruppe vil motta lys-stimulering gjennom et par spesialbriller, den andre gruppen vil motta nevrofeedback-trening, begge metodene brukes i håp om å fremme gammaoscillasjoner.
Stimuli med lys vil helt enkelt foregå ved at du får på deg et par briller som vil stimulere med blinkende lys i 40Hz, dette med mål om å stimulere hjernen til å fyre i gammafrekvens.
Nevrofeedback går ut på å sitte foran en skjerm med tre elektroder festet på hodet. Man vil få instrukser fra skjermen, og skjermen vil gi tilbakemelding på din hjerneaktivitet (feedback). Denne type trening går ut på at hjerne skal trene seg selv opp til ønsket hjerneaktivitet. I dette tilfelle vil vi forsøke å hente frem hjernebølger som fyrer i gammafrekvens.

For at intervensjonen skal kunne ha effekt må vi utføre repeterte treninger, i dette prosjektet vil det være 5 økter med intervensjon på en periode på 2-4 uker.
I prosjektet vil vi innhente og registrere opplysninger om dine hjernebølger. Vi vil ikke innhente og registrere andre opplysninger som navn, bosted eller lignende.
Prosjektet vil foregå med tett veiledning fra førsteamanuensis Stig Arvid Hollup.

Mulige fordeler og ulemper

Gjennomføringen av testingene er uten risiko, ubehag eller bivirkninger. Det er svært viktig å klarere at hver enkelt deltakers behov og begrensninger kommer i første rekke og vil være hovedprioritet i gjennomføringen av prosjektet.

Mulige ulemper med studien er tiden du må bruke på prosjektet gjennom å møte opp for testingene. Vi vil legge til rette for at dette ikke skal være i veien for din timeplan og vi vil være fleksibel for når testingene kan gjennomføres.

Hva skjer med informasjonen om deg?

Informasjonen som registreres om deg skal kun brukes slik som beskrevet i hensikten med prosjektet. Opplysningene vil bli behandlet konfidensielt og i samsvar med personvernregelverket. Alle opplysninger vil bli behandlet uten navn og fødselsnummer eller andre detaljer som gjør det gjenkjennelig (avidentifisert). Vi vil gi dine opplysninger en ID i en navneliste, som vil være oppbevart innelåst ved NTNU. Denne listen vil kun prosjektleder ha tilgang til, og vil makuleres etter prosjektets slutt.

Godkjenning

Prosjektet er godkjent av Regionale komiteer for medisinsk og helsefaglig forskningsetikk (REK).

Frivillig deltakelse og mulighet for å trekke sitt samtykke

Det er frivillig å delta i prosjektet. Dersom du ønsker å delta, undertegner du samtykkeerklæringen på siste side. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke. Dersom du trekker deg fra prosjektet kan du kreve å få slettet innsamlede opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner. Hvis du har spørsmål eller lurer på noe i forbindelse med forskningsprosjektet er du velkommen til å kontakte prosjektleder eller student på mail eller telefon.

Prosjektansvarlig og kontaktperson:

Epost: rikkekj@stud.ntnu.no

Telefon: 957 70 978

Rikke Kjølberg

Masterstudent

Psykologisk institutt, NTNU

Trondheim

Appendix 2

Samtykke til deltakelse i prosjektet

Jeg er villig til å delta i prosjektet

Sted og dato	Deltakers signatur
	Deltakers navn med trykte bokstaver

NTNU
Norwegian University of
Science and Technology