THE FACIAL INVERSION EFFECT THROUGHOUT HEALTHY ADULT AGING: A STUDY OF EVENT-RELATED BRAIN POTENTIALS

By

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Age-associated cognitive decline (AACD) is a natural part of life. The difference between malignant and benign AACD can be difficult to determine in the early stages of dementia. Many factors affect an individual's brain changes throughout their life; therefore, the detection of dementia commonly requires longitudinal studies. By the time the symptoms of dementia manifest the damage to one's central nervous system is irreversible. The investigation of biomarkers for the early detection of dementia is ongoing. Electroencephalogram (EEG) research, along with other neuroimaging and clinical testing, has shown that it is possible to detect subtle changes to the central nervous system before the onset of behavioral changes due to dementia. In this research, a sequential imaging oddball paradigm that utilizes upright and inverted familiar and unfamiliar faces were used to scrutinize the effect of facial inversion throughout healthy adult aging. The results indicate that late event-related potentials such as the P300 and late positive potential may be biomarkers for the tracking of age-related changes. Additionally, it may be concluded that the oddball paradigm is not the optimal way to elicit the face inversion effect. Further research is recommended in order to develop conclusions which could not be determined due to limited population and sample size.

THE FACIAL INVERSION EFFECT THROUGHOUT HEALTHY ADULT AGING: AN EVENT-RELATED BRAIN POTENTIAL STUDY

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Thank you to all of my professors at East Carolina University that helped me get to where I am today. Your guidance, understanding, and patience were imperative to my success. Thank you to my parents for raising me the way they did. Mom, I know this would have made you proud.

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CHAPTER 1: Introduction

Aging is a cardinal feature. Many factors affect aging-related physiological changes that individuals experience. For example, heavy cigarette and alcohol consumption can cause internal bodily stresses that may enhance the effects of aging. On the other hand, having an active lifestyle and healthy diet may prolong some of the negative effects of aging. The topic of aging has been a significant field of research for many years, utilizing a variety of methods for measuring the effects due to aging. By understanding how the body changes under normal aging conditions, it may become possible to detect the early onset of dementia or other malignant, age-related conditions. The information presented in the introduction is essential for the critical analysis of the background, results, and conclusions of this research.

1.1 Age associated cognitive decline

Performance in cognitive and physical tasks reach a maximum in early adulthood and then performance on the majority of those tasks declines throughout senescence [1]. The first widely accepted claim suggesting a distinction between malignant and benign aging was made in 1962 [2]. The claim suggested that malignant aging resulted in dementia and early death while benign aging was relatively static. The original claim was not operationally defined but was widely supported by workers in the geriatrics discipline. The National Institute of Mental Health began work to develop criteria for the age-associated memory impairment which finally made its way into the DSM-IV as Age-Associated Cognitive Decline (AACD) [2]. The diagnostic criteria of which have been defined as such [2]:

(1) The individual or a trusted companion must have noticed cognitive decline.

(2) Onset of decline must be gradual and constant over at least a 6-month period.

(3) Any reported difficulties with the following: memory and learning, concentration and attention, thinking (problem solving, etc), language (word finding, comprehension), and visuospatial function.

(4) Performance on quantitative cognitive assessments (for which there are age and education norms available for healthy individuals) must be at least 1 standard deviation below mean value for the appropriate population.

(5) Exclusion criteria: "None of the abnormalities listed above is of sufficient degree for a diagnosis of mild cognitive disorder or dementia to be made." Other exclusion criteria would be as follows: (a) depression, anxiety, or other significant psychiatric disorders that may contribute to observed difficulties; (b) organic amnestic syndrome; (c) delirium; (d) postencephalitic syndrome; (e) postconcussional syndrome; (f) persisting cognitive impairment due to psychoactive substance use or the effects of any centrally acting drug.

Currently, the cause and effects of aging remains a significant and important field of research. Aging has been related to the deterioration of numerous biological systems and functions in the human body [3]. The underlying cause of senescence has been shown to entail changes in cellular metabolism, cell structure, cell-matrix interactions, neurotransmitter systems, and the rate and accuracy of DNA replication [3]. Further research has shown that the functional decline of mitochondria and stem cells during aging is related to the shortening of telomeres [4]. Telomeres are a structure at the end of each chromosome that is believed to be responsible for protecting genetic information during and after mitosis. The effects of telomere shortening were found to cascade and manifest as macro-scale issues such as oxidative stress, cancer, and functional decline of major organs (e.g. brain, liver, heart) [4]. It appears as if these biological functions can be influenced by interactions among genetics, environmental

and social factors [1]. However, there are those that think of aging as a disease that can be treated with pharmacologic interventions [4].

Apart from cellular studies, macro-scale imaging methods such as functional (blood oxygen level dependent) magnetic resonance imaging (fMRI), MRI, and positron emission tomography (PET) have been used to investigate physiologic changes due to aging. In the systematic review by M. N. Rajah *et al* (2005), it was found that working and episodic memory abilities, which are related to the prefrontal cortex (PFC), declined in elders [3]. This phenomenon is believed to be related to the observed deficits in the right dorsal and anterior PFC, along with changes to the bilateral ventral PFC. As a result, functional compensation in left dorsal and anterior PFC may occur [3]. That review was consistent with other research studies that utilized fMRI and PET. For example, R. Cabeza *et al* (2002) showed similar working memory changes throughout aging with fMRI and PET, and that the PFC activity tends to be less asymmetric in older than younger adults [5]. The discussed neuroimaging studies are consistent with previous psychometrics of behavioral performance, shown in Fig 1.

While MRI, fMRI, and PET remain as part of the gold standard in clinical brain imaging, their relatively low temporal resolution (1-10 s) does not always allow for the distinction of the temporal order of events [6]. Aside from the high cost of use and poor temporal resolution, fMRI, MRI, and PET have relatively high spatial resolution (1-10 mm). While current medical imaging techniques are impressive, they still lack the signal to noise ratio (SNR) and spatial resolution required for non-invasively visualizing changes on a neuronal scale (1-10 μm) [R. M. Natasha]. Some researchers have chosen EEG to address the issues presented by other neuroimaging methods. EEG boasts a relatively high temporal resolution (1 ms), which allows for the investigation of the temporal order in which brain areas are activated [6]. A tradeoff of EEG is the significantly lower spatial resolution (~1 cm) and issues with imaging deep into the brain [7]. With regards to cost, fMRI MRI, and PET have a high principle (~1 million

USD) and high annual upkeep (100,000-300,000 USD) in comparison with EEG; costs of which can be as low as 10,000 USD, but get more expensive with high-density arrays, and have minimal maintenance costs across the lifetime of the device [7].

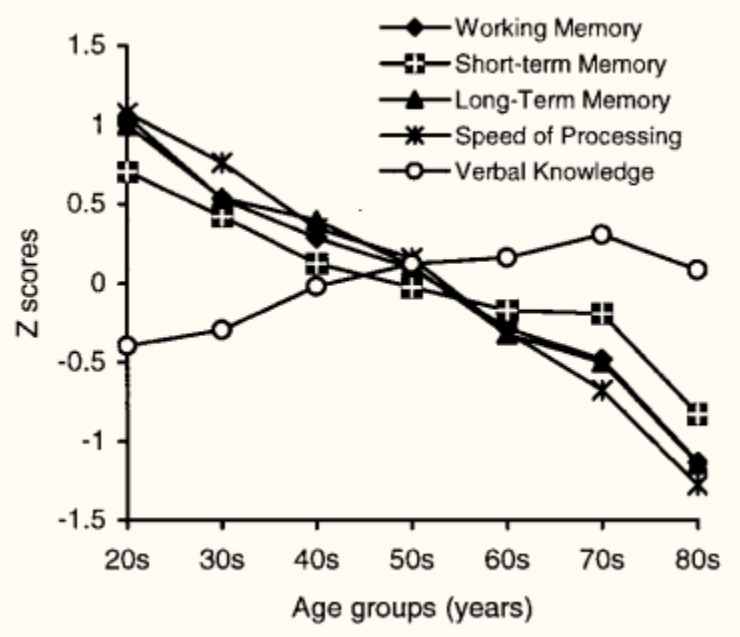


Figure 1. Behavioral manifestation of neurological changes due to aging [8].

Distinguishing benign and malignant AACD from dementia remains a common research problem for many; therefore, guidelines have been set by the National Institute on Aging for ideal biomarkers. The ideal biomarker will be relatively uncomplicated to use, simple in design and implementation, and inexpensive [9]. It is believed that EEG may hold the key for these biomarkers, as it is cheaper to purchase, easier to maintain, and relatively simple to administer in comparison to other neuroimaging methods. However, the issue of identifying reliable biomarkers remains largely investigational. It is known that there are many differences between young and old EEG recordings under various conditions, which will be discussed in greater detail in Chapter 2 [10]. EEG studies of face perception have been widely investigated and suggested as a reliable source of biomarkers [11]. It has been shown that there can be statistically significant effects on preconscious face perception when EEG recordings of

old and young are compared [12]. Manipulations to the faces, such as scrambling, color inversion, and rotation are also different between young and old individuals [13][12]. Therefore it is believed that a trend may exist that shows electrophysiological changes in featural facial perception across the spectrum of healthy adult aging.

1.2 The Electroencephalogram

The recording of oscillations of brain electric potentials on the human scalp was first investigated by Hans Berger in the 1920s and was referred to as electroencephalography [14]. Berger's invention has led to the recording of electrical potentials on the surface of the brain, which is referred to as the surface EEG (sEEG) or electrocorticograms (EcoG). The standard scalp EEG is sufficient to provide large-scale and robust measures of neocortical dynamic function, and a single electrode can provide estimates of synaptic activation averaged over tissues masses containing roughly 100 to 1,000 million neurons. Many clinical applications of EEG have since been developed, such as measurements for the severity of schizophrenia, epilepsy, autism, and Alzheimer's disease (AD) [15][16][17][18].

1.2.i Signal Source

The electrical activity on the scalp recorded by EEG is largely due to the excitatory postsynaptic potentials of synchronized neocortical pyramidal cells. The brain areas that are responsible for the EEG signal are thought to be areas of higher order processing that are only activated when deep brain structures relay to them [19]. In mammals, the nervous system is divided into two main organizational groups: the central nervous system (CNS) and the peripheral nervous system (PNS). The CNS has three major structures: the brain stem, the cerebellum, and the cerebrum, shown in Fig 2 [20]. The brain stem is made of the spinal cord, medulla, and pons and is responsible for basic living functions such as breathing and allowing the CNS to communicate with the PNS, i.e. the rest of the body. The cerebellum is a highly dense and uniquely organized structure that is largely responsible for fine motor control. The

cerebrum is by far the largest structure in the brain. Smaller brain areas, such as the midbrain and diencephalon contain “relay stations,” such as the hippocampus, entorhinal cortex, thalamus, and hypothalamus that contain many projections to other brain areas, primarily the cerebrum [21]. Medical professionals have concluded that the EEG signal is unable to reliably measure these deep brain areas, and the EEG signal is largely limited to the cortical surface, which is composed primarily of vast branches of the apical dendrites from pyramidal cells [21].

Scalp recordings are subject to several sources of noise as well as signal blurring due to volume conduction issues. Recording of noise from non-brain areas has been referred to as artifacts. Artifacts in EEG can include the electrical activity of muscles (eyes, tongue, face, neck, etc.), movement of the EEG electrodes, environmental noise (60 Hz lights, thermal changes), as well as electrical noise from the EEG amplifiers [21]. These artifacts can manifest as amplitude bursts in the EEG recording, or they can manifest as line noise that is constant throughout the entire recording. Electrical recordings of brain activity on the scalp are direct measures of brain function; albeit the brain signal must travel through seven layers of tissue to reach the scalp [14]. That electrical signal will be blurred, or spread out, as the voltage propagates through each layer due to conductivity, density, and volume changes. Volume conduction is a fundamental issue in EEG and the result is spurious coupling between electrodes due to common sources influencing two or more electrodes and producing apparently synchronous activity [20].

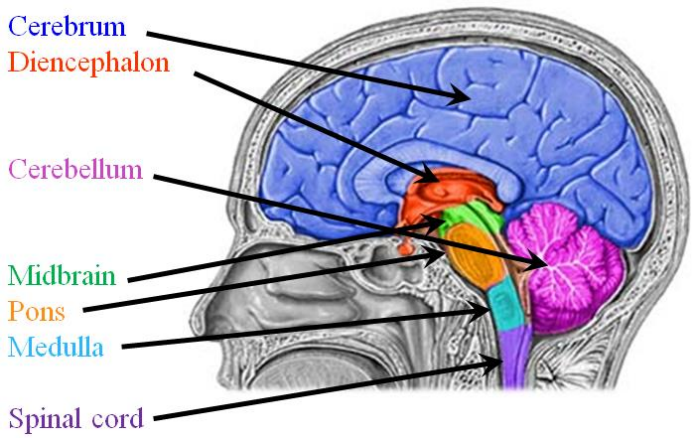


Figure 2. Sagittal cross-section of the human brain. [22]

An individual neuron's activity contributes very little to the resultant EEG signal. It is the summed activity of clusters of neurons, specifically postsynaptic potentials, which get measured by EEG, shown in Fig 3. The cortical surface is where most of the brain's gray matter is found, which is primarily myelinated neuron dendrites. The myelination causes the presynaptic current to be quick and quadripolar, which results in a cancellation of the measured signal from the neuron. On the other hand, the postsynaptic axonal current is unidirectional and is relatively slow (unmyelinated), thus allowing clusters of postsynaptic currents to sum above the minimum detectable voltage [20].

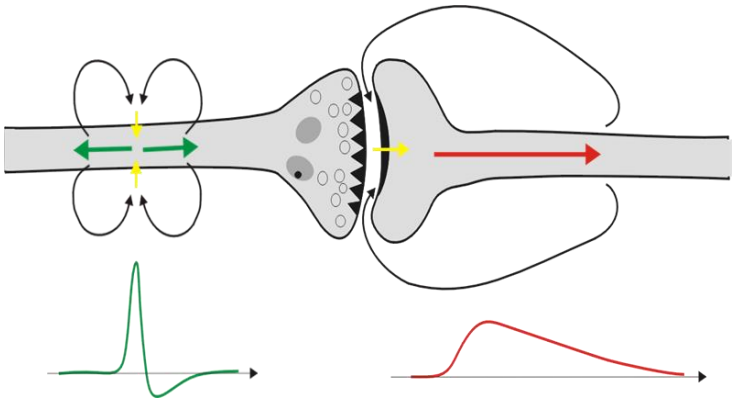


Figure 3. Presynaptic (left) and postsynaptic (right) currents. The presynaptic current is quadripolar and

quick, which make it difficult to measure. The postsynaptic current is relatively slow, which causes a summation effect in the dendrite. [22]

1.2.ii EEG Circuit, Electrodes, and 10-20

The EEG is similar to other biopotential measurements. It is a differential circuit with reference and ground electrodes placed on symmetric locations where no brain activity is present; such as the ear lobes, mastoids, or nostrils [21]. EEG electrodes can be either wet or dry. Wet electrodes require a conductive electrolyte gel to be applied to the scalp which improves electrode SNR and impedance; while dry electrodes may be capacitive or have arrays of prongs (i.e. spikes) that are in direct contact with the scalp [23]. Each electrode measures the difference between one channel and the average of all other electrodes [14]. For the purpose of this research, dry electrodes will be used, due primarily to availability.

Dry EEG electrodes are commonly made with tin alloys, gold alloys or silver/silver-chloride alloys, and may come in a variety of shapes and configurations, example in Fig 5. Scalp data are largely independent of electrode size due to volume conduction, although the electrode layout is critical [20]. The international 10-20 system is a standardized method for determining electrode placements, Fig 6 [21]. The first letter is in respect to the anatomic location, e.g. P for parietal, O for occipital, while the numbers dictate the distance from the sagittal plane.

Figure 4. Example of dry gold-plated EEG electrode, the g.SAHARA.

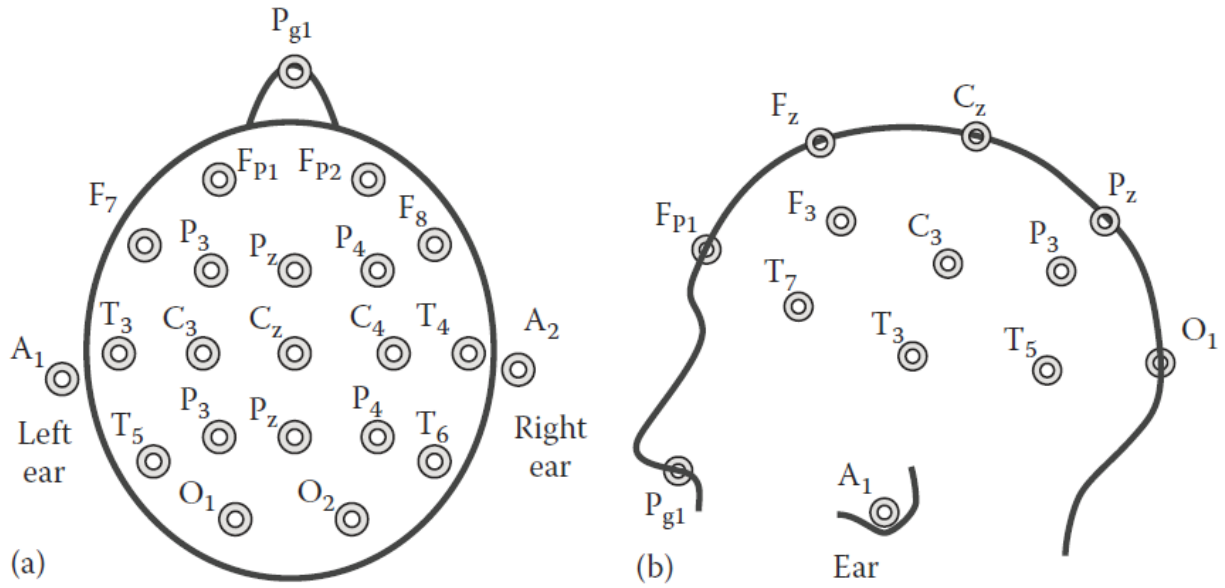


Figure 5. International 10/20 EEG electrode placement system. The letters represent anatomical sections, e.g. frontal, central, parietal, and occipital, while the letters represent distance from the sagittal plane. (a) Top view for a modified 21 electrodes plus reference (P_{g1}, A_1, A_2). (b) Left side view of symmetric electrodes [21].

The 10-20 system has been adjusted to fit anywhere from 16 to 256 electrodes, and each different configuration is referred to as a montage of electrodes. The density of the montage can help by estimating the signal at a noisy electrode, source localization calculations, and higher resolution scalp current density mapping, to be discussed in subsequent sections [24].

1.3 Event-related potentials

There are many experimental designs for EEG studies; such as assessing power and spectral changes over time during different experimental conditions, or assessing the temporal order of events in response to stimuli. The recording of the brain's time-locked response to sensory stimuli is referred to as event-related potentials (ERPs) [25]. The event-related potential (ERP) is composed of various peaks and troughs that are named after their time signature and amplitude. For example, a positive deflection

point at about 300 ms is called P300, while a negative deflection point at about 200 ms is called N200. It has been widely accepted that the earlier (< 300 ms) ERP components reflect exogenous characteristics of the stimuli (e.g. volume, luminescence) while later ERP components are dependent on the mental operation being performed on the stimuli [23]. One of the most well understood paradigms for eliciting reliable ERPs is the oddball paradigm, first documented by Sutton *et al* in 1965 for the investigation of uncertainty and lie detection [27]. The oddball paradigm is dependent on a rare and unpredictable target stimuli interspersed with distractor stimuli. Subjects are instructed to focus on and respond to the target by either mentally counting or physically responding with various cues, such as finger or toe movements [28]. The oddball can elicit many different ERP components that are dependent on the stimuli, and many other ERP paradigms exist that can elicit other ERPs as well; although for the purpose of this experiment the following ERP components must be understood.

1.3.i N170 and FIE

The human brain has a specialized area simply for the processing of human faces and is called the fusiform face area (FFA) [29]. In EEG studies there is an ERP signature specific to that region of interest called the N170 [11]. The typical N170 is about -5 μV and within 150 to 250 ms after stimulus onset and is maximal for normal upright human faces [11]. The N170 has been linked specifically to the processing of human faces or face like objects and familiarity has no influence on latency or amplitude [30].Clinical investigations of the N170 have shown that featural changes to faces (e.g. scrambled, size miss-match, color changes) along with configural changes (e.g. rotations, relative shapes/locations) can impact the N170 signature [11][31]. A common configural change that has yielded consistent results across research groups is the 180 degree rotation, or the inversion, of faces [32].

When the human brain is shown an inverted image it causes the brain to work harder; i.e. an increase in working memory, thus increasing the time to process the image [32]. This change in working

memory load and processing power has been referred to as the face inversion effect (FIE). The N170 was the first ERP component to be investigated for the FIE [13]. For inverted images the N170 was more negative which peaked about 7 ms later than for upright faces [13]. Again, the FIE feature was more consistent for complete face images as opposed to objects, face components, and scrambled face images. The FIE was quantified as the different between the upright and inverted ERP, but has since been investigated with more holistic processes [13][12].

1.3.ii P300

Cognitive processes such as reading, driving, or having a conversation are largely dependent upon one's ability to direct their attention. The ERP component that best reflects this ability is the P300, which is found maximally along the longitudinal fissure in response to rare, anticipated stimuli [27]. The oddball paradigm has been a reliable method of eliciting two types of P300, the P3a and P3b. When the oddball paradigm includes distractor stimuli that are about as frequent as the target stimuli, the distractors can elicit a slightly different P300, called the P3a, while the target stimuli elicit the larger, broader P3b [33]. For the purposes of this research, the P3b shall be referred to as P300. The amplitude of the P300 has been related to attentional resource allocation when memory updating is engaged, is typically larger for salient stimuli, and requires the stimuli to be presented for 50 to 3000 ms [34][25]. The P300 latency is dependent on the time required to categorize the stimulus; therefore, more complex stimuli and attention tasks prolong its latency [25]. Research on the P300 has included the effects of mind-altering substances, tracking neurodegenerative diseases, and applications in brain-computer interfaces [28].

1.3.iii N400

In respect to faces, objects, and words, the ability to retrieve semantic information is imperative. ERPs have been used in the investigation of semantic and episodic memory retrieval and

updating. Semantic processing demands have been related to the frontal-central N400 ERP component [26]. The N400 has been demonstrated across recognition memory paradigms at bilateral frontal electrode sites around 300 to 500 ms and has a larger amplitude when familiar faces, words, objects, or tones are presented [35][36]. The N400 has also been modulated by configural changes in familiar and unfamiliar recognition paradigms. When the object, word, or person to be recognized is inverted, the N400 was shown to decrease in amplitude and increase in latency [37]. One could suggest that an increase in working memory load also impacts the N400.

1.3.iv LPP

As stated earlier, later ERP components generally reflect higher order processing demands and are largely dependent on the experimental condition and task. The late positive potential (LPP) has been referred to as the "parietal old/new effect" and can occur between 500 to 1000 ms post stimulus onset [35]. The LPP may be referred to as the P500, P600, P700, and so on. In respect to recognition, the LPP is believed to reflect the semantic recall/recognition, and is maximal for correctly recalled stimuli at centro-parietal locations [35][26]. Modulations to the LPP have been demonstrated for repetition; the LPP amplitude and latency will decrease when familiar stimuli are correctly recalled multiple times in a row [38]. Configural changes to familiar stimuli, such as inversion, also modulate the LPP by decreasing the amplitude and increasing the latency, while also introducing a false-positive for recognition effects [37].

CHAPER 2: Background Literature Review

Treatment of AD would benefit greatly from effective biomarkers for presymptomatic or preclinical stages of AD. The beginning mechanisms of AD are still not clearly understood; however, it is known that amyloid beta accumulation and synaptic dysfunction are among the first assay biomarkers to be known [9]. Autopsies have shown that the buildup of amyloid beta plaques and tau fibrillary protein dysfunction can occur before the manifestation of behavioral deficits [9]. In the vast majority of cases, the variance in dementia severity could be accounted for by neuron density and presynaptic changes [26]. There are researchers that believe it is possible to detect these subtle neuronal changes via EEG before the onset of dementia symptoms [39]. Trends in EEG recordings for aging, MCI, and AD all follow a similar pattern at varying intensities. That is, a slowing of the EEG signal, reduced complexity of the signal, and pertubations in EEG synchrony [10]. These trends can manifest in several forms which are dependent on the EEG paradigm in question; although it is important to note that EEG research tends to have large variability among patients, specifically with dementia [10]. Because of this, it is currently difficult to reliably identify EEG biomarkers indicating the early onset dementia.

Slowing of the EEG signal can present themselves in two different ways: ERP components have increased latency and the fundamental frequencies are lower [10]. This is true for event-related spectral perturbations (ERSP) and event-related synchronization (ERS) and desynchronization (ERD) as well. Reduced complexity of the EEG signal has the following implications: there are less neural circuits involved in processing stimuli when compared to youth and the neural processing is more lateralized (symmetric) [38]. Reduced synchrony measures suggest a decrease in coherence, as it were, a decrease in communications between neural circuits [38]. These trends in EEG into senescence are exaggerated for dementia; although reproducing these results for discriminating AD patients from age matched controls remains difficult [40].

Several ERP components have been scrutinized for changes due to senescence and dementia. In elders the N170 is not lateralized, while in youth it is right lateralized; although there are not always significant changes in N170 amplitudes due to aging [32][12]. The FIE in elders has also been shown to be attenuated; elders had no amplitude differences when compared to youths, but had similar latency changes as youth [12]. For AD and MCI, the FIE is commonly absent across many ERP components (N170, P300, N400, P600) [18][31]. This may be due to neural circuitry differences between elders and young adults. It has been argued that elders have different processing of faces altogether when compared to youth. Rossion *et al* (2008) argued that elders use a more holistic approach when processing faces, that is to say that their perception is most dependent on the ability to perceive simultaneous multiple features of a face as a whole [41]. Eye tracking studies have supported this notion; children and adolescents tend to have more featural processing of faces [42][43].

As discussed earlier, increased aging suggests decreased mental capacity and working memory. As one may expect, ability to engage in mentally demanding tasks decreases with increased age [1]. This phenomena has been related to P300 amplitude and latency. P300s follow the trend that mental performance ability improves until early adulthood, at which point it slowly begins to decline into senescence [44]. Results from the critical analysis by Dinteren *et al* (2014) on P300s throughout aging are summarized in Fig 6 and 7; of which follow the mental performance trends identified by many behavioral psychologists [1][8]. These age related changes in performance ability and speed are analogous to white matter integrity [44]. For healthy young adults, the FIE for P300s is manifest as an increase in latency and decrease in amplitude; these changes are missing in demented patients and are commonly diminished in age matched elders [18][28].

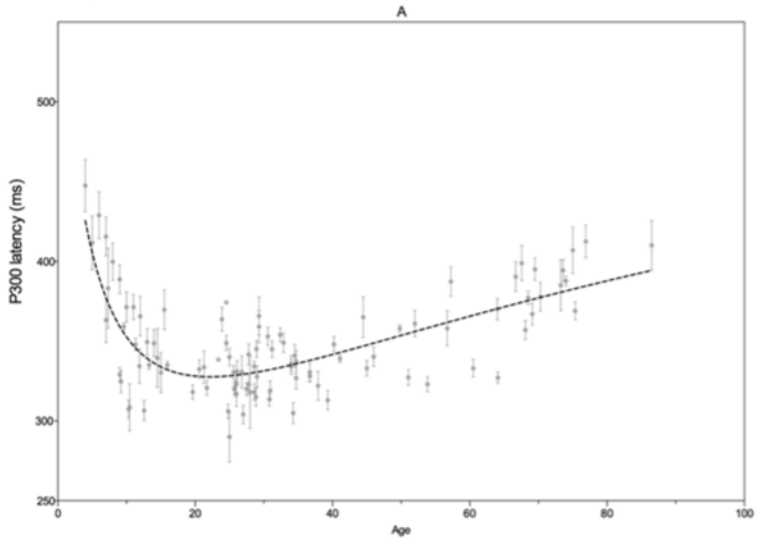


Figure 6 Regression analysis of P300 latencies throughout the lifespan [44].

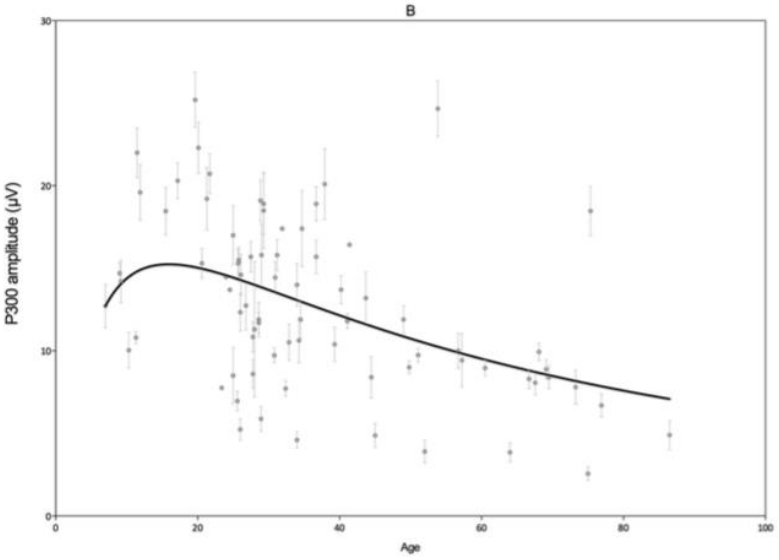


Figure 7 Regression analysis of P300 amplitude throughout the lifespan [44].

Aging's effects on familiarity ERPs has also been scrutinized. When elders are compared to youth groups, it is typical that familiarity is slower to recall; albeit face processing may be quicker or about the same [45]. In a study conducted by Galdo-Alvarez *et al* that investigated face processing of correctly recalling famous faces compared, a group of elders (60-81) and young adults (19-24) were

compared [37]. The study used a subjective measure of recognition that seemed to be correlated with familiarity ERP responses. Subjects were shown 200 images of famous faces and were instructed to respond with one of four possible button presses: (1) definitely know name and profession, (2) recognize but do not recall name, (3) unsure if familiar, and (4) definitely do not know. The results showed strong N400/P600 pairs for both groups in response to one and two button presses; however, the option one and two button presses were different (higher amp for one) for the young group but not for the elders. Additionally, the P600s amplitudes were consistently lower for elders than the young group. The FIE was also investigated in this study, and the results showed weakened amplitudes and increased latencies for the young group but no discernable N400/P600 ERP components for elders [37]. The results of that study suggest that advanced age can impair one's ability to correctly recognize and recall information about a familiar person, which can be inferred based on the AACD theory [2].

In a similar study on familiarity by Saavedra *et al*, a familiar vs unfamiliar face recognition task was given to a group of young adults (20-37) [30]. The faces used were gray scale and matched controlled for luminescence, although there was one trial where faces were emotional (happy, sad) and the second trial with emotionally neutral faces. It was found that both trials elicited posterior temporal N170s and was modulated by the perception of facial emotional expression, as it were, higher amplitude for happy and lower for sad faces [30]. Additionally, several groups have reported repetition effects for the N170 in response to faces. An N250 is apparent when learned face images are repeatedly shown [30][46].

The culmination of this research can be succinctly stated as follows: elders have had more time to use their brains and prune unnecessary synapses, so one may assume their brains can be fine-tuned to optimally perform simple operations that young adults may still do faster, yet less efficiently. Of all of the research discussed, none of these researchers have examined the FIE throughout aging; only as a comparison between young and old. The face familiarity effects were shown to manifest as increased

P300, N400, and P600 amplitudes with minimal effects to latency. The FIE was shown to increase N170 amplitude and latency while reducing P300, N400, and P600 amplitudes yet increasing their respective latencies. The research by Li *et al* showed face images can be used to distinguish between healthy aging, MCI, and AD; albeit with a small sample size. There exists the possibility that face images hold additional biomarkers that require scrutinizing.

CHAPER 3: Research Problem

3.1 Specific Aim

The specific aim of this research was to scrutinize the FIE differences across healthy adult aging with a unique paradigm. The suggested paradigm incorporates visually evoked ERPs where stimuli include three types of visual cues such as familiar faces, unfamiliar faces, and objects. What makes the paradigm unique is that it has less total image presentations than other paradigms used in research, although the inter-stimulus interval, image presentation times, and methods remain consistent with modern literature. The success of this research may obviate the need or reduce the time for longitudinal study to diagnose early onset malignant AACD such as MCI and AD by introducing new biomarkers that can be used with classification techniques. Advanced machine learning techniques may be applied in future research for further scrutiny of the recorded ERPs.

3.2 Rationale

Current diagnostic tools for AD and MCI begin with a cognitive exam, such as the Montreal Cognitive Assessment (MoCA); however, the exams may be subjective and are only required if behavioral changes have been consistently evident for prolonged periods of time [2][Z. Nasreddine]. If the cognitive assessment score suggests malignant AACD, then a follow up test such as spinal tap, fMRI, and/or PET will be conducted to quantify the physiological progression of dementia. Behavioral symptoms of MCI and AD are only present when irreversible damage has been done to the CNS [9]. If a fast, non-subjective, and easily quantifiable screening method could be employed regularly at doctor's visits for elderly patients, it is possible that clinical intervention could begin before the onset of malignant AACD.

Research has shown the potential of EEG to detect signs of dementia before onset of behavioral changes in the form of spectral changes and ERPs [39][48]. It is believed that well-known ERP

components, such as the N170, P300, N400, and LPP that have been compared between young and old groups can be used as biomarkers for early identification of MCI. This researcher team is unaware of any researchers that have investigated the FIE across the entire aging spectrum in a single study; albeit the FIE has been examined in multiple studies in children, adolescents, young adults, and elders. The goal of this research was to scrutinize the FIE across aging to determine if a trend similar to age-related changes in P300s exists. This could lead to the identification of possible biomarkers for the early detection of MCI.

CHAPER 4: Methods

4.1 Sequential Image Paradigm

A Standard oddball paradigm was used. There were three classes of gray-scale, similar luminance and resolution images displayed in the center of a TV screen. The TV was a 1080p, 42-inch LG TV. The first class of images were the target group, which were familiar faces that consisted of well-known US presidents and A-list actors; specifically former president Barack Obama, current president Donald Trump, and the actors Robert Downey Jr. (Iron Man, Sherlock Holmes), and Dwayne 'The Rock' Johnson. These faces were chosen because they were used in a similar sequential imaging paradigm in the Biomedical Instrumentation & Data Analysis laboratory at East Carolina University. The second class was unfamiliar faces, which consisted of unknown model faces. The third class of image was objects, which consisted of non-face-like objects, such as flower vases and chairs. All images were be cropped in an oval fashion in order to exclude hair, ears, neck, and any background, example in Fig 8, and were taken from publicly available databases.

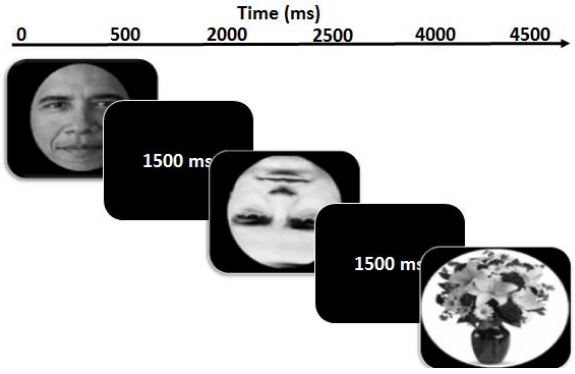


Figure 8. Example of sequential imaging paradigm. A familiar face (former president Barack Obama), an inverted unfamiliar face, and a random object.

There were four familiar faces, four unfamiliar faces, and eight random object images, making for a total of 16 unique images and a total of 32 possible images to be shown. Each of the 32 images

were shown 5 times for a total of 160 image flashes. Each image was shown for 500 ms with an inter-stimulus interval of 1500 ms. The order of the images was a deterministic order set by the researcher to ensure that target images were never shown consecutively. Through the use of BCI2000 the images were shown and data were recorded in a format compatible with MATLAB [49]. In compliance with the standard P300 oddball paradigm, participants were instructed to respond with a dominant index finger button press when shown a familiar face, and a dominant middle finger button press when shown any other image [25].

4.2 Participants and age groups

A total of 28 subjects were recruited, although 16 were included in the analysis. The excluded 11 subjects had unremovable high frequency noise, lack of consistent ERP components, and one subject was excluded due to low MoCA score. For more details on subject metadata, see section 5.1. All recruited participants were volunteers with no effects from coercion. Recruitment was advertised via email list-servers through the university, by flyers posted on ECU's campus, and by word of mouth. Interested volunteers were instructed to contact the researchers via email, at which time they were given more information about the study and were able to choose their time and date to have a recording session. This study aims to scrutinize the FIE across all of adulthood in healthy aging adults. Adulthood was divided into four age groups: developing adult (18-25), young adult (26-40), adult (41-59), and elder adult (60+). For a statistical power of at least 80%, 12 participants are required for each group.

The age groups were based on the developmental psychology research presented by Craik and Bialystok as well as Park *et al*, and the P300 developmental study presented by R. v. Dinteren *et al* (refer to Fig 1, 7, and 8) [1][8][44]. The developing adult group (18-25) was chosen because with respect to United States law adulthood begins at 18, even though the gray matter in both the frontal and occipital

lobes are still developing well into the 20's. In the developing adult range, variability was expected due to different rates of development and other life choices such as substance abuse and sleep deprivation. The young adult (26-40) group was chosen because that is the age range where memory and cognitive decline should be the slowest. It is believed this age range will have confounding variables from various life choices, such as sleep deprivation from having children, years of experience working, substance abuse, and physical activity. The adult age range (41-59) addresses middle-aged adults, which makes up the largest portion of the work force in the United States today [50]. It was believed this age group will show evidence of AACD regardless of lifestyle choices, although the extent of which will vary among individuals due to lifestyle choices. The elder group (60+) was chosen because this is when cognitive performance and memory functions have dropped about one standard deviation from peak performance in young adulthood, shown in Fig 1. It is believed that changes in fluid intelligence throughout aging are largely responsible for changes in P300 and other ERP components; on the other hand, crystallized intelligence continues to rise until 70 or so, shown as verbal knowledge in Fig 1. Elders were expected to have the largest variability due to the largest possible age range of any of the four groups.

4.3 Exclusion criteria

Subjects were not allowed to participate if they had any internal pace-maker or electrical stimulator, as is specified in the g.tec SAHARA manual [51]. A MoCA score of 25 (out of 30) or below must be excluded from the study as well, because that indicates poor cognitive performance [47]. Participants data would be excluded if they had a history of seizures, schizophrenia, epilepsy, or mild to advanced autism, or if the participant was taking any selective serotonin reuptake inhibitors as this would impact the validity of their EEG recording [15][28][17] . Participants' data would be not be used for analysis if after preprocessing and averaging epochs there was evidence of excessive artifacts, high

frequency noise that would not filter out, and/or if three or more of the ERP components to be investigated (N170, P300, N400, P600) were missing.

4.4 Procedure

All participants were shared with a fellow researcher, Austin White, in the Biomedical Instrumentation & Data Analysis lab. Austin was also conducting his own thesis study using his own unique ERP paradigm. Both ERP paradigms were shown to each participant during each recording session. The order of the paradigms was alternated for each age group as to reduce any possible learning or nuisance variables. As stated in the IRB (MS1_UMCIRB 18-001073), participants were not to be kept for over 40 minutes. The following electrodes were used in the international 10-20 montage: FP1, FPZ, FP2, F7, F3, FZ, F4, F8, FC5, FC1, FC2, FC6, T7, C3, CZ, C4, T8, CP5, CP1, CP2, CP6, P9, P7, P3, PZ, P4, P8, P10, PO O1, OZ, O2.The abided procedure is as follows:

1. Participants arrived at their schedule time to the Biomedical Instrumentation and Data Analysis lab in the Science and Technology building (SZ 132).
2. Informed consent was presented and the experimental protocol was elaborated before receiving a consent signature. All participants received a copy of the informed consent and protocol to take home.
3. The MoCA (version 8.1) was administered and scored in order to assess their current state of cognitive well-being. Participants were blind to their score until recording was finished. If their score was 25 or below, their data was excluded from analysis.
4. A questionnaire, in Appendix B, was given to each participant to document their hand dominance, years of education, visual acuity, medications, history of seizures or mental illness, quality of sleep, and consumption of caffeine/energy drinks. If there is an extensive history of seizures and mental illness as described in the exclusion criteria, participants were excluded.

5. Each participant was seated in a comfortable chair five feet away from the 42” television monitor and was shown the target images in order to ensure familiarity.
6. Once each participant was ready, the g.SAHARA cap was placed on their head with reference and ground electrodes attached to their ear lobes. An Impedance check was then done to ensure all impedances were below 5 kOhms [51].
7. The lights were turned off and white noise was played at a volume appropriate to drown any noises from outside the lab. All of the windows within the lab were covered to promote sensory deprivation.
8. Participants were asked to remain still and to blink as little as possible during the paradigm.
9. The participants were instructed to close their eyes for 10 to 30 seconds to ensure signal clarity before beginning all ERP paradigms.
10. The first ERP paradigm was run. Participants were told to fixate their gaze on the center of the television screen for the duration of the ERP paradigm, which lasted last about seven minutes. Participants’ finger tap responses to stimuli were recorded to assess accuracy.
11. Upon finishing the first ERP paradigm, each participant was asked if there was any discomfort. Then the second ERP paradigm was started as quickly as possible after another 10 to 30 seconds of closed eyes. The second ERP paradigm will begin and lasted about seven minutes.
12. At the end of the second ERP paradigm, both data sets were preprocessed and the epochs were averaged, then visually inspected for clarity of signal. If one or both of the ERP paradigms yielded excessively noisy data, then they were repeated a maximum of one time each.
13. When any repeated ERP paradigms had been completed, the volunteer’s participation was considered complete. The lights were turned back on and the g.SAHARA cap was removed along with the reference electrodes.

4.5 Control of Variability

By administering the questionnaire, it is ensured that participants are not taking any neuroleptic medications and do not have a history of neurological disorders. The questionnaire, in Appendix B, records possible sources of confounding or nuisance variables commonly seen in EEG research; such as quality of sleep (i.e. sleep deprivation), years of education, prescription medication, and caffeine use [52][53][54]. Participants were also instructed to remain as still as possible during the recording procedure in an effort to reduce possible artifacts. Additionally, signal clarity was assessed by running an impedance check as well as administering the same procedure to each participant.

4.6 Data Processing

4.6.i Description of Techniques

The first and possibly largest hurdles in EEG signal analysis techniques are the removal of noise and isolation of brain signals. Frequency filtering techniques are typically the first wave of defense against artifacts. Hence bandpass filters (0.01 – 100 Hz) are often included in commercial EEG systems [21]. Following the bandpass filter, a variety of noise reduction techniques are possible; such as independent/principle component analysis (ICA/PCA), wavelet analysis, or predictive artifact removal algorithms.

PCA seeks to identify the successive signal components that account for as much as possible of the activity uncorrelated with previously determined components [55]. The utilized artifact removal algorithm in this research was artifact subspace reconstruction (ASR), which was developed for use in a MATLAB (Mathworks) plugin called BCILAB [56]. ASR can be used in real time or post-processing by utilizing a sliding-window PCA, which then statistically interpolates any high-variance signal components exceeding a specified threshold [56].

After filtering and artifact removal, it is common in ERP studies to segment the data into epochs. The length of these epochs will vary dependent on the ERP components of interest. Each channel's epochs will be stored relative to the channel. The epochs can then be studied as single-trial ERPs, which exposes the ongoing dynamics of the brain [55]. Alternatively, the epochs can be averaged for each stimuli type in order to improve SNR, smooth the ERP waveform, and to nullify random variance in the amplitude, latency, and scalp distribution of the ERP components [57]. Each channel's averaged ERP waveform can then be investigated for ERP component's amplitude and latency differences between stimuli and participants.

Other methods of signal analysis include scalp current density (SCD), dipole fitting, and source localization. As the voltage generated by the brain propagates through the scalp, it is already known that volume conduction will disperse the signal throughout the scalp. The calculation and visualization of the current measured on the scalp is referred to as SCD. The SCD makes no assumptions about the neural generators and any deeper media, and is dependent only on the scalp conductivity [J. Pernier]. Dipole fittings are the localization of a single equivalent vector that represents the center of gravity of the brain's electrical activity in a given time range and region of interest [48]. These dipoles can be utilized to estimate the neural generators and the direction of signal propagation, thus allowing the researcher to make assumptions about brain dynamics. Source localization techniques are distinctly different from dipoles, as the source localization assumes *a priori* knowledge of the neuroanatomy [56]. The recorded scalp data is used to calculate the inverse solution, which is the projection of the scalp data through the skin, skull, and then onto the brain. There are programs designed specifically to calculate and visualize the inverse solution, such as the Low-Resolution brain Electromagnetic Tomography (LORETA) developed by Pascual-Marqui *et al* [58].

Frequency analysis in EEG research is very common, and changes in the frequency spectrum were some of Hans Berger's first observations [14]. In general, the degree of cerebral activity is related to the average frequency of the EEG rhythm; that is to say, the frequency progressively increases with higher and more complicated degrees of activity [14]. Brain oscillations tend to be synchronized or desynchronized. Synchronized oscillations have high power over time and suggest that the brain is "idling," or no motor or demanding cognitive tasks are being performed. Desynchronous activity is the opposite, and it shows that areas of the brain will act independently of one another in order to perform a rigorous task [14].

The spectrum of neurophysiological frequencies ranges from 1 to about 60 Hz and is broken into frequency bands. In order of lowest to highest these frequency bands are: delta (1 – 4 Hz), theta (4 – 8 Hz), alpha (8 – 12 Hz), beta (13 – 30 Hz) and gamma (30+ Hz) [21]. Each band reflects various states of cognition and are commonly assessed in sleep studies. The delta band is observed during deep sleep; theta is present during resting or meditation, alpha is commonly seen during visual tasks, beta is associated with motor movements and logical thinking, and gamma waves are still poorly understood but are present in a wide variety of EEG recordings [21]. These frequency bands are used in the assessment of event-related synchronization (ERS) or desynchronization (ERD) as well as event-related spectral pertubations (ERSPs). The time-frequency response to presented stimuli can be presented as an ERSP. The difference between ERSPS and ERS/ERD is the length of time over which power changes are measured. ERSPs are quicker and show the average frequency response over that short time span while ERS/ERD evaluates long-term changes in states of consciousness [59].

4.6.ii Processing Methods

All recorded EEG data was first loaded into MATLAB for preprocessing. A high pass filter of 0.1 Hz and low pass filter of 30 Hz was applied before applying ASR for predictive artifact correction [56].

The filtered and artifact corrected EEG data were then divided into epochs with the stimulus code metadata included in the BCI2000 recording output [49]. The epochs were averaged for each stimulus type (FF, UF, etc) and the data were plotted for initial assessment. In this assessment, if three or more ERP components were missing or unclear, or if there were excessive artifacts, then that participant's data would be excluded from the assessment.

After preprocessing in EEGLAB, the filtered epochs were exported into FieldTrip for post-processing [60]. FieldTrip is an open source MATLAB-based EEG/MEG data processing developed at the Donders Institute for Brain, Cognition and Behaviour [60]. Each individual's data were averaged and group-wise grand averages were calculated and displayed using FieldTrip. The SCD calculations, frequency analysis, dipole fitting, and source analysis were all executed in FieldTrip. For additional information on the FieldTrip toolbox, see www.fieldtriptoolbox.org.

4.7 Feature Extraction and Statistical Analyses

All features were extracted using custom scripts in MATLAB edited from the FieldTrip toolbox. ERP features were extracted from each individuals' averaged epochs at their respective time ranges. The N170 was 0.15 to 0.25 s, the P300 was 0.25 to 0.36 s, the N400 was 0.3 to 0.6 s, and the LPP was 0.5 to 1.0 s. A peak detection algorithm was used to extract peak latency and amplitude values for each ERP component. These amplitude peaks were examined for clustering as a function of latency. Additionally, each amplitude and latency peak were plotted as a function of the respective participants' age in an effort to identify trends. In order to investigate the FIE, upright ERP components were compared to the inverted ERPs. The difference between upright and inverted peak latencies and amplitudes were found. In other words, subtract the inverted peak from the upright peak to yield a quantity that represents the FIE.

The figures generated from the peak detection algorithms were examined for clustering and potential trends as a function of age. The features that were found to have favorable clustering or trends had their data points exported into SPSS (IBM). The Pearson correlation coefficients were calculated for those features as a function of age. The Pearson coefficients show the strength of association and direction of trend between the independent and dependent variables. A linear regression was then run on the data as a function of age. Similar to the Pearson coefficients, the strength and direction of the relationship of the variables was found with regression analysis. Univariate analysis of variance (ANOVA) was utilized to examine the between subject's effects of all identified features. The output from ANOVA was used to assess the means and variances between the groups, which is quantified as the p-value and effect size (η^2) in the form of $F(df_t, df_e)$ = p-value (η^2). This is for df_t the degrees of freedom (number of subjects, *k*) in each group and the df_e the total subjects, *N*, minus the group size (N-k). The p-value represents the probability of choosing a new, randomly sampled feature that is outside of the critical range. The effect size (η^2) represents the percent variability in the dependent variable that is accounted for in the independent variable. It is common to assume that as p-value decreases, the effect size increases [61].

CHAPER 5: Results

5.1 Participants

The mean and sample standard deviation of the age for each age group is shown in Table 1 along with the gender distribution, MoCA score, and years of education past high school or GED. All subjects reported on the questionnaire that they have normal or corrected 20/20 or 20/30 vision, which indicates they could see the presented stimuli clearly. All subjects considered for analyses were right handed. The button clicks recorded for accuracy showed no significant differences between or within groups; although, one participant misunderstood the direction and only clicked for target faces for their first paradigm. Some of the subjects were taking medications for birth control, type II diabetes, prostate health, and/or gastrointestinal steroids; although none of the medications listed in the questionnaire were known to be psychoactive or neuroleptic.

Table 1. Mean and (sample standard deviation) for participants included in analyses.

Group	Age (years)	MoCA	Gender (M/F)	Education (years)
18-25	21.3 (0.5)	29.5 (0.5)	2/2	3.5 (0.5)
26-40	31.3 (3.9)	28.8 (1.3)	3/1	6.5 (2.4)
41-59	49.0 (8.1)	28.0 (0.8)	4/0	3.8 (1.3)
60+	66.5 (5.8)	27.3 (1.5)	1/3	4.8 (1.5)

5.2 FIE Features

The grand averages of each age group at channel CZ are shown for upright and inverted images in Fig 9 and 10. The response to upright images was consistently larger amplitude for all ERP components, although the latency changes from the FIE are subtle when referring to Fig 9 and 10. The

LPP's amplitude differences among different age groups are clearly illustrated in Fig 9 with the LPP of the youngest group being the highest amplitude. One may also suggest the N170 is present in Fig 9, albeit the physiological significance at channel CZ of the N170 is inconsistent with other literature and the N170 should be present for inverted faces in Fig 10, too.

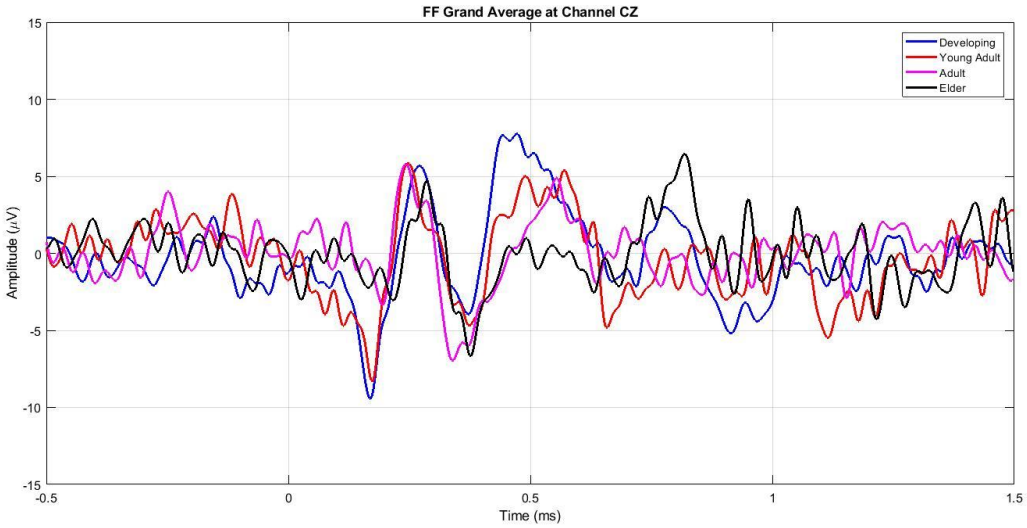


Figure 9. Grand average response to familiar faces at channel CZ.

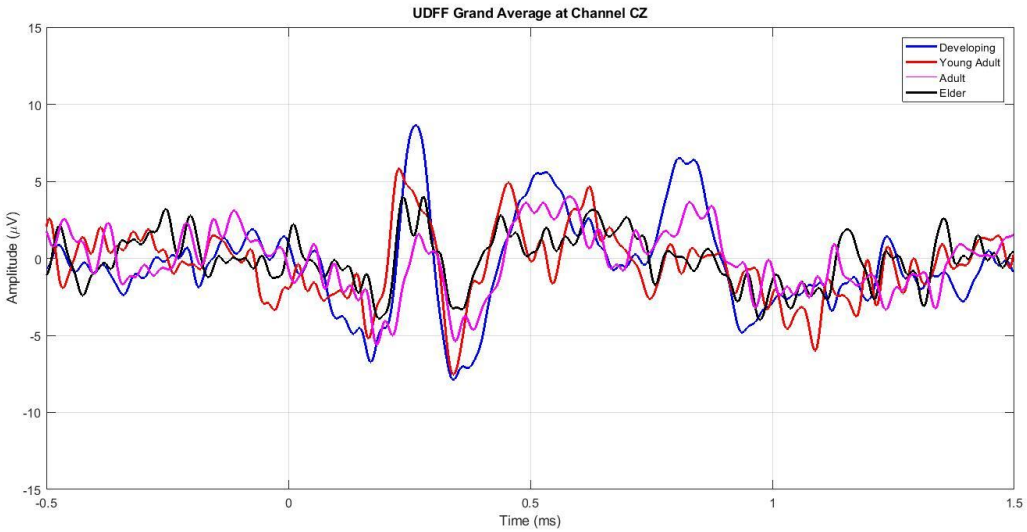


Figure 10. Grand average response to inverted (upside down) familiar faces at channel CZ.

In respect to the N170, the FIE was expected to manifest as an increase in amplitude and increase in latency. The FIE features were extracted by applying a peak detection algorithm to the filtered ERPs. Peaks for inverted faces were subtracted from upright faces for their respective channel and stimuli. At the ROI of the N170 (fusiform face area) no trends as a function of age were observed for peak amplitude, latency, or the FIE, examples in Fig 11 and 12. This trend was also true for the N400 FIE. No trends were observed for ERSP analysis, either. It must also be noted that dipole fitting and source analysis yielded inconsistent results for all participants, which is likely due to small sample sizes and using only 32 electrodes when 64 or more electrodes are recommended for those analysis techniques [24].

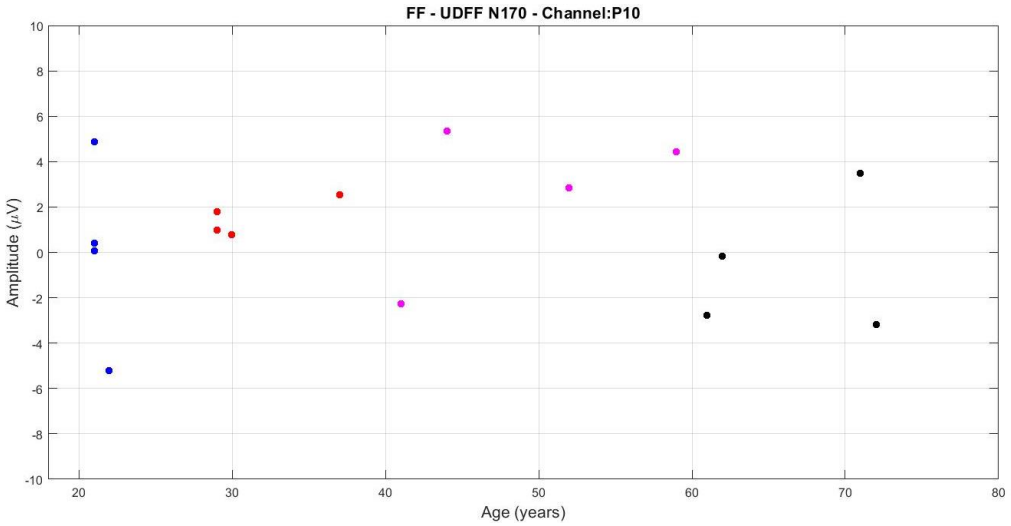


Figure 11. Result of upright minus inverted peak amplitudes for the N170 at channel P10.

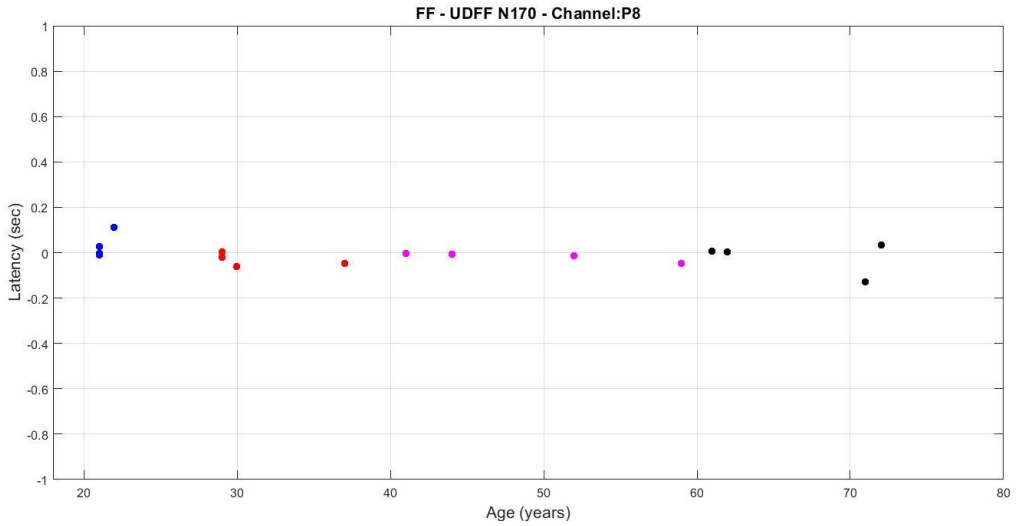


Figure 12. Result of upright minus inverted peak amplitude latencies for the N170 at channel P8.

The only ERP components to display any FIE trends were the P300 and LPP. There were four noticeable FIE trends with between-subjects effects: FF FIE LPP latency at CZ, $F(3,12) = 0.273$ ($\eta^2 = .268$), FF FIE P300 amplitude at FZ, $F(3,12) = 0.047$ ($\eta^2 = 0.471$), UF FIE P300 at P4, $F(3,12) = 0.55$ ($\eta^2 = 0.155$), UF FIE P300 Latency at OZ, $F(3,12) = 0.133$ ($\eta^2 = 0.362$), detailed in Table 2. A positive Pearson correlation suggests that as age increases there is a positive trend in the difference between the upright and inverted image, and vice versa. Table 2 also includes the t-values and p-values from regression analysis. It should be noted that there were several observed trends for familiarity as a function of age. For the P300, the absolute value Pearson correlation range was about 0.26 to 0.44. For the LPP, the absolute value Pearson correlation range was about 0.30 to 0.58. For the N400, the absolute value Pearson correlation range was 0.45 to 0.57. The LPP and N400 correlations were all in response to familiar faces, indicating a familiarity effect due to aging. The P300 is also known to change throughout aging, which supports the claim that the methods used were valid [44].Familiarity was not the key feature to investigate in this research, but the results were consistent with the other researcher in the BIDA lab.

Table 2. Calculated Pearson correlation coefficients, the 2-tailed t tests and p-values from linear regression analysis of the most significant features along with the two example non-results features.

Features	Pearson Correlation Coefficient	t-value (two-tailed)	p-value (α = 0.10)
FF FIE N170 Amp P10	0.010	0.036	0.972
FF FIE N170 Lat P8	-0.368	-1.479	0.161
FF FIE LPP Lat CZ	0.389	1.578	0.137
FF FIE P300 Amp FZ	0.438	1.821	0.090
UF FIE P300 Lat P4	-0.355	-1.908	0.077
UF FIE P300 Lat OZ	-0.551	-2.471	0.27

There were two features to reach statistical significance (α = 0.10) in the regression analysis; the FF FIE P300 amplitude at channel FZ, and the UF FIE P300 latency at channel P4, shown in Fig 13 and 14. The other two FIE features are shown in Appendix A. The only feature to achieve significance in both the between-subjects analysis and regression analysis was the FF FIE P300 amplitude at channel FZ. Both of the significant features' respective t-values were not significant for two-tailed tests ($t \geq 2.35$), although this is likely due to all groups having few samples (n = 4) and moderate variability in both age distribution and feature magnitude, shown in Fig 13 and 14. These statistics suggest the FIE for P300s at channel FZ is the most likely to be a reliable biomarker of age related changes; thus, one can support the claim that as age increases the P300's amplitude in response to inverted faces decreases drastically while the response to upright faces decreases slightly. Also, the P300's latency is prolonged as age increases.

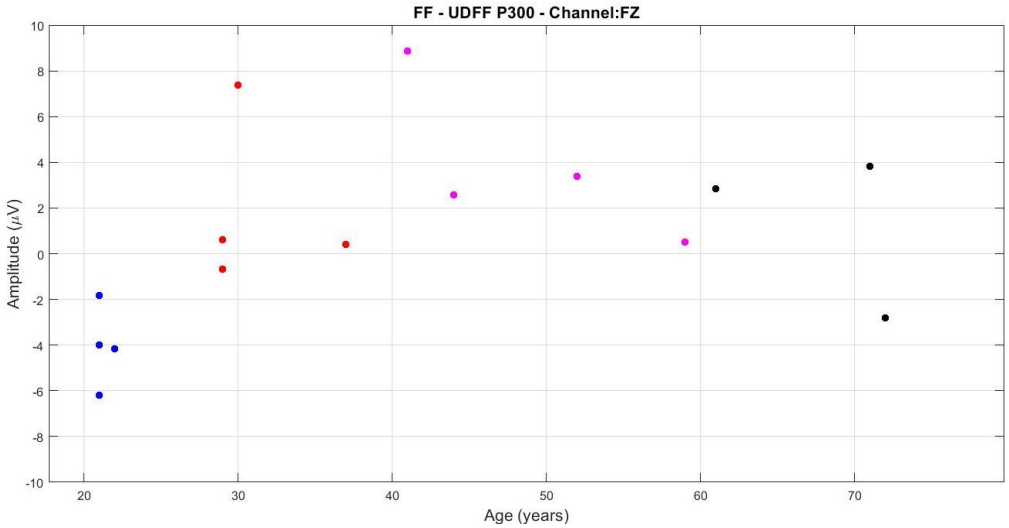


Figure 13. Result of upright minus inverted peak P300 amplitudes at channel FZ.

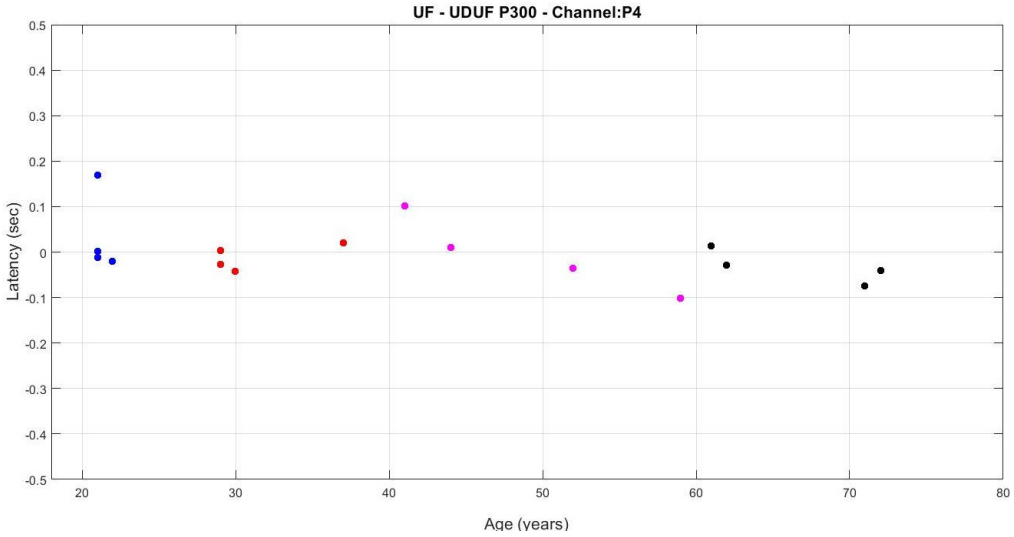


Figure 14. Result of upright minus inverted peak amplitude latencies at channel P4.

The grand average scalp voltage topography is shown for each age group in Fig 14 and 15, which shows an interpolated sliding time window of the measured EEG signal across the entire scalp. The other holistic analysis techniques, such as SCD, ERSPs, dipole fitting, and source analysis, yielded inconsistent results across and within age groups. The voltage topography can be related to the grand average ERPs and peak detection algorithms by displaying the time windows of activation. The peak detection

algorithm simply isolates one electrode on the scalp within the ERP component's respective time range. For voltage topography plots of other stimuli and ERP components, see Appendix A.

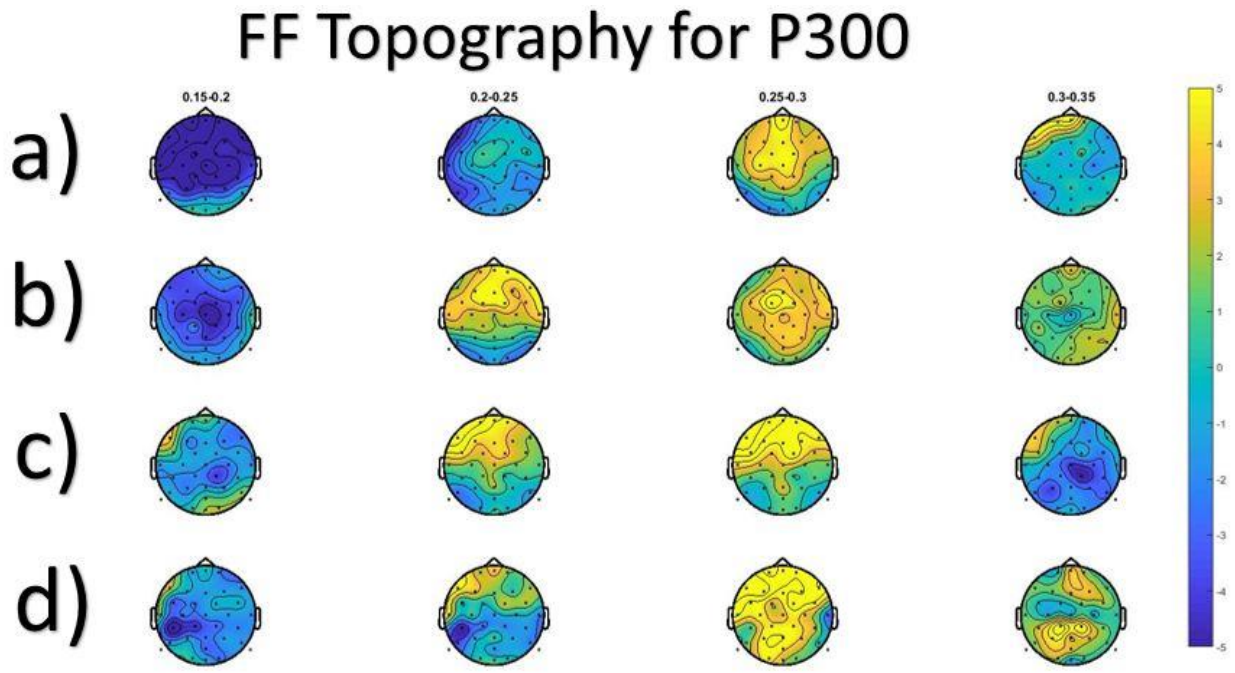


Figure 15. Grand average scalp voltage topography in response to familiar faces for P300s. a) 18 to 25, b) 26 to 40, c) 41 to 59, and d) 60+.

A noticeable feature of the scalp voltage topography is the increased negativities in the youth groups, which suggests the cortex may be projecting towards the center of the brain (inward dipoles). A different feature is that the overall response to inverted faces is consistently less positive (more negative) than that of upright faces. Also, the response to inverted faces consistently has less activation than that of upright faces. The time course of the scalp voltage topography suggests the youth group has a faster P300, although it may start later than the older groups. The eldest group is shown to have the longest period of high activation, suggesting their P300s may be the slowest to reach peak activation and have a larger period than the other groups.

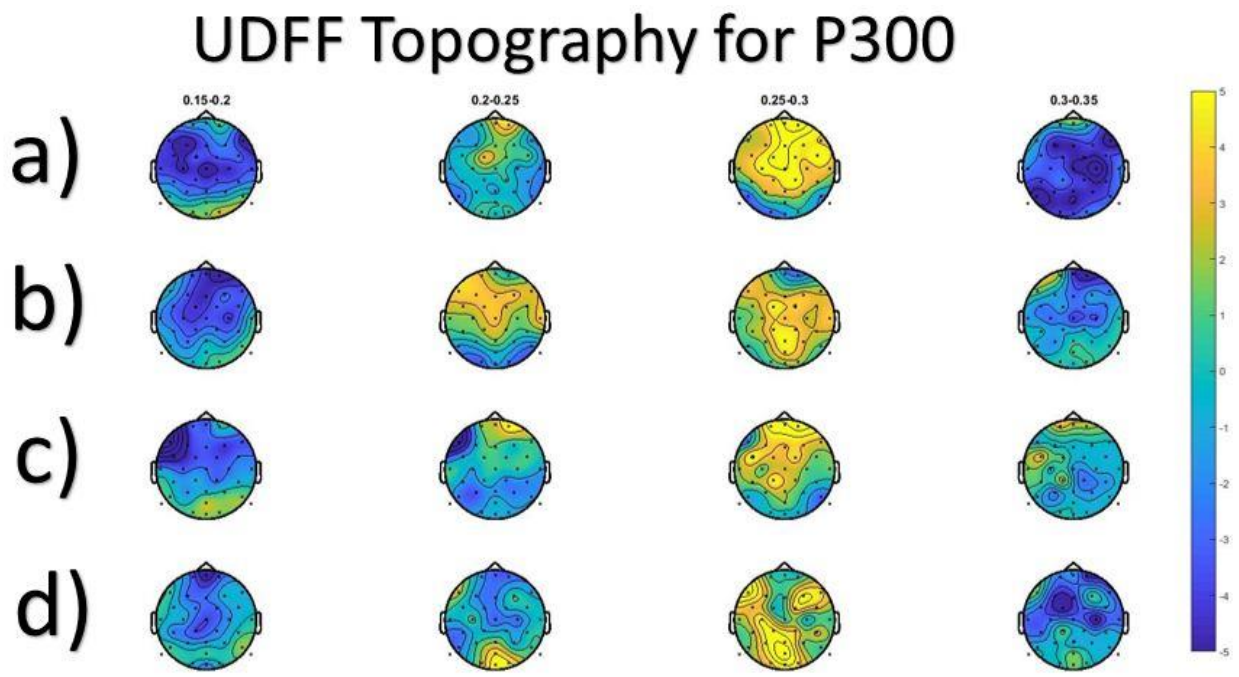


Figure 16. Grand average scalp voltage topography in response to inverted familiar faces for P300s. a) 18 to 25, b) 26 to 40, c) 41 to 59, and d) 60+.

CHAPER 6: Discussion

This research was designed to investigate healthy age-related changes to the brain's response to upright and inverted face images. The FIE can be described as the difference between upright and inverted face images. It was found that not all of the discussed ERPs showed significant differences throughout aging or even the traditional FIE discussed in other research [13]. Despite the negative results of the majority of investigated features and channels, there were some significant results that were consistent with literature [41].

6.1 The N170 and N400

The FIE of the N170 and N400 were both illusive components that showed no meaningful statistical significance throughout the duration of this research. Literature has shown that in response to inverted faces the N170 increases in amplitude and latency while the N400 decreases in amplitude and increases in latency [41][13]. The strongest N170 feature found in this study was a weak correlation (Pearson = -0.368) between the FIE and aging at channel P8 in response to familiar faces; otherwise, no significant trends at any other channels were noticed, and that goes for the N400 as well. Channel P8 is in close proximity to the fusiform face area, so there is likely physiological significance to this correlation [62]. Although, no other channels in that area showed the same strength of correlation, and the unfamiliar faces did not show any correlation. One may interpret those results as a lack of attention to detail during recording, poor SNR, and/or the sequential image paradigm was lacking.

It is the opinion of the author that the unfavorable ERP components are likely due to two main issues: effects due to repetition and participants' individuality. The repetition effect is the brain's ability to adapt to repeatedly presented stimuli. It is almost as if the brain anticipates the stimuli or is desensitized to the stimuli [63]. In respect to the N170, the repetition effect will extend the N170 out to about 250 ms and lower the amplitude slightly [46]. However, the face images were shown as the rare

stimuli in an oddball paradigm. It is possible that the participants' brains began to anticipate the object images and the oddball face images were thus processed differently. Other studies to successfully show the N170 and FIE showed face images at higher rates [13][64][11]. It is entirely possible that the oddball paradigm is less adapted to producing reliable N170s, and therefore the FIE for N170s.

Genetic heritability may have had an impact on the performance of the N170 and N400, which has been shown to be true for the P300 by Anokhin *et al* [65]. This genetic influence on ERP components could have been avoided by recruiting more participants. Personal beliefs could have also factored into the performance of those ERP components. For the familiar faces used in the study, the current and preceding US presidents were used along with two famous actors, Robert Downey Jr and Dwayne 'The Rock' Johnson. It is possible that political preference or emotional memories associated with Trump or Obama's elections could have impacted the ERP recordings, specifically for later ERP components [66]. The same could be true for emotional memories or personal preferences associated with movies in which the two famous actors appeared.

There are many personality factors that could have influenced the outcome of the later ERP components, such as the P300, N400, or LPP. Palomba *et al* has shown that the P300 and other late ERP components can be modulated by emotionally pleasant and unpleasant images [66]. Specifically, the P300 increases for emotionally pleasant and unpleasant images, while fronto-centrally located peaks around 400 to 500 ms can be increased for emotionally stimulating images. In the case of Palomba's research, images of sexually attractive people or unpleasant images of accidents (e.g. car crashes) were shown. Similarly, Osterhout and Mobley *et al* have shown that different types of disagreements or semantic incongruences in sentences and word-object pairs can modulate late ERP components [67]. These reported results could lead one to believe that in the case of this study political preference and other individual beliefs may have impacted the performance of the N400 or LPP.

The large negativity at the beginning of the P300, shown in Fig 15 and 16, suggests that there is an increase in excitatory projections from the hippocampus [44]. It is possible that this broad negativity interfered with the detection of the N170 via volume conduction. A broad negativity was also present at the end of the P300, shown in Fig 15 and 16, was found to be stronger for inverted images. This negativity may be the beginnings of the N400 and may stem from subcortical regions such as the hippocampus (memory) or thalamus (relay station) [25]. The thalamus may be relaying the motor movements to the PNS, or the hippocampus may be more active for inverted images than for upright images due to difficulties recognizing and remembering associated memories.

6.2 The P300 and LPP

The FIE was expected to manifest as a delay in latency and a decrease in amplitude for both the P300 and LPP in response to inverted faces [44][37]. Also, the difference between upright and inverted images were expected to decrease with advanced aging [37][12]. The results of the current study were mixed for familiar faces. The latency difference between upright and inverted images was found to increase for the LPP and decrease for the P300 at channels CZ, P4 and OZ respectively. Also, the amplitude difference between upright and inverted images was found to increase as a function of age. It is known that increases in working memory, especially with advanced aging, will cause a decrease in P300 [25]. Therefore one may interpret the P300 amplitude results as the inverted faces having drastically lower amplitudes for elders than the other groups. While the latency changes are a different story.

Two hypotheses have been presented on the brain's functional changes throughout healthy aging. The first has been referred to as HAROLD, or Hemispheric Asymmetry Reduction in Old Adults, and the second is the dedifferentiation hypothesis [5]. Lateralization of the PFC activations tends to reduce throughout aging, which has been empirically shown in many high performing adults. That

evidence is what led to the HAROLD hypothesis [5]. Although, other evidence, such as reduced hemispheric asymmetry reflecting age-related difficulties in recruiting specialized neural mechanisms, has led to the dedifferentiation hypothesis. Both theories are credible, but research comparing high and low-performing elders has leaned more in favor to the dedifferentiation hypothesis [42]. To relate this to the results at hand, elders have been shown to develop "*more automatic and efficient networks associated with effortless identification of faces which allows the emergence of human-specific social and communication skills*," [42]. In other words, high-performing elders may have fewer neurons allocated to specific simple functions, such as facial recognition. This phenomenon could manifest as P300 latency similar to that of a young adult for facial recognition tasks, although more complex neural functions such as recall could become more difficult for elders. This may account for the decrease in P300 FIE while the LPP was more pronounced.

The response to unfamiliar faces may be confounding the results of the research. The only noticed latency trends were for the P300 were for unfamiliar faces. As age increases the difference between upright and inverted face P300 latencies decreased. Eimer *et al* found that the FIE for the LPP was less exaggerated for unfamiliar faces [13]. It is known that P300's are larger for human faces than other random objects in steady-state visual evoked potentials for brain-computer interfaces [Jin et al]. It may be possible that, in the context of the oddball paradigm, the inverted unfamiliar faces were just as salient, or even more so, than the familiar inverted faces. Especially in the case of high performing adults, the difference between inverted and upright faces could have been smaller due to the dedifferentiation hypothesis while the younger groups simply had increases in working memory to delay their P300s.

The P300 is thought to have many neural generators, such as the ventrolateral PFC, superior temporal sulcus, anterior cingulate cortex and the intraparietal sulcus [25]. These areas of activity

typically manifest the P300 best at or adjacent to central locations such as electrodes CZ and PZ. The PFC and cingulate cortex are believed to be active during decision making and emotional judgement or regulation [25], which can make them susceptible to modulation during stimulus presentation tasks. It may be possible that the inverted faces caused a delay in PFC or cingulate cortex activity due to processing difficulties; thus manifesting as an increased positivity in upright (Fig 15) and attenuated negativity and positivity in inverted (Fig 16).

6.3 Familiarity

The goal of this study was to investigate the FIE throughout healthy aging in order to predict early-onset dementia. Both familiar and unfamiliar faces (FF and UF) were used along with random objects. Investigating familiarity was not a part of the specific aims of this research, although there were noticeable trends consistent with existing literature on the topic of familiarity in ERPs [13][30].

It is known that the N170 is unaffected by familiarity even in the context of the FIE [13]. But all other ERP components investigated can be influenced by familiarity [13][37][30]. In the context of this research it was noticed that the LPP was particularly affected by familiarity. Specifically, the LPP was larger for familiar faces and then diminished for inverted familiar faces while for unfamiliar faces the LPP was smaller and even more attenuated for inverted faces. These results serve to validate our ERP paradigm and methodologies; however, improvements could still be made. This may suggest that a different paradigm, possibly with a block-style sequential imaging as opposed to oddball, may be better for identifying trends for aging.

6.4 Limitations

First and foremost the largest limitation of this study was the small sample size. Limitations to the recruiting area and an inability to pay volunteers severely curbed volunteer turnout. The other main limitation was poor recording quality. EEG research is plagued with many nuisance variables [28]. It is

the belief of the author that the 12 unsuitable datasets had to be rejected as the result of uncontrollable and random features of the respective participants; features such as genetics, diet, hair type, etc. As with other medical imaging techniques, each method has its pros and cons. MRI and PET have much higher spatial resolution but are more expensive for that reason. EEG has the fundamental inability to imagine deep within the brain and is influenced by volume conduction, but it has the highest time resolution of modern neuroimaging methods [14]. This volume conduction, and therefore EEG recording quality, can be impacted by features that change throughout aging, such as skull and skin composition and conductivity [68]. Neural changes due to aging can still be detected with EEG, although larger sample sizes are imperative.

For future recommendations, a block style single-trial ERP study should be considered. A higher density electrode montage would be preferred to facilitate dipole and source analyses. The brain's ability to habituate to stimuli could be exploited in order to examine a dynamic contrast between young and old participants. It may be possible to show a participant a large number (e.g. 30 to 50) of consistent objects (e.g. cars), then show them a smaller block (e.g. 10 to 20) of random (familiar and/or unfamiliar) face images in order to clarify the brain's ability to habituate then readapt to new stimuli. This block style may shed more light on age-related changes on ERPs. Alternatively, multimodal investigations such as eye tracking or reaction timing may contain additional age-related biomarkers [35].

CHAPTER 7: Conclusions

The research study presented in this thesis was designed to scrutinize the FIE throughout healthy adult aging in an effort to find additional biomarkers for the onset of malignant AACD. Using ERPs may obviate or reduce the need for longitudinal study to detect early onset cognitive decline. The outcome of this research was that there are subtle changes in the FIE throughout adult aging; specifically, the changes in the LPP and P300 in response to inverted face images as opposed to upright yielded moderate correlations with age. Despite the small sample size of the final analyses performed, these outcomes suggest the FIE could be used to track brain changes due to aging. Future studies may include a block style single-trial ERP analysis that further scrutinizes the FIE between age groups. The dynamical contrast of changes to habitual stimuli may elucidate more brain changes that may benefit the current MCI and AD detection methods. Dementia is a serious disorder that is still not perfectly understood, and any way to detect its onset earlier may improve quality of life for elders or even save lives. The earlier dementia is detected, the sooner preventative actions can be taken in order to prolong healthy brain function and potentially halt disease progression.

CHAPTER 8: REFERENCES

[1] F. I. M. Craik and E. Bialystok, “Cognition through the lifespan: mechanisms of change,” *Trends in Cognitive Sciences*, vol. 10, no. 3, pp. 131–138, Mar. 2006.

[2] R. Levy, “Aging-Associated Cognitive Decline,” *International Psychogeriatrics*, vol. 6, no. 1, pp. 63–68, Mar. 1994.

[3] M. N. Rajah and M. D’Esposito, “Region-specific changes in prefrontal function with age: a review of PET and fMRI studies on working and episodic memory,” *Brain*, vol. 128, no. 9, pp. 1964–1983, Sep. 2005.

[4] E. Sahin and R. A. DePinho, “Linking functional decline of telomeres, mitochondria and stem cells during ageing,” *Nature*, vol. 464, no. 7288, pp. 520–528, Mar. 2010.

[5] R. Cabeza, N. D. Anderson, J. K. Locantore, and A. R. McIntosh, “Aging Gracefully: Compensatory Brain Activity in High-Performing Older Adults,” *NeuroImage*, vol. 17, no. 3, pp. 1394–1402, Nov. 2002.

[6] C. M. Krause *et al.*, “The effects of memory load on event-related EEG desynchronization and synchronization,” *Clinical Neurophysiology*, vol. 111, no. 11, pp. 2071–2078, Nov. 2000.

[7] D. Ariely and G. S. Berns, “Neuromarketing: the hope and hype of neuroimaging in business,” *Nat Rev Neurosci*, vol. 11, no. 4, pp. 284–292, Apr. 2010.

[8] D. Park, G. Lautenschlager, T. Hedden, N. Davidson, D. Anderson and P. Smith, "Models of visuospatial and verbal memory across the adult life span," *Psychology and Aging,* vol. 17, no. 2, pp. 299-320, 2002.

[9] R. A. Sperling *et al.*, “Toward defining the preclinical stages of Alzheimer’s disease: Recommendations from the National Institute on Aging-Alzheimer’s Association workgroups on diagnostic guidelines for Alzheimer’s disease,” *Alzheimer’s & Dementia*, vol. 7, no. 3, pp. 280–292, May 2011.

[10] J. Dauwels, F. Vialatte, A. Cichocki. “Diagnosis of Alzheimer’s Disease from EEG Signals: Where Are We Standing?”, *Bentham Science Publishers,* vol 7, pp. 487-505, Sep 2010.

[11 S. Bentin, T. Allison, A. Puce, E. Perez, and G. McCarthy, “Electrophysiological Studies of Face Perception in Humans,” *J Cogn Neurosci*, vol. 8, no. 6, pp. 551–565, Nov. 1996.

[12] L. Gao, J. Xu, B. Zhang, L. Zhao, A. Harel, and S. Bentin, “Aging effects on early-stage face perception: An ERP study,” *Psychophysiology*, vol. 46, no. 5, pp. 970–983, 2009.

[13] M. Eimer, “Effects of face inversion on the structural encoding and recognition of faces: Evidence from event-related brain potentials,” *Cognitive Brain Research*, vol. 10, no. 1, pp. 145–158, Sep. 2000.

[14] J. G. Webster, *et al*. “Medical Instrumentation Application and Design”, *John Wiley & Sons, Inc.*, fourth edition, 2010.

[15] S. R. Sponheim, B. A. Clementz, W. G. Iacono, and M. Beiser, “Clinical and biological concomitants of resting state EEG power abnormalities in schizophrenia,” *Biological Psychiatry*, vol. 48, no. 11, pp. 1088–1097, Dec. 2000.

[16] F.-B. Vialatte, M. Maurice, J. Dauwels, and A. Cichocki, “Steady-state visually evoked potentials: Focus on essential paradigms and future perspectives,” *Progress in Neurobiology*, vol. 90, no. 4, pp. 418–438, Apr. 2010.

[17] C. A. Nelson and J. P. McCleery, “Use of Event-Related Potentials in the Study of Typical and Atypical Development,” *J Am Acad Child Adolesc Psychiatry*, vol. 47, no. 11, pp. 1252–1261, Nov. 2008.

[18] A. Horvath, A. Szucs, G. Csukly, A. Sakovics, G. Stefanics and A. Kamondi, "EEG and ERP biomarkes of Alzheimer's disease: a critical review," *Frontiers in Bioscience,* vol. 23, pp. 183-220, 2018.

[19] M. Steriade, *et al*. “Basic Mechanisms of Cerebral Rhythmic Activity”, *Electroencephalography and clinical Neurophysiology*, vol. 76, pp. 481-508, Jun 1990.

[20] P. L. Nunez, R. Srinivasan, “Electric Fields of the Brain: The Neurophysics of EEG”, *Oxford University Press*, 2006, ISBN: 0-19-505038-X.

[21] K. Najarian, R. Splinter, “Biomedical Signal and Image Processing Second Edition”, *CRC Press,* 2012.

[22] C. Mizelle, “M/EEG Introduction and Methods,” *Department of Kinesiology East Carolina University College of Health and Human Performance*, PowerPoint KINE 6803, Fall 2017.

[23] M. A. Lopez-Gordo, D. Sanchez-Morillo, and F. P. Valle, “Dry EEG Electrodes,” *Sensors (Basel)*, vol. 14, no. 7, pp. 12847–12870, Jul. 2014.

[24] J. Song *et al.*, “EEG source localization: Sensor density and head surface coverage,” *Journal of Neuroscience Methods*, vol. 256, pp. 9–21, Dec. 2015.

[25] C. C. Duncan *et al.*, “Event-related potentials in clinical research: Guidelines for eliciting, recording, and quantifying mismatch negativity, P300, and N400,” *Clinical Neurophysiology*, vol. 120, no. 11, pp. 1883–1908, Nov. 2009.

[26] J. M. Olichney, J.-C. Yang, J. Taylor, and M. Kutas, “Cognitive Event-Related Potentials: Biomarkers of Synaptic Dysfunction Across the Stages of Alzheimer’s Disease,” *J Alzheimers Dis*, vol. 26, no. 0 3, pp. 215–228, 2011.

[27] S. Sutton, M. Braren, J. Zubin, and E. R. John, “Evoked-Potential Correlates of Stimulus Uncertainty,” *Science*, vol. 150, no. 3700, pp. 1187–1188, Nov. 1965.

[28] J. Polich, “P300 Clinical Utility and Control of Variability,” *Journal of Clinical Neurophysiology*, vol. 15, no. 1, p. 14, Jan. 1998.

[29] M. J. Herrmann, A.-C. Ehlis, A. Muehlberger, and A. J. Fallgatter, “Source Localization of Early Stages of Face Processing,” *Brain Topogr*, vol. 18, no. 2, pp. 77–85, Dec. 2005.

[30] C. Saavedra, J. Iglesias, and E. I. Olivares, “Event-Related Potentials Elicited by the Explicit and Implicit Processing of Familiarity in Faces,” *Clin EEG Neurosci*, vol. 41, no. 1, pp. 24–31, Jan. 2010.

[31] D. Feuerriegel, O. Churches, J. Hofmann, and H. A. D. Keage, “The N170 and face perception in psychiatric and neurological disorders: A systematic review,” *Clinical Neurophysiology*, vol. 126, no. 6, pp. 1141–1158, Jun. 2015.

[32] S. Daniel and S. Bentin, "Age-related changes in processing faces from detection to identification: ERP evidence," *Neurobiology of Aging,* vol. 33, pp. 206.e1-206.e28, 2012.

[33] S. Debener, S. Makeig, A. Delorme, and A. K. Engel, “What is novel in the novelty oddball paradigm? Functional significance of the novelty P3 event-related potential as revealed by independent component analysis,” *Cognitive Brain Research*, vol. 22, no. 3, pp. 309–321, Mar. 2005.

[34] P. Anderer, B. Saletu, H. V. Semlitsch, and R. D. Pascual-Marqui, “Non-invasive localization of P300 sources in normal aging and age-associated memory impairment,” *Neurobiology of Aging*, vol. 24, no. 3, pp. 463–479, May 2003.

[35] M. Mitchell, S. Shirk, D. McLaren, J. Dodd, A. Ezzati, B. Ally and A. Atri, "Recognition of faces and names: multimodal physiological correlates of memory and executive function," *Brain Imaging and Behavior,* vol. 10, pp. 408-423, 2016.

[36] M. Kutas and K. D. Federmeier, “Thirty Years and Counting: Finding Meaning in the N400 Component of the Event-Related Brain Potential (ERP),” *Annual Review of Psychology*, vol. 62, no. 1, pp. 621–647, 2011.

[37] S. Galdo-Alvarez, M. Lindin and F. Diaz, "The effect of age on event-related potentials associated with face naming and with the top-of-the-tongue (TOT) state.," *Biological psychology,* vol. 81, no. 1, pp. 14-23, 2009.

[38] C. E. Jackson and P. J. Snyder, “Electroencephalography and event-related potentials as biomarkers of mild cognitive impairment and mild Alzheimer’s disease,” *Alzheimer’s & Dementia*, vol. 4, no. 1, Supplement 1, pp. S137–S143, Jan. 2008.

[39] J. C. McBride *et al.*, “Spectral and complexity analysis of scalp EEG characteristics for mild cognitive impairment and early Alzheimer’s disease,” *Computer Methods and Programs in Biomedicine*, vol. 114, no. 2, pp. 153–163, Apr. 2014.

[40] J. Li *et al.*, “A cognitive electrophysiological signature differentiates amnestic mild cognitive

impairment from normal aging," *Alzheimer's Research & Therapy*, vol. 9, p. 3, Jan. 2017.

[41] B. Rossion, "Understanding face perception by means of human electrophysiology," *Trends in Cognitive Sciences*, vol. 18, no. 6, pp. 310–318, Jun. 2014.

[42] E. Meaux, N. Hernandez, and I. Carteau-Martin, "Event-related potential and eye tracking evidence of the developmental dynamics of face processing," *European Journal of Neuroscience*, p. 14, 2014.

[43] J. B. Wagner, S. B. Hirsch, V. K. Vogel-Farley, E. Redcay, and C. A. Nelson, "Eye-Tracking, Autonomic, and Electrophysiological Correlates of Emotional Face Processing in Adolescents with Autism Spectrum Disorder," *J Autism Dev Disord*, vol. 43, no. 1, pp. 188–199, Jan. 2013.

[44] R. van Dinteren, M. Arns, M. L. A. Jongsma, and R. P. C. Kessels, "P300 Development across the Lifespan: A Systematic Review and Meta-Analysis," *PLOS ONE*, vol. 9, no. 2, p. e87347, Feb. 2014.

[45] C. Saavedra, J. Iglesias, and E. I. Olivares, "Event-Related Potentials Elicited By Face Identity Processing In Elderly Adults With Cognitive Impairment," *Experimental Aging Research*, vol. 38, no. 2, pp. 220–245, Mar. 2012.

[46] S. R. Schweinberger, E. C. Pickering, I. Jentzsch, A. M. Burton, and J. M. Kaufmann, "Event-related brain potential evidence for a response of inferior temporal cortex to familiar face repetitions," *Cognitive Brain Research*, vol. 14, no. 3, pp. 398–409, Nov. 2002.

[47] Z. Nsareddine, N. Phillips, V. Bedirian, S. Charbonneau, V. Whitehead, I. Collin, J. Cummings and H. Chertko, "The Montreal Cognitive Assessment, MoCA: a Brief Screening Tool for Mild Cognitive Impairment," *Journal of the American Geriatrics Society,* vol. 53, no. 4, pp. 695-699, 2005.

[48] C. Huang, L.-O. Wahlund, T. Dierks, P. Julin, B. Winblad, and V. Jelic, "Discrimination of Alzheimer's disease and mild cognitive impairment by equivalent EEG sources: a cross-sectional and longitudinal study," *Clinical Neurophysiology*, vol. 111, no. 11, pp. 1961–1967, Nov. 2000.

[49] G. Schalk, D. McFarland, T. Hinterberger, N. Birbaumer and J. Wolpaw, "BCI2000: A General-Purpose Brain-Computer Interface (BCI) System," *IEEE Transactions on Biomedical Engineering,* vol. 51, no. 6, pp.

1034-143, 2004.

[50] OECD, "Employment rate by age group," OECD Data, United States, 2018.

[51] GUGER TECHNOLOGIES, “g.SAHARAsys Active Dry Electrode System”, 4521 Schiedlberg, Sierningstrasse 14, Austria, V1.14.01, 2014.

[52] M. Corsi-Cabrera, C. Arce, I. Y. D. Río-Portilla, E. Pérez-Garci, and M. A. Guevara, “Amplitude Reduction in Visual Event-related Potentials as a Function of Sleep Deprivation,” *Sleep*, vol. 22, no. 2, pp. 181–189, Mar. 1999.

[53] M. M. Lorist and M. Tops, “Caffeine, fatigue, and cognition,” *Brain and Cognition*, vol. 53, no. 1, pp. 82–94, Oct. 2003.

[54] A. B. Ilan, A. Gevins, M. Coleman, M. A. ElSohly, and H. de Wit, “Neurophysiological and subjective profile of marijuana with varying concentrations of cannabinoids,” *Behavioural Pharmacology*, vol. 16, no. 5–6, p. 487, Sep. 2005.

[55] T.-P. Jung, S. Makeig, M. Westerfield, J. Townsend, E. Courchesne, and T. J. Sejnowski, “Analysis and visualization of single-trial event-related potentials,” *Human Brain Mapping*, vol. 14, no. 3, pp. 166–185, 2001.

[56] T. Mullen *et al.*, “Real-Time Modeling and 3D Visualization of Source Dynamics and Connectivity Using Wearable EEG,” *Conf Proc IEEE Eng Med Biol Soc*, vol. 2013, pp. 2184–2187, 2013.

[57] A. Delorme and S. Makeig, “EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis,” *Journal of Neuroscience Methods*, vol. 134, no. 1, pp. 9–21, Mar. 2004.

[58] R. D. Pascual-Marqui, “Standardized low resolution brain electromagnetic,” *Clinical Pharmacology*, p. 16, 2002.

[59] S. Makeig, S. Debener, J. Onton, and A. Delorme, “Mining event-related brain dynamics,” *Trends in Cognitive Sciences*, vol. 8, no. 5, pp. 204–210, May 2004.

[60] R. Oostenveld, P. Fries, E. Maris, and J.-M. Schoffelen, “FieldTrip: Open Source Software for Advanced Analysis of MEG, EEG, and Invasive Electrophysiological Data,” *Intell. Neuroscience*, vol. 2011, pp. 1:1–1:9, Jan. 2011.

[61] M. A. Pett, N. R. Lackey, J. J. Sullivan, “Making Sensor of Factor Analysis, The Use of Factor Analysis for Instrument Development in Health Care Research,” *SAGE Publications, Inc*. 2003.

[62] P. Vuilleumier, J. L. Armony, J. Driver, and R. J. Dolan, “Effects of Attention and Emotion on Face Processing in the Human Brain: An Event-Related fMRI Study,” *Neuron*, vol. 30, no. 3, pp. 829–841, May 2001.

[63] R. N. Henson, Y. Goshen-Gottstein, T. Ganel, L. J. Otten, A. Quayle, and M. D. Rugg, “Electrophysiological and Haemodynamic Correlates of Face Perception, Recognition and Priming,” *Cereb Cortex*, vol. 13, no. 7, pp. 793–805, Jul. 2003.

[64] R. J. Itier and M. J. Taylor, “Inversion and Contrast Polarity Reversal Affect both Encoding and Recognition Processes of Unfamiliar Faces: A Repetition Study Using ERPs,” *NeuroImage*, vol. 15, no. 2, pp. 353–372, Feb. 2002.

[65] A. P. Anokhin, S. Golosheykin, and A. C. Heath, “Heritability of Individual Differences in Cortical Processing of Facial Affect,” *Behav Genet*, vol. 40, no. 2, pp. 178–185, Mar. 2010.

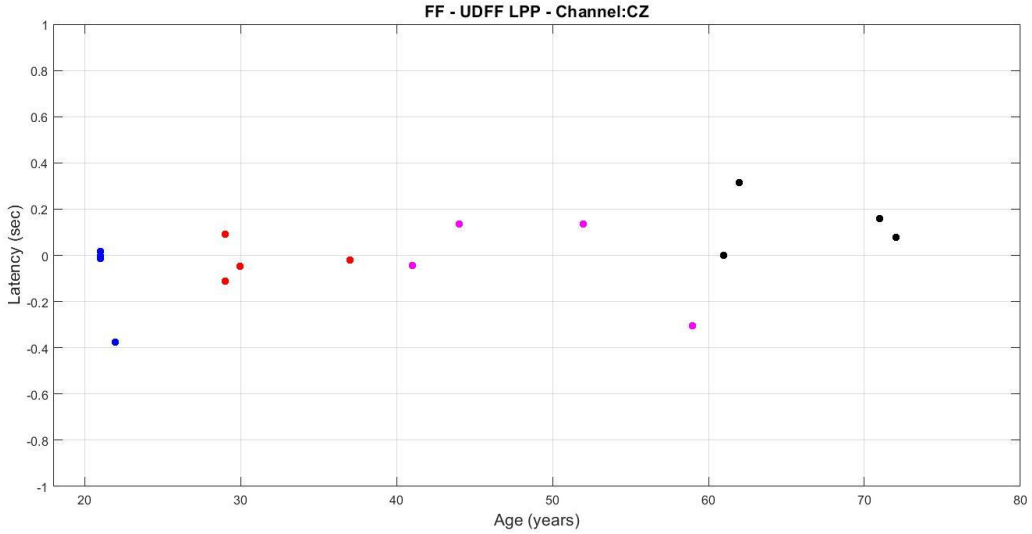
[66] D. Palomba, A. Angrilli, and A. Mini, “Visual evoked potentials, heart rate responses and memory to emotional pictorial stimuli,” *International Journal of Psychophysiology*, vol. 27, no. 1, pp. 55–67, Jul. 1997.

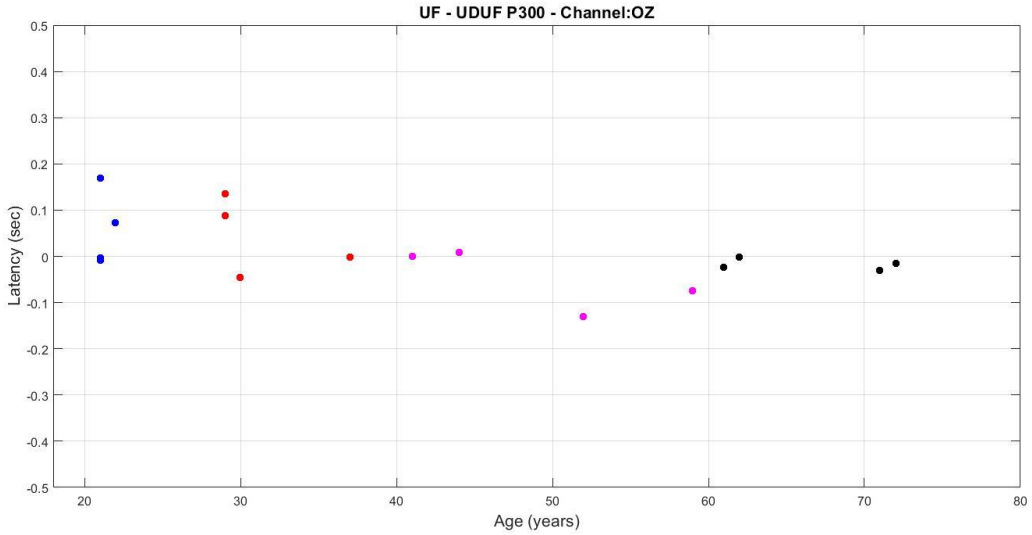
[67] L. Osterhout, L. A. Mobley, “Event-Related Brain Potentials Elicited by Failure to Agree,” *Journal of Memory and Language*, vol. 34, no.6, pp. 739-773, Dec. 1995.

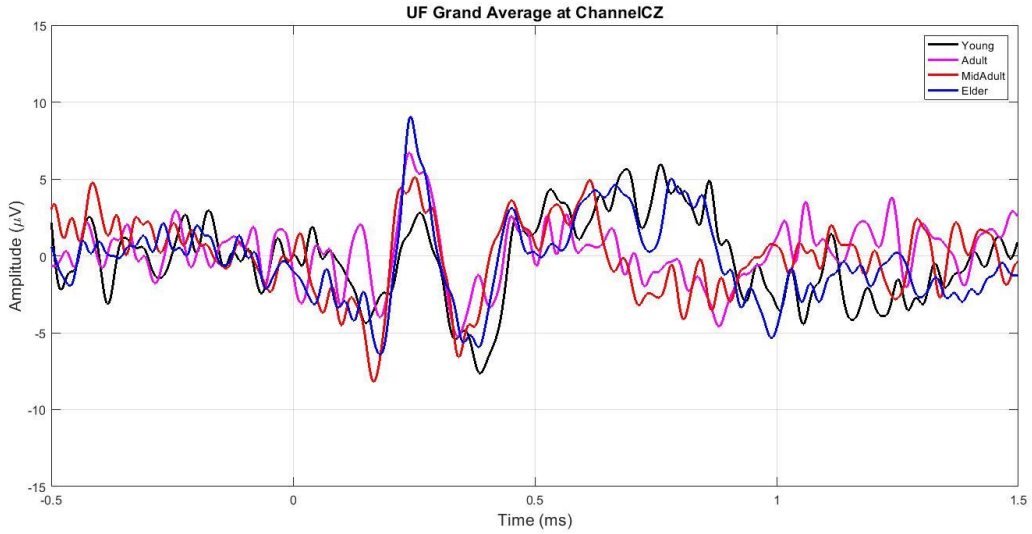
[68] K. Wendel, J. Väisänen, G. Seemann, J. Hyttinen, and J. Malmivuo, “The Influence of Age and Skull Conductivity on Surface and Subdermal Bipolar EEG Leads,” *Intell. Neuroscience*, vol. 2010, pp. 9:3–9:3, Jan. 2010.

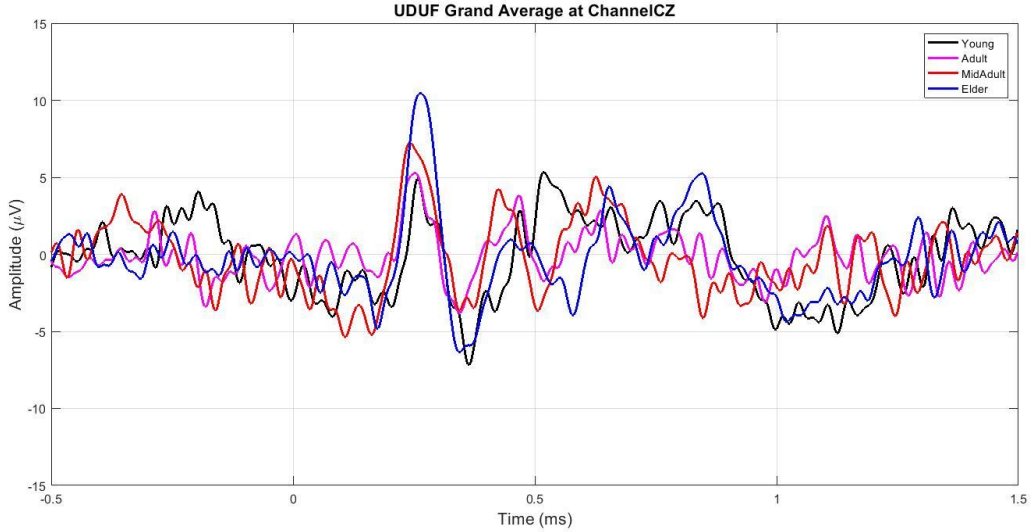
APPENDIX A

Additional plots of investigated images, FIE at different channels, and scalp voltage topography time windows.






UF Grand Average at ChannelCZ
Young
Adult
MidAdult
Elder
Amplitude (μV)
Time (ms)
15
10
5
0
-5
-10
-15
-0.5
0
0.5
1
1.5


UDUF Grand Average at ChannelCZ
Young
Adult
MidAdult
Elder
Amplitude (μV)
Time (ms)
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-15
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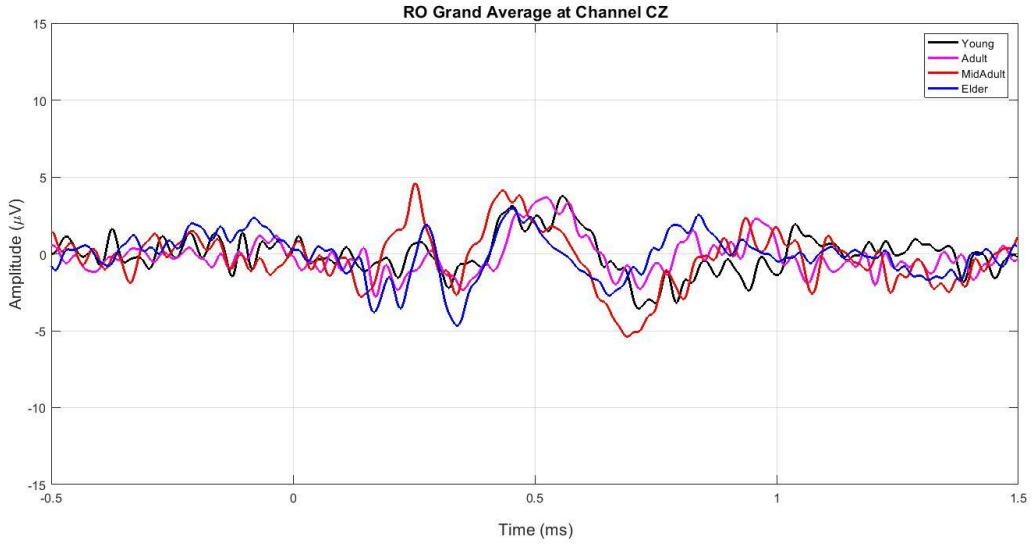
1
1.5


RO Grand Average at Channel CZ
Young
Adult
MidAdult
Elder
Amplitude (μV)
Time (ms)
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-10
-15
-0.5
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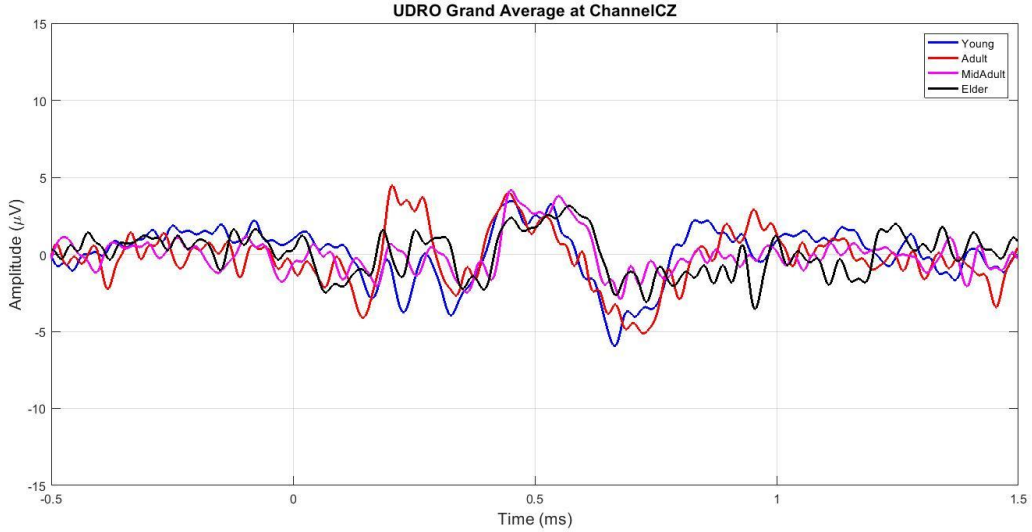
0.5
1
1.5


UDRO Grand Average at ChannelCZ
Young
Adult
MidAdult
Elder
Amplitude (μV)
Time (ms)
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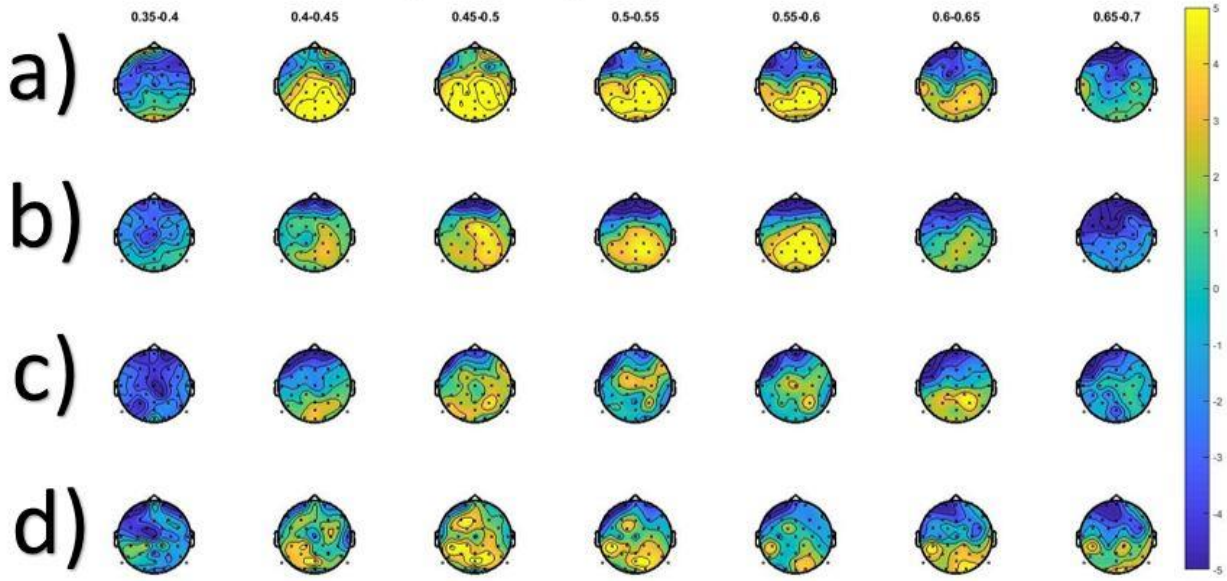
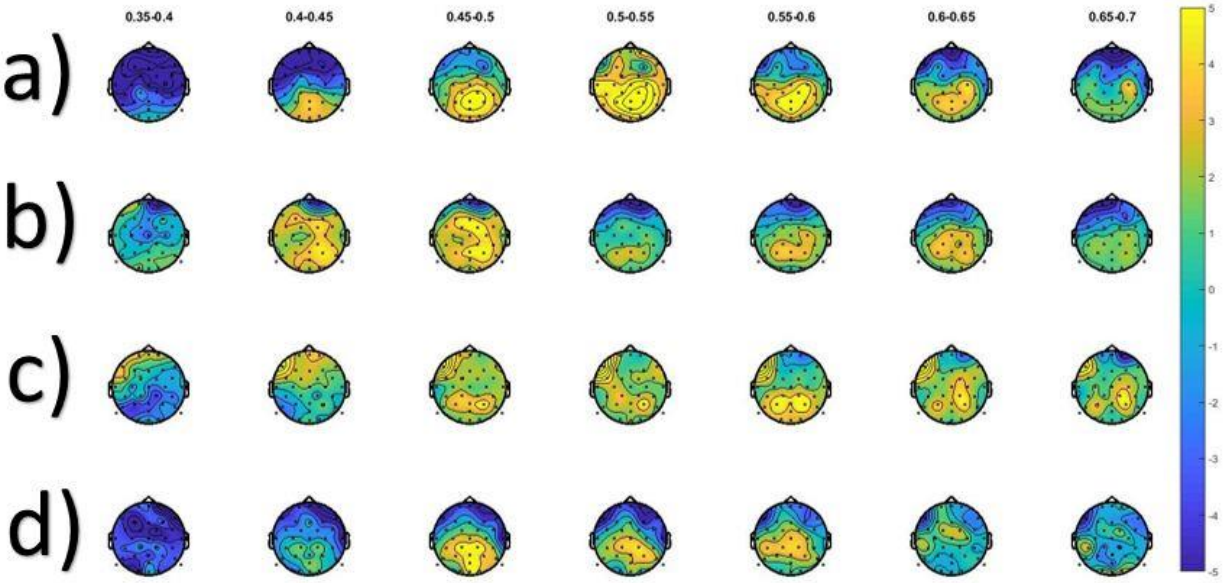
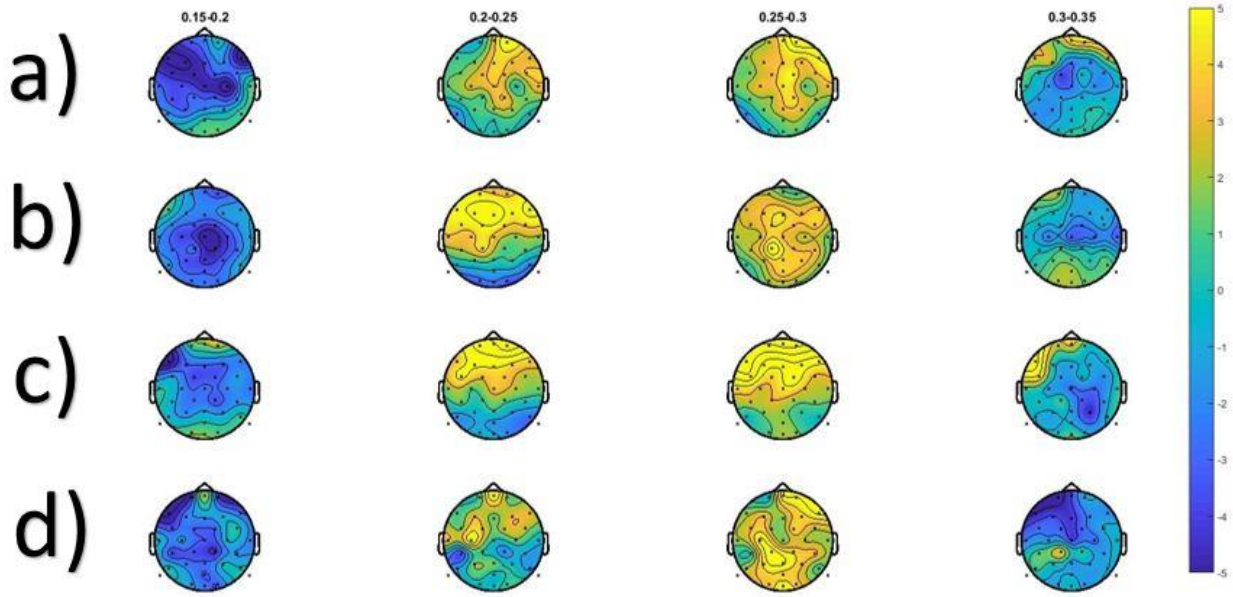
5
0
-5
-10
-15
-0.5
0
0.5
1
1.5

FF Topography for LPP



UDFF Topography for LPP




UF Topography for P300
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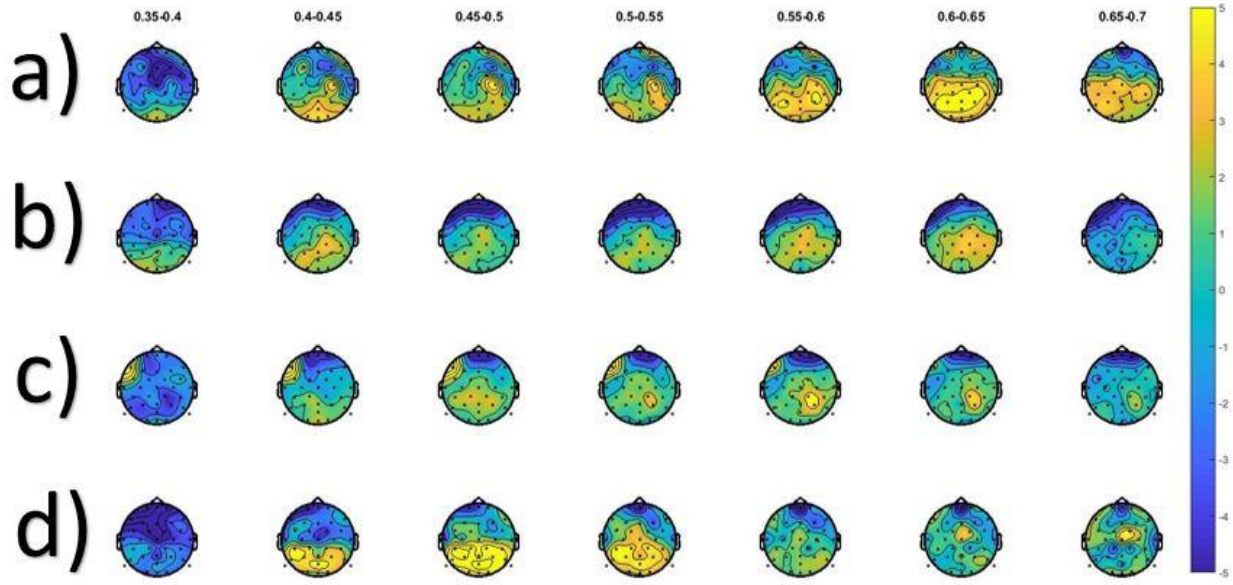
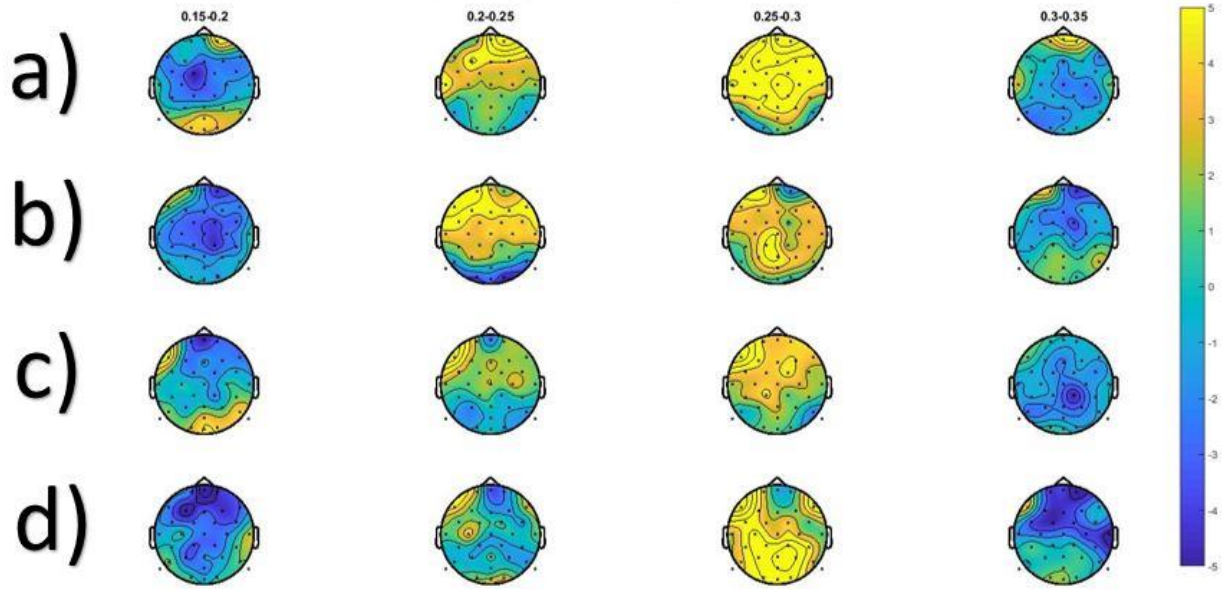
0.2-0.25
0.25-0.3
0.3-0.35
a)
b)
c)
d)


UF Topography for LPP
0.35-0.4
0.4-0.45
0.45-0.5
0.5-0.55
0.55-0.6
0.6-0.65
0.65-0.7
a)
b)
c)
d)

UDUF Topography for P300



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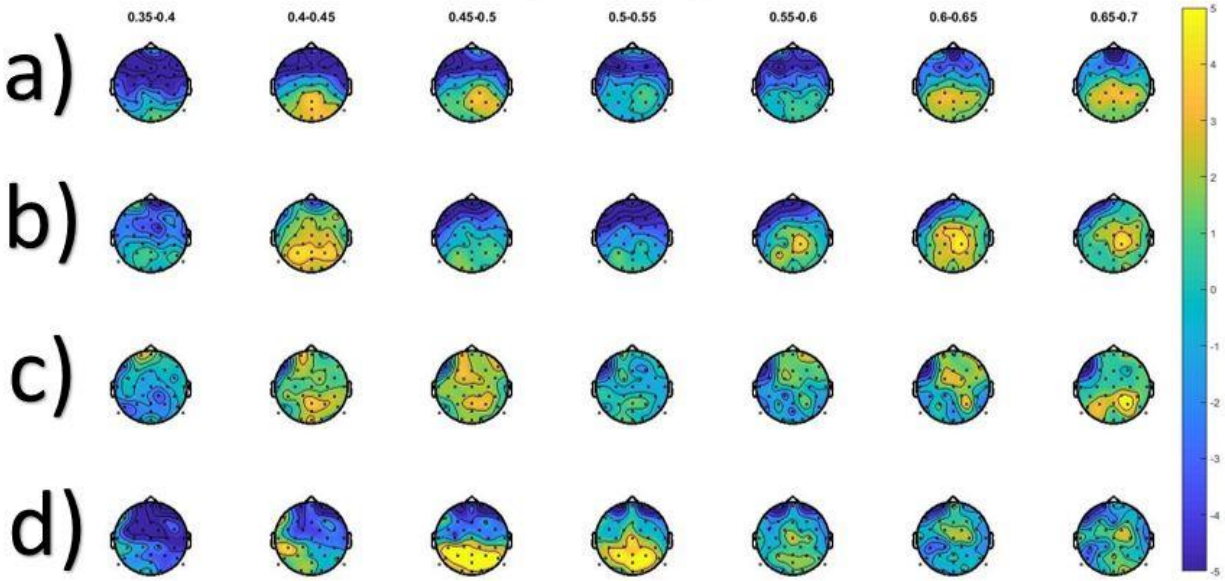
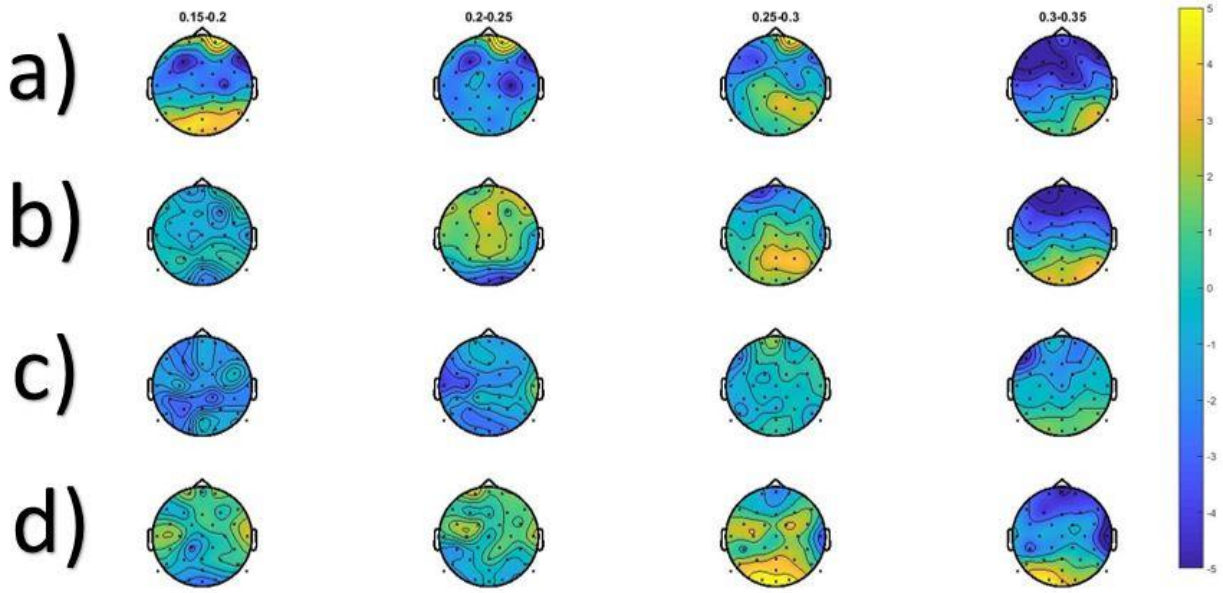


RO Topography for P300



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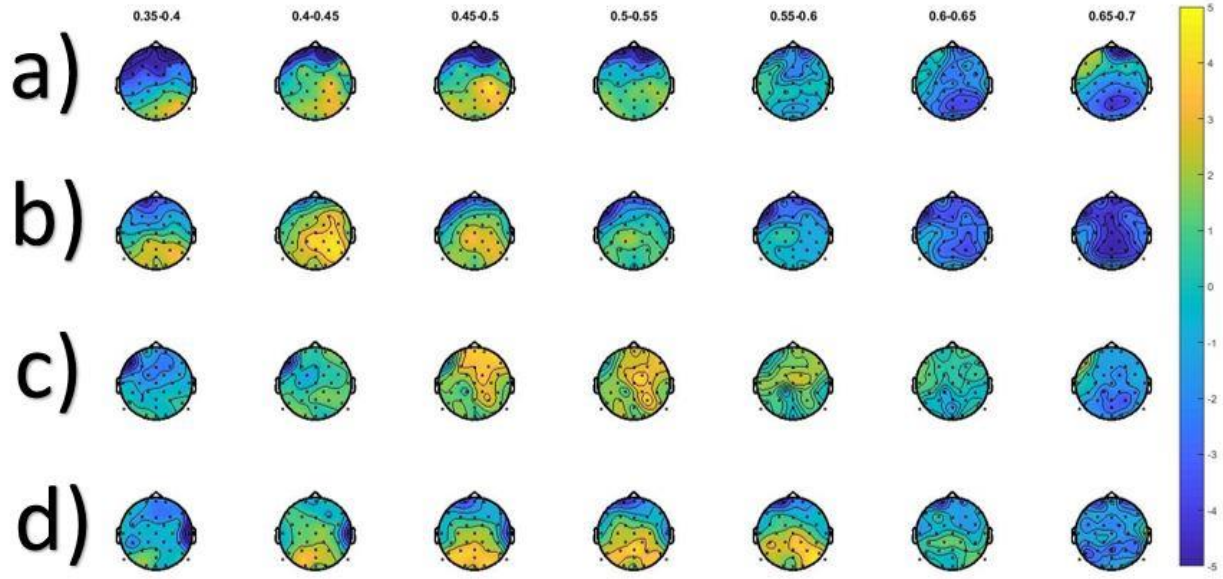

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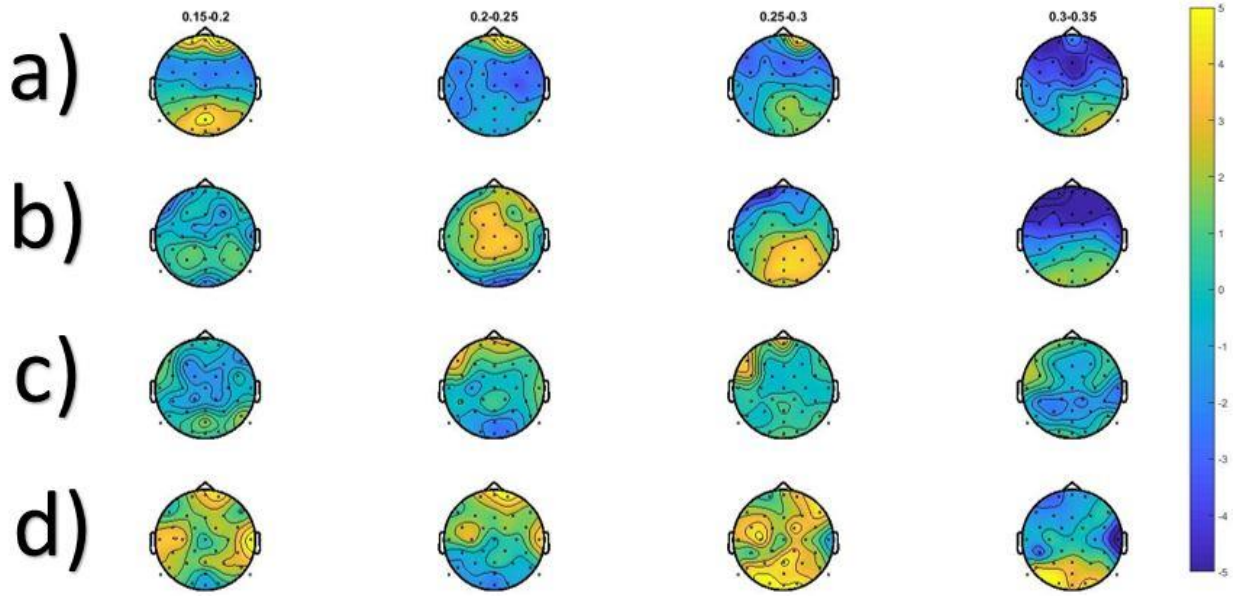
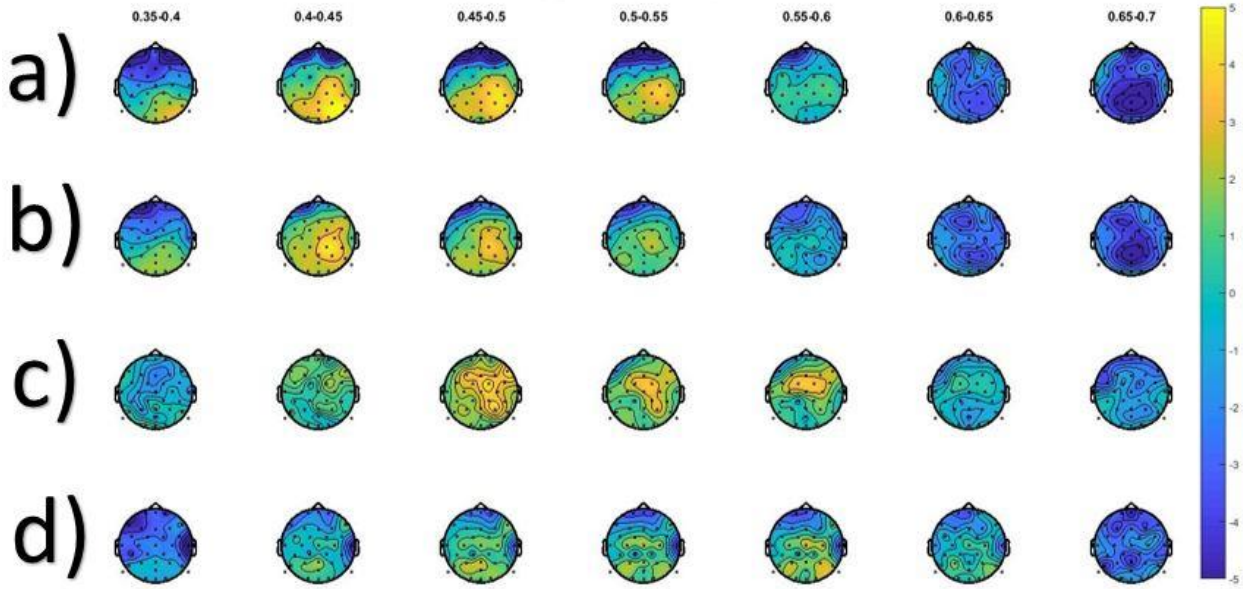


UDRO Topography for LPP



APPENDIX B

Facial Processing in Age Groups Questionnaire

Participant ID: _____

Age: _____

Biological sex: **M / F**

Ethnicity: _____

Hand dominance: **RIGHT / LEFT / BOTH**

Did you earn a high school diploma or GED? **Y / N**

Years of education past high school: _____

Visual acuity: _____ and I wear: **GLASSES / CONTACT LENSES / NONE**

Medications: _____

_____

History of seizures or mental illness: _____

_____

How well rested are you?

Sleep deprived 0 1 2 3 4 5 6 7 8 9 10 Very well rested

When did you last sleep? _____

For how long did you sleep? _____

Have you had caffeine or any energy drink today? **Y / N**

If you answered yes, what did you drink, when did you drink it, and how much did you drink?

_____

_____

Do you have an internal pacemaker, defibrillator, or other internal electrical devices? **Y / N**

EAST CAROLINA UNIVERSITY
University & Medical Center Institutional Review Board
4N-64 Brody Medical Sciences Building· Mail Stop 682
600 Moye Boulevard · Greenville, NC 27834
Office 252-744-2914 · Fax 252-744-2284 ·
www.ecu.edu/ORIC/irb

Notification of Initial Approval: Expedited

From: Biomedical IRB
To: Austin White
CC: Sunghan Kim
Date: 7/31/2018
Re: UMCIRB 18-001073
Facial Processing Across Age Groups

I am pleased to inform you that your Expedited Application was approved. Approval of the study and any consent form(s) is for the period of 7/31/2018 to 7/30/2019. The research study is eligible for review under expedited category #4. The Chairperson (or designee) deemed this study no more than minimal risk.

Changes to this approved research may not be initiated without UMCIRB review except when necessary to eliminate an apparent immediate hazard to the participant. All unanticipated problems involving risks to participants and others must be promptly reported to the UMCIRB. The investigator must submit a continuing review/closure application to the UMCIRB prior to the date of study expiration. The Investigator must adhere to all reporting requirements for this study.

Approved consent documents with the IRB approval date stamped on the document should be used to consent participants (consent documents with the IRB approval date stamp are found under the Documents tab in the study workspace).

The approval includes the following items:

Name	Description
Email Advertisement	Recruitment Documents/Scripts
Flyer	Recruitment Documents/Scripts
Informed Consent.docx	Consent Forms
Montreal Cognitive Assessment Test	Standardized/Non-Standardized Instruments/Measures
Participant Questionnaire	Surveys and Questionnaires
Protocol-2018-3.doc	Study Protocol or Grant Application

The Chairperson (or designee) does not have a potential for conflict of interest on this study.