

DOI: 10.36648/2171-6625.11.1.339

Effects of Healthy Aging on Semantic Processing of Familiar Faces

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Abstract

Neurodegenerative disorders such as Alzheimer's disease (AD) and mild cognitive impairment (MCI) remain significant health and economic burdens affecting millions worldwide. Developing affordable and accurate early diagnostic instruments for these disease states can contribute to the improvement of those patients's quality of life by providing sufficient time for individuals to begin preventative pharmacotherapies before AD/MCI symptoms ensue. The current study aims to examine the subtle changes in electroencephalogram (EEG signals) recorded from a cognitively healthy population (n = 21) of varying ages (aged 20- 72) to assess the effects of normal, healthy aging on semantic processing of familiar faces. Analysis of the results demonstrated that age had a significant effect on event-related potential (ERP) components such as the latency of P600 at electrode Pz which had a negative correlation with age ($p = -0.697$). Results from scalp current density (SCD) analysis supported these findings indicating that the semantic process of familiar faces was faster among older groups while the overall cortex activation was more prominent among younger groups. The findings from this study highlight potential neural biomarkers that may be used to differentiate healthy elderly populations from those affected by AD and MCI.

Keywords: Alzheimer's disease; Electroencephalogram; Event related potential; Mild cognitive impairment; Time-locked topography

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Citation: White AT, Williams PM, Mizelle JC, Kim S (2020) Effects of Healthy Aging on Semantic Processing of Familiar Faces. J Neurol Neurosci Vol.11 No.6:339

Received: July 09, 2020; **Accepted:** October 09, 2020; **Published:** October 16, 2020

Introduction

It has been estimated that 20% of individuals above the age of 60 develop a certain form of dementia, with Alzheimer's disease (AD) being the most common [1,2] is a neuro-degenerative disorder, characterized by a gradual cognitive decline that is likely a result of the accumulation of beta- amyloid plaques and tau neurofibrillary tangles occurring at the cellular level within the brain [3,4]. Mild cognitive impairment (MCI) is known as a transitional state to AD. MCI characterizes a memory deficit that extends beyond what is expected due to normal aging in healthy elderly populations [5]. It is critical to have reliable early-diagnostic tools for MCI since the brain damage resulting from AD is irreversible. Early detection of MCI and AD symptoms provides the opportunity to begin various interventions, such as medications and cognitive rehabilitation therapies, for those who are affected. The early detection of MCI and AD symptoms is likely to increase quality of life before more serious cognitive deficits ensue.

Currently, the primary method for detecting and diagnosing MCI is to administer various cognitive assessment tests. These

tests, however, can be subjective and may be influenced by the test administrators and/or the patient's age and educational background [6]. Additionally, these tests may require further diagnostic procedures such as functional magnetic resonance imaging (fMRI) or positron emission tomography (PET) to validate the initial evaluation. The need to validate the cognitive test assessments can be problematic because fMRI and PET methodologies are expensive, time-consuming and not available in many clinical centers. This may leave underserved communities without an opportunity to receive thorough assessments. Furthermore, fMRI and PET methodologies have a poor temporal resolution to examine the electrophysiological activities of the brain occurring at the millisecond level.

A shift to EEG can be a more desirable alternative methodology due to its cost- effectiveness, ease of use, and high temporal resolution; especially when it is necessary to for examining the cortical activities at the millisecond level. EEG is of the most practical options. The most common approach to studying EEG signals is the frequency-band analysis where a given EEG signal is split into different sub-frequency bands such as δ (0-4 Hz), θ

(4-8 Hz), α (8-12 Hz), β (12-30 Hz) and γ (>30 Hz). Although it does reveal insights into the cognitive states of the brain, this frequency-based approach is not suitable for studying the time-sensitive cognitive activities of the brain.

Over the last few decades, researchers have focused on the relationship between subtle changes in event-related potentials (ERPs) and cognitive functions [7,8]. ERPs are measured brain responses that result directly from an event (i.e., somatosensory, cognitive, or motor events) stimulus. It has been well established in literature that several components of ERPs (e.g., P300, N400) have prolonged latencies and reduced amplitudes associated with increasing age in healthy populations [9-11]. These increased latencies and diminished amplitudes have been described as older adults possessing fewer cognitive resources available combined with brain cortex degeneration and deficient cortical interconnections [12,13].

The late positive potential (LPP), which refers to a positive deflection occurring around 400 ms and 600 ms after the onset of a stimulus, is an important ERP component in studies of age-related long-term memory in the context of familiarity recognition. Wanager and his colleagues reported that the amplitude of the LPP was significantly suppressed in the MCI cohort during standard image recognition memory task in comparison to the healthy control group [14]. These age-related cortical alterations have been reported to produce tomographic anterior shifts with increasing age; resulting in increased activity of prefrontal regions and diminished recruitment of posterior regions during cognitive tasks in older populations [7]. Although prior research on aging and cognition has shown differences in processing across age groups, there is no known literature that details the most meaningful cortical biomarkers indicative of healthy aging.

This study focuses on semantic memory retrieval, which is sensitive to cognitive changes due to aging. Semantic memory has been defined as long-term memory or general decontextualized knowledge [15-17]. Common examples of semantic memory include remembering a friend's name and identifying famous figures such as presidents. With respect to healthy aging, numerous experiments have produced conflicting results on its effects on retrieval and storage of semantic memories. A few research studies reported that the effects of aging on semantic autobiographical memories were preserved among older adults [18,19]. Conversely, Chaby and his colleagues reported significant latency delays in middle-aged adults compared to young participants [20]. With respect to tomography of semantic memories, it has been reported that semantic retrieval activates the caudal portions of the hippocampal formation, left frontal cortex, left posterior temporal areas, and the right prefrontal cortex [21,22].

The objective of this study was to study the effects of healthy aging on semantic memory by examining several components of visually evoked ERPs including N170 (face-recognition), P300 (attention), N400 (semantic memory), and LPP (long-term memory). Specifically, our focus was on identifying

electrophysiological biomarkers of healthy aging by analyzing the correlation between age and the amplitude and latency of ERP components.

Research Methodology

Subject recruitment

A total of 28 participants above the age of 20 were recruited through email and flyer postings around the main campus of East Carolina University. Of the 28 enrolled, 7 participants did not meet the inclusion criteria or had a very poor signal quality and were therefore excluded from the analysis portion of the study. Preliminary mental/cognitive screening and informed consent was performed by two authors, who were graduate students. All participants were right-handed, completed at least 2 years of education past high school, and had normal-to-corrected vision. Subjects were excluded from the study if they were visually impaired, had an internal defibrillator or pacemaker, had a history of seizure disorder, has been diagnosed with depression, or were currently taking selective serotonin reuptake inhibitors or neuroleptic medications. Medications treating depression and sleep disorders have been shown to interfere with resting state brain activities and were therefore considered in the exclusion criterion. Additionally, subjects were excluded from the study if the participant was unable to provide their own informed consent to participate in the experiment. This study was approved by East Carolina University's Institutional Review Board (UMCIRB 18-001073).

Cognitive assessment

In addition to preliminary screening, a Montreal Cognitive Assessment test (MoCA) was administered to each of the subjects to assess their cognitive health. The MoCA test is a 30-point assessment that evaluates seven cognitive processes, including short-term memory recall, visuospatial abilities, abstraction, concentration and attention. Only those participants with MoCA scores above 26 were considered cognitively healthy and were included in the study. The participants enrolled in the study were only provided their MoCA scores after successful completion or withdrawal from study. Additionally, to de-identify participants in our study, an identity code was provided for each subject in the form of sequential numbers (i.e., Subject-001 and Subject-002). The two graduate students carrying out the experiment were trained by two certified nurses at East Carolina University's College of Nursing on how to correctly administer and score the latest version of MoCA (version 8.2).

EEG data collection

Following initial screening and the MoCA questionnaire, the subjects were seated in a chair and fitted with an electrode cap containing 32 gold-plated, dry electrodes (g.SAHARA, g.tec, Austria). To ensure standardized classification of electrode locations during the analysis, the electrodes were placed according to the 10-20 international system (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). Recorded data

from these electrodes were then amplified and acquired utilizing a g.US Bamp amplifier (g.tec, Austria). Then, the amplified biosignals were transferred via USB to a secured laptop running BCI-2000 where the data was stored for post-processing.

Each participant was seated five feet away from a computer monitor and instructed by the experimenter as to the protocol of the test. The participant focused on a series of familiar faces, unfamiliar faces, and non-facial images (i.e., ordinary objects) acting as the visual stimuli. The familiar facial stimuli included president and celebrity portraits of Barack Obama, Donald Trump, Dwayne Johnson, and Robert Downey Jr. while unfamiliar facial stimuli were composed of 16 faces found on Google Images whose rights were labeled for reuse. To ensure all participants recognized the familiar faces, individuals were presented each of the famous faces prior to being fitted with the EEG cap and were asked to recall the name of each. All facial stimuli were cropped to exclude head hair, ears, and necks and were selected to only display neutral expressions as illustrated in **Figure 1**. Non-facial stimuli included 8 random objects (e.g., flowers, clocks) that were cropped to the same oval shape as the above-mentioned faces. All stimuli were converted to gray scale and filtered to have identical brightness values to ensure homogeneity. A total of 28 stimuli were included in the study paradigm. ERPs were elicited from participants by randomly presenting each stimulus 5 times (utilizing the oddball paradigm) with stimulus durations of 500 ms and inter-stimulus intervals of 1,500 ms as depicted in **Figure 1**. The participants were exposed to each of the stimuli in a random sequence following the oddball paradigm. They were instructed to click the left mouse button with their dominant hand each time a familiar face was presented and to perform a right mouse button click each time an unfamiliar or object stimuli was presented. Finger taps were recorded utilizing a free-to-use click counter to ensure that all participants understood the protocol of the study and were in fact able to distinguish between familiar and unfamiliar/object stimuli. Each trial lasted for approximately 7 minutes per participant after learning the protocol, completing the MoCA questionnaire, and being fitted with the electrode cap and testing for proper impedance values ($< 5\Omega$). The entire experiment lasted approximately 50 minutes per participant.

Data processing

Raw data collected during trial sessions were then processed utilizing the open-source MATLAB software toolbox EEGLAB [23]. Data was separated into each of the stimulus types (i.e., facial vs. non-facial) and then epoched into 800 ms blocks (0- 800 ms post stimulus onset). Individual epochs for each stimulus type were then averaged, obtaining an average ERP for each subject per stimulus type per channel. The subjects were then separated into four age groups: Young (20-25 y/o), Low-mid (26-40 y/o), High-mid (41-59 y/o), and Old (60+ y/o) and additional averaging was completed to obtain a grand average ERP per age group per stimulus type per channel.

In addition to the resulting waveform analysis from the grand averaged ERPs, the processed/epoched EEG data was fed into another open-source MATLAB software toolbox Fieldtrip,

which includes various algorithms for advanced analysis of electrophysiological data such as EEG [24]. From the Fieldtrip results, regions of greatest activation were acquired, providing other possible features for displaying age-related topographical differences across each of the age groups.

Data analysis

Channel-specific ERP analysis: The latency and amplitude values, i.e., features, of several ERP components, i.e., N170, P300, N400, and LPP, were extracted from the maximum peak or minimum trough of each participant's average ERP occurring during specified ERP component time windows (e.g., 250- 400 ms post stimulus onset for P300 classification). **Table 1** lists the time windows of four ERP components analyzed in our study.

Eight potential biomarkers (two features \times four ERP components) were extracted from each subject's average ERP per channel, which was elicited by familiar faces. Since the number of EEG channels was 32, the total number of potential biomarkers per subject was 256. The correlation between each of those potential biomarkers and the subjects' age was calculated in order to study the effects of healthy aging on semantic memory.

Topographic ERP analysis: Time-Locked Topography: Along with the conventional channel-specific ERP analysis, a more advanced topographic ERP analysis was adopted to illustrate a holistic view of cortical activities over the scalp. Unlike the conventional channel-specific ERP analysis the time-locked topography (TLT) method displays the spatial voltage distribution across the entire scalp by collectively analyzing ERP signals from all electrode channels via interpolation algorithms. The purpose of adopting the TLT method was to examine how the topographic patterns of ERP signals reflect the age-dependent trend of the channel-specific ERP features, i.e., latency and amplitude.

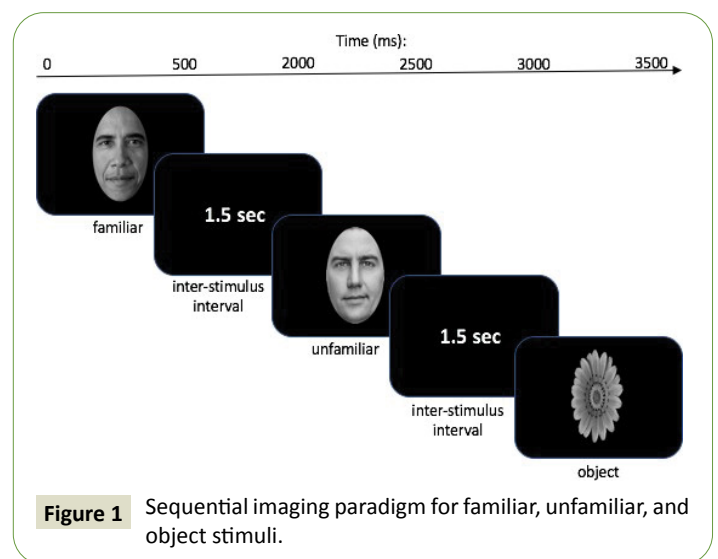


Table 1 A list of ERP components and their corresponding time windows.

Component Name	N170	P300	N400	LPP
Time Window (ms)	120-200	250-400	250-500	400-650

Correlation analysis

Correlation analysis is a simple statistical method that can be used to evaluate the strength of the linear relationship between two variables. Correlation analysis is not designed to determine a cause and effect relationship between two variables. In our study, however, the cause and effect relationship between variables doesn't need to be addressed since age is the independent variable and biomarkers extracted from ERPs are dependent variables. In order to determine the effects of healthy aging on semantic processing of familiar faces, we examined the Pearson correlation coefficient, r , between the subject's age and each of the 256 potential biomarkers described in Section II-E-1. The p -value of the correlation test was also calculated to determine whether the correlation between age and the biomarkers is truly significant meaning that the p value is not zero.

SPSS Statistics 24 (IBM) was used to perform correlation analysis. Additionally, a linear regression line was fitted to a scatter plot of age versus each potential biomarker in order to better illustrate the relationship between them.

Results

Channel-specific ERP analysis

The channel-specific ERP analysis utilizing the Pearson correlation coefficient identified two ERP-based biomarkers, which were well correlated with the subjects' age, among the 256 potential biomarkers. The first biomarker was the latency of LPP of ERPs for familiar face stimuli at electrode Pz. **Figure 2** illustrates each of four age groups' grand-average ERP waveforms for familiar face ERPs at electrode Pz. The LPPs of the high-mid (yellow) and old (green) age groups peaked significantly earlier than those of the young (blue) and low-mid (red) age groups did. This trend is better illustrated in the scatter plot of each subject's age (x-axis) versus the latency of LPP of each subject's average ERP (y-axis) as shown in **Figure 3**. The regression line was fitted to the scatter plot to better illustrate the negative trend. This strong negative trend, which indicates that the latency of LPP decreased as age increased, yielded the Pearson correlation coefficient value of -0.697 and the p -value of virtually 0.

The second biomarker was the amplitude of LPP of ERPs elicited by familiar face stimuli at electrode Cz. **Figure 4** shows that the young (blue) age group's grand-average ERP waveform had the largest LPP component while the high-mid (yellow) and old (green) age groups' grand-average ERP waveforms had substantially smaller LPP components. The scatter plot shown in **Figure 5** indicates that the LPP amplitude of the individual subjects' average ERPs indeed become smaller as age increases. The initial Pearson correlation coefficient value was -0.301 with the p -value of 0.185 indicating the correlation between age and the amplitude of LPP component was not strong enough to be statistically significant. However, the Pearson correlation coefficient value was -0.464 with the p -value of 0.03 when only two "outliers" in the red circles were removed from the analysis. The grand-average ERP waveforms of four age groups shown in **Figure 4** may appear to indicate that the latency of LPP of the

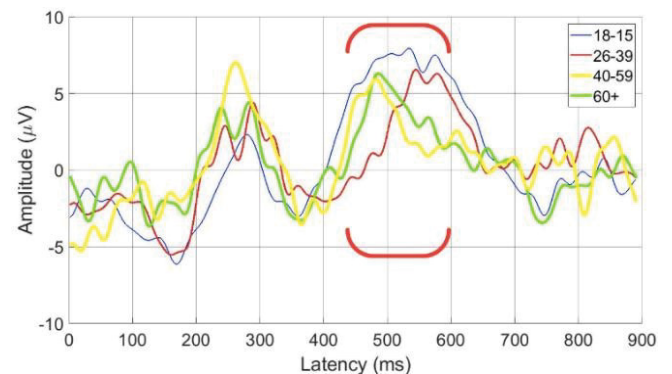


Figure 2 Grand-average familiar face ERP recorded at electrode Pz for young (blue), low-mid (red), high-mid (yellow), and old (green) groups.

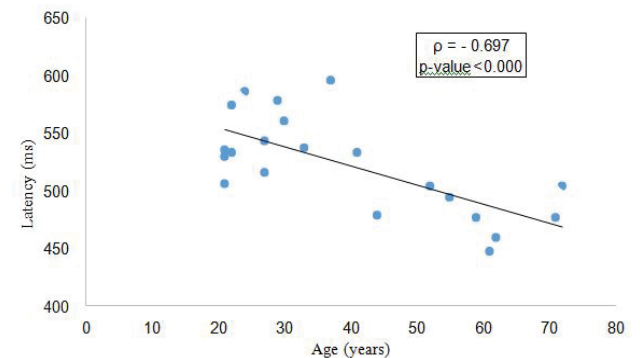


Figure 3 Familiar face LPP latency (y-axis) for each participant recorded at electrode Pz.

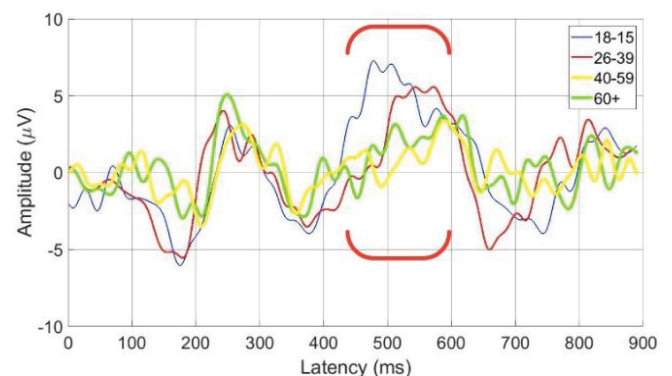


Figure 4 Grand-average familiar face ERP recorded at electrode Cz for young (blue), low-mid (red), high-mid (yellow), and old (green) groups.

grand-average ERP waveforms is positively correlated with the subjects' age. However, our correlation analysis based on the individual subjects' average ERPs did not reveal any significant correlation between the LPP latency and age at channel Cz.

Topographic ERP analysis: Time-locked topography

The age-dependent trend of the channel-specific biomarkers

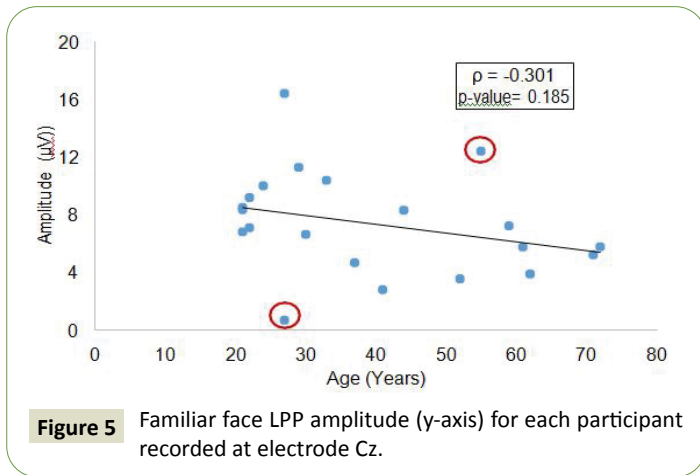


Figure 5 Familiar face LPP amplitude (y-axis) for each participant recorded at electrode Cz.

reported in the previous section is limited only to examine spatially localized brain activities. The time-locked topographic (TLT) method was aimed to study whether the topographic patterns of ERP signals across the entirety of the scalp actually reflect the age-dependent trend of the channel-specific biomarkers.

Figure 6 depicts the topographic maps of grand average ERPs of four groups between 400 and 600 ms post-stimulus onset in 25 ms time increments. The peak activation (bright yellow) of LPP occurred much earlier (450-500 ms) in the old (bottom) group than the young (top) group (525-575 ms). The TLT result was congruent with the correlation analysis result shown in **Figure 2** where the LPP latency decreased as age increased.

Figure 7 illustrates the topographic maps of grand average ERPs of four groups over the entire LPP period (400-600 ms post-stimulus onset) showing the averaged brain activity level along the scalp. The young group had a greater activation across the parietal lobe.

Discussion

P600 latency familiar face Pz

From the ERP analysis on familiar face stimuli shown in **Figure 3**, a very strong negative correlation between age and the LPP latency at Pz (p of -0.697 with the p -value of virtually 0) was observed. The TLT analysis shown in **Figure 6** demonstrated a similar trend of earlier peak activation occurring for the older groups compared to younger groups supported. These findings may indicate that as we get older, the processing speed of familiar face recognition becomes faster and requires fewer neural resources to be recruited. This assertion comes from findings that older individuals rely on holistic processing of faces more so than younger populations [25]. In spite of the small sample size (i.e., 21 subjects), it appears to be a compelling argument that the LPP latency for familiar facial processing is a reliable neurophysiological biomarker indicative of healthy aging due to its high correlation and corroboration with TLT analysis.

It is worth noting that the most activated area during the LPP period, which was marked in the red oval in **Figure 6**, was mainly the medial parietal region. This region corresponds to Brodmann's area 5 and area 7 which were theorized by Sommerhoff to be associated with language use and generating

conscious construction of objects in space [26]. It is possible that the LPP component in our study reflected the activation of these two Brodmann's areas as the study participants were recalling the name of each celebrity whose face was shown to them and remembering three-dimensional facial features of those familiar faces.

Another interesting finding from the TLT analysis result show in **Figure 6** was the prolonged activation (i.e., 450-575 ms) of the LPP component among the young group. It may imply that younger individuals took more time to process familiar faces than older adults, although this argument is quite controversial in the literature [8,20] and may require follow-up experiments with a larger sample size to be validated.

P600 amplitude familiar face Cz

The LPP amplitude for familiar faces at electrode Cz was weakly correlated with age (Pearson correlation coefficient value p of -0.301 and the p -value of virtually 0.185). Although the numerical correlation analysis result seemed to indicate a nominal correlation between age and the LPP amplitude, the regression line shown in **Figure 5** suggested that the LPP amplitude did decrease as age increased. As a matter of fact, the correlation between age and the LPP amplitude became statistically significant (p value of -0.464 with the p -value of 0.03) when two "outliers" marked in the red circles were removed from the analysis. Given the small sample size it may be arguable that those two samples were truly outliers. Nevertheless, the TLT analysis result in **Figure 6** suggested that within the LPP time window the sustained high level of cortical activity was present only in the young group not in any other age groups. Also, the grand average ERPs (blue) of the young group at Pz and Cz shown in **Figure 2** and **Figure 4**, respectively, were greater in their amplitude than those of the other age groups during the LPP time window. These results hint towards the age-related decrease of the amplitude of LPP component in the semantic process of familiar faces.

Limitations

A major limitation of this study was the low sample size ($n = 21$) which likely resulted in the low correlation for many of the

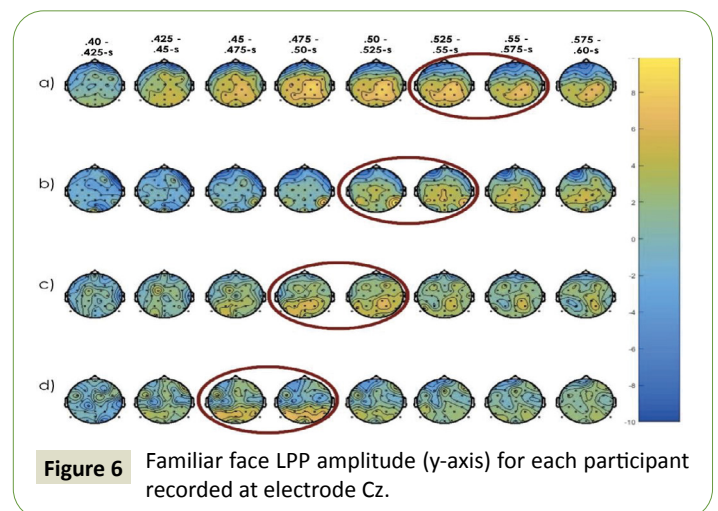


Figure 6 Familiar face LPP amplitude (y-axis) for each participant recorded at electrode Cz.

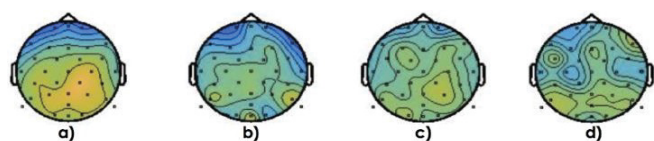


Figure 7 TLT of grand average P600 response for a) Young, b) Low-mid, c) High-mid, and d) Old age.

ERP components discussed. It is likely that less significant ERP components ($p < 0.4$) would be revealed as highly correlated with age if the current sample size were increased by one order of magnitude. Future studies therefore recommend recruiting a higher number of individuals across all age groups to obtain greater statistical power. Another limitation was the use of a 32-electrode EEG system, lowering the accuracy of time-locked topography analysis due to interpolation of current values between electrodes. Future studies should attempt to utilize 64- or 128-electrode systems if operating inverse solutions to their EEG data. Interestingly, despite the few electrodes utilized, the two channels that revealed correlation with age were P600 ERPs at Cz and Pz electrodes, sites previously found to be linked with semantic memory storage and retrieval [26]. Additionally, it should be noted that time-locked topography measures only voltage fluctuations occurring at the very surface of the cortex, decreasing the accuracy of recordings below the cortex. Future studies should attempt to implement techniques such as Low

Resolution Brain Electromagnetic Tomography (LORETA) and scalp-current density (TLT) to reveal depth and current-source density information from EEG waveforms.

Conclusion

The findings from this experiment illustrated two ERP components that may serve as reliable biomarkers to show healthy aging effects on semantic processing. Although five ERP components revealed statistical correlation with age, TLT analysis revealed that only P600 latency and P600 amplitude for familiar faces presented clear differences between age groups. The major findings from this study suggest that as age increases, both latency and amplitude of familiar facial processing decreases across the cortex. Additionally, this study suggests that more advanced EEG analysis techniques are required to uncover reliable cortical biomarkers of healthy aging effects on cognition. From simple single-channel ERP analysis, several ERP components were revealed that did not show major differences across the cortex, highlighting the importance of inverse solutions such as TLT on ERP analysis. The study revealed potential differences in cognition that are associated with healthy aging which may eventually serve as a comparison in future studies where semantic processing is assessed in cognitively diseased populations (e.g., AD, MCI, dementia, etc.) These findings serve as the beginning stages of developing a non-invasive cognitive assessment tool capable of differentiating healthy and diseased populations through quick EEG measurement.

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