Brain vital signs:
Auditory to Visual Translation

by

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Abstract

An objective measure is greatly needed to monitor the impacts of injury or disease on our brain health. In order to provide such a measure, the brain vital sign framework utilizes an established, non-invasive, and physiology-based technology, Electroencephalogram (EEG), along with a rapid auditory sequence used to elicit and assess specific markers of cognitive function (marked by event-related potentials (ERPs)). To date, applications for brain vital signs have included evaluation of cognitive function in healthy and patient populations. To expand the applications, this study aims to translate the established rapid auditory sequence to a visual based assessment. The objectives are to: 1) demonstrate the viability of visual brain vital signs assessment and 2) examine the differences between the two modalities. EEG data was collected in 30 healthy adults (33±14yrs) and analyzed at central electrodes. Similar to the interlaced auditory sequence, the visual sequence utilized an oddball paradigm (standard vs. deviant stimuli) to evoke a sensory (N100) and attention (P300) response, and a word pair paradigm (congruent vs. incongruent stimuli) to evoke a semantic language response (N400). Comparison of mean amplitudes between stimuli revealed the targeted ERPs were successfully evoked in the visual modality at a group-level as expected (N100: $p < 0.001$; P300: $p < 0.0001$; N400: $p = 0.0105$). Attention processing (P300) was found to be the most transferrable across modalities, with no group-level differences and correlated peak amplitudes (rho = 0.7, $p = 0.0001$) across individuals. Auditory P300 latencies were shorter than visual ($p < 0.0001$) but normalization and correlation ($r = 0.5$, $p = 0.0033$) implied a potential systematic difference across modalities. Reduced auditory N400 amplitudes compared to visual ($p = 0.0061$) paired with normalization and correlation across individuals ($r = 0.6$, $p = 0.0012$), also revealed potential systematic modality differences between reading and listening language comprehension. This study provides initial understanding of the relationship between the visual and auditory sequences, while importantly establishing a visual sequence within the brain vital signs framework as a potential translational tool to monitor brain health over the human lifespan in broader populations, such as those with hearing impairments, congenital or due to injury or aging.

Keywords: EEG; ERPs; evoked potentials; vital signs; cognitive processing; cognitive neuroscience

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List of Acronyms

EEG	Electroencephalogram
ERP	Event-related Potential
BVS	Brain vital signs
HCS	Halifax Consciousness Scanner
MCI	Mild Cognitive Impairment
mTBI	Mild Traumatic Brain Injury
ICA	Independent component analysis
ISI	Inter stimulus interval
IBI	Inter-block interval
PSP	Post-synaptic potentials

Executive Summary

An objective measure is greatly needed to monitor the impacts of injury or disease on our brain health. In order to provide such a measure, the brain vital sign framework utilizes an established, non-invasive, and physiology-based technology, Electroencephalogram (EEG), along with a rapid auditory sequence to assess specific markers of cognitive function. To date, applications for brain vital signs have included evaluation in healthy and patient populations (i.e. strokes, traumatic brain injury, and mild traumatic brain injury). To expand the applications, this project aimed to translate the established rapid auditory assessment to a visual based assessment. This project demonstrated the viability of visual brain vital signs assessment and examined the differences between the two modalities. The addition of a visual assessment within the brain vital signs framework will allow for monitoring brain health over the human lifespan in broader populations in need, such as those with hearing impairments, congenital or due to injury or aging.

Chapter 1.

Introduction

Standardized measures of function exist for our hearts through an easily accessible and quick test, blood pressure. However, for our brain, such an essential and vital assessment is not yet widely accessible. Cognitive assessments that rely on behaviour-based measures have been traditionally used to assess the state of our brain function, however, they are subjective and not always reliable (Gawryluk, D'Arcy, Connolly, & Weaver, 2010). Due to the critical need for a physiological and unbiased cognitive function assessments, extensive research has been done leading up to the development of the brain vital signs framework (J F Connolly & D'Arcy, 2000; Gawryluk et al., 2010; Ghosh-Hajra et al., 2016; Sculthorpe-Petley et al., 2015). The brain vital sign framework utilizes Electroencephalography (EEG) technology and a rapid, auditory sequence to measure markers of specific cognitive functions. While other neuroimaging technologies, such as functional magnetic resonance imaging (MRI) or Magnetoencephalography (MEG), have provided powerful objective physiological measures of brain activity, EEG is a portable, lower-cost technology that provides easily accessible and practical measures of brain function. EEG is an established brainwave technology that has demonstrated a resurgence of potential in clinical applications for evaluating the neural basis of cognitive functioning (J F Connolly & D'Arcy, 2000). EEG technology has thus far been used in our past research to monitor cognitive function in patients with disorders of consciousness, and acquired brain injuries (i.e. strokes and traumatic brain injuries) (HCS; D'Arcy, Hajra, Liu, Sculthorpe, & Weaver, 2011; Fleck-Prediger, Hajra, Dick, & Gray, 2015; Sculthorpe-Petley, Liu, Hajra, et al., 2015). The brain vital sign framework more recently has been used to measure changes in cognitive function in healthy adults across different age groups, as well as monitor cognitive impacts of mild traumatic brain injury (mTBI) (Ghosh-Hajra et al., 2016; Fickling et al., 2018). Properly understanding the effects of impairment or injury on cognitive function is essential for effective intervention and management strategies. The initial and established assessment utilizes a rapid, auditory sequence to assess sensory, attention and language

(semantic) processing. Similar brain processing can be monitored using the visual modality. Therefore, the application of brain vital signs can be expanded in order to provide critical assessment and monitoring of brain health in populations that have hearing impairments.

The goals of this thesis are:

1. To provide background information on EEG, ERPs, the evolution of brain vital signs and EEG/ERP analysis techniques;

2. To present and discuss the study carried out, which aimed to:

   a) Translate the established, rapid, auditory brain vital signs sequence into a rapid, visual sequence and validate it through neuroanatomical event related potential (ERP) response characterization; and

   b) Evaluate differences of the levels and speeds of cognitive processing being evoked at a group level between auditory and visual processing, as well as the relationship of processing level and speed within individuals across modalities.

1.1. Electroencephalography (EEG)

Hans Berger obtained the first human Electroencephalography (EEG) recording in 1929 and ever since it has been used extensively in research and clinical settings evaluating cognitive functioning. This well-established technology's strengths lie in being non-invasive and having better time resolution (milliseconds) compared to other neuroimaging technologies (i.e. fMRI).

EEG measures voltage (electrical potential) changes over time, at the electrodes placed on the scalp. The neurophysiological source of voltage fluctuations originates from voltage changes across a neuron's cell membrane caused by either an action potential (AP) or postsynaptic potential (PSP). An AP occurs when voltage changes travel from the start of the axon at the cell body to the axon terminals, where neurotransmitters are released. Due to the short duration, asynchronous timing of individual APs, and the physical arrangement of axons, APs often cancel each other out and are mostly not detectable at the scalp surface (Gawryluk et al., 2010; Steven J. Luck,

2014, pp.12-13). A PSP occurs when neurotransmitters bind to the post-synaptic cell's membrane, causing ion channels to either open or close (Steven J. Luck, 2014, pp. 12-13; see review paper Jackson & Bolger, 2014). This produces a change in extracellular voltage, which can create separated regions of positive and negative charge, forming a dipole. A single neuron's activity is too small to be measured as far away as the scalp electrodes; hence the EEG signal measured at the scalp arises from a summation of dipoles from multiple proximal neurons. The main input-output cells of the cerebral cortex, cortical pyramidal neurons, are thought to produce most of the measured EEG signals because they tend to be organized in parallel fashion perpendicular to the cortical surface along cortical columns, and tend to have synchronized synaptic activity (Jackson & Bolger, 2014; Gawryluk, J. R., and D'Arcy, R. C. N., 2010, pp 24-1 – 24-3). Therefore, instead of cancelling each other out, these neurons can summate into a larger dipole, known as an equivalent current dipole. These summated dipoles are large enough to create a voltage field throughout the head, which propagates through volume conduction to the scalp electrodes, passing through several layers of the brain, dura layers, skull layers, the scalp, and electrode gel. At the electrodes, a deflection of voltage difference compared to the reference is recorded as either positive or negative deflections, depending on the region of the scalp. Different dipoles around the brain can sum together as they propagate to the surface. Therefore, the waveforms we record at the surface electrodes is potentially a summation of different underlying patterns of positive and negative peaks (Steven J. Luck, 2014, p. 43).

1.1.1. Event-related potentials (ERPs)

The evolution of inexpensive computers has allowed continuous EEG waveforms to be recorded alongside timing of stimulus events, resulting in conditional segmentation and averaging (see Figure 1.1). This signal averaging technique allowed researchers to capture certain cognitive processing, rapidly becoming a crucial tool for cognitive neuroscientists (Woodman, 2010). These time-locked stimuli specific responses are extracted from the continuous EEG signal through segmentation, and referred to as event-related potentials (ERPs) waveforms (see Figure 1.1). An ERP waveform therefore represents the average pattern of response measured from a particular stimulus or

response. From these waveforms, researchers look at ERP components, which are identified by their: polarity (positive or negative voltage), timing, scalp distribution and sensitivity to task manipulations. For instance, the N100, is a component known to have a negative going peak around 100ms in response to changing sensory input. Traditionally, ERP components are identified by these factors. However, these factors do not necessarily fully define an ERP component, but they do serve as physiological markers for specific cognitive processes, allowing for easy communication across studies, paradigms and scientific fields (Steven J. Luck, 2014).

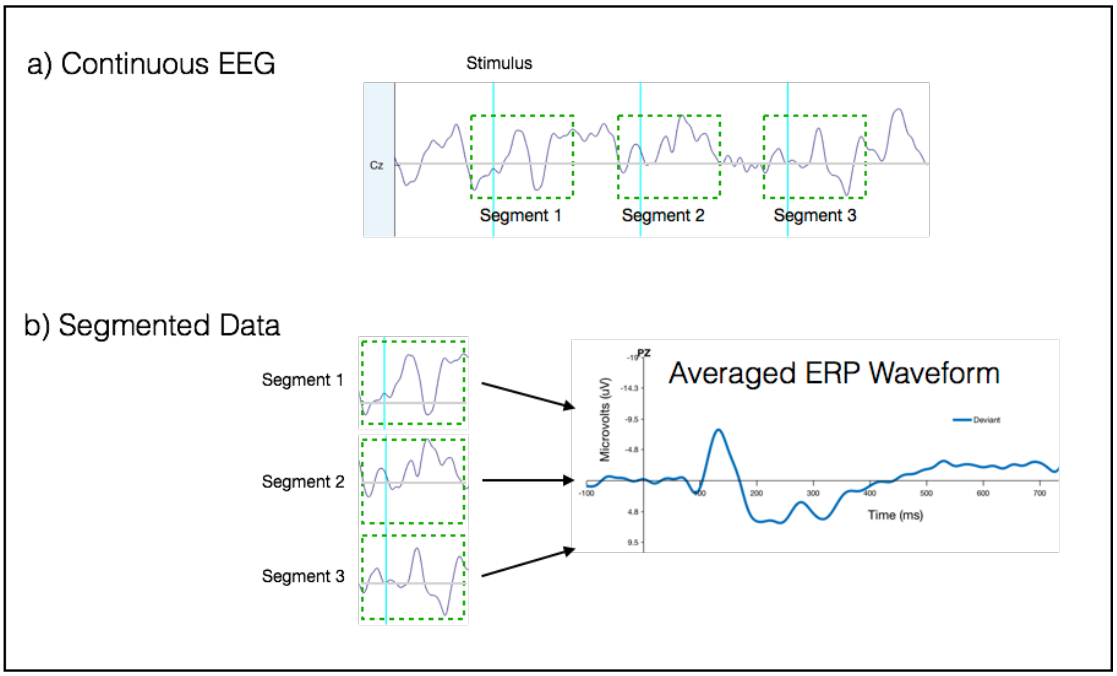

Figure 1.1. Process of taking continuous EEG data to averaged ERP waveforms, through segmentation around stimulus markers and averaging.

Defining an ERP component conceptually and operationally can be difficult when taking into account what the EEG data actually represents and how it associates with cognitive functioning and neural sources. As discussed above, the source of the recorded voltages to particular stimuli, ERPs, is from the synchronous and summed PSP activity of one or more large groups of aligned cortical pyramidal neurons, forming several equivalent current dipoles from several different unknown neuroanatomical sources. An observed waveform, showing an ERP, could be considered the same thing as an equivalent current dipole, if it is from a single functional brain region; however, this is

not often the case. In some instances, components have been separated into sub-components because it was found that they consisted of more than one identifiable individual underlying component. Other current components may in the future also be spilt, but for now methods have not yet developed to isolate the potential individual subcomponents (Steven J. Luck, 2014). Therefore an ERP, represented by a set of voltage changes, may be initially assumed to be from just one specific neuroanatomical generator source, but consideration that it may represent a summation of activity from potentially several large groups of neurons (dipoles) around the brain is needed (Handy, 2005; Steven J. Luck, 2014). To help narrow the operational definition of an ERP, Luck (2014) builds on Donchin et al., (1978) statement that an ERP component should vary systematically across different factors such as experimental conditions, age, time, etc. (Steven J. Luck, 2014, pp. 67-68)). Hence, by carefully following methods used to previously elicit specific responses, and recognizing converging evidence, expected scalp-recorded ERPs can be isolated and identified.

Despite some newer neuroimaging technologies, there are several advantages of the established EEG/ERP technique, which continue to make it one of the most widely used methods to study cognitive processing. ERPs have particular strengths in millisecond temporal resolution during information processing and are more sensitive to subtle cognitive dysfunctions with better test-retest reliability than current standardized cognitive tests (Broglio, Moore, & Hillman, 2011; Segalowitz & Barnes, 1993; Williams, Simms, Clark, & Paul, 2005; Cassidy, Robertson, & Oapos; Connell, 2012). The practical features of being non-invasive, accessible, low-cost, and portable, make EEG technology particularly well-suited for point-of-care and clinical applications (Gawryluk et al., 2010; Ryan C N D'Arcy et al., 2011; Giacino, Fins, Laureys, & Schiff, 2014; Sculthorpe-Petley et al., 2015; Ghosh-Hajra et al., 2016).

1.2. Evolution of Brain Vital Signs

ERPs have been extensively studied in research; however, clinical applications have been limited, despite the critical need for objective measures of brain health. Over the last 20 years, researchers have worked to fill this critical gap by combining the

extensive ERP research with standardized neuropsychological tests to develop new diagnostic tools utilized in both healthy and patients populations (J F Connolly & D'Arcy, 2000; D'Arcy et al., 2003, 2011; Yannick Marchand, D'Arcy, & Connolly, 2002; Sculthorpe-Petley et al., 2015; Ryan C.N. D'Arcy, Connolly, & Eskes, 2000; Kotchoubey et al., 2005; Yannick Marchand, Lefebvre, & Connolly, 2006; Wijnen, van Boxtel, Eilander, & de Gelder, 2007). The translation process of ERP research into clinical application, gave rise to rapid, automated tools, such as the Halifax Consciousness Scanner (HCS; D'Arcy et al., 2011; Fleck-Prediger, Hajra, Dick, & Gray, 2014; Sculthorpe-Petley et al., 2015) and more recently, brain vital signs (Ghosh-Hajra et al., 2016). These applications have successfully utilized key ERPs to identify specific cognitive processes, providing a way to address the critical gap in bringing EEG/ERP research to clinical applications.

The Halifax Consciousness Scanner (HCS) was initially developed as a rapid evaluation of neurological status after severe acquired brain injuries (principally traumatic brain injury and stroke) (D'Arcy et al., 2011). This provided a needed alternative to other subjective, behaviour-based tests that were used to measure individual brain function in acquired brain injury patients and non-responsive patients (i.e. coma, vegetative state, minimally conscious state, and locked in syndrome) (Gawryluk et al., 2010). Behaviour-based tests tend to be subjective and not very effective because they rely heavily on the capacity of a patient to produce certain responses, which may be limited or not possible (J F Connolly & D'Arcy, 2000). The HCS provided a powerful alternative to other common tests, such as the Glasgow Coma Scale (GCS), to evaluate the level of conscious awareness and wakefulness following brain injury (D'Arcy et al., 2011; Fleck-Prediger et al., 2015). The HCS established auditory-based methods to examine five key ERP responses linked to sensation (N100), perception (mismatch negativity, MMN), attention (P300), memory for one's own name (early negative enhancement, ENE), and semantic speech processing (N400). The initial framework was established by measuring and validating ERPs across a large sample of healthy individuals as well as monitoring individual changes in brain function over time, possibly related to dysfunction (Sculthorpe-Petley et al., 2015; Fleck-Prediger et al., 2014).

Building on the HCS research and findings, the brain vital signs framework was developed to measure and monitor brain health and function effectively over time, by developing a simpler sequence and translating the ERPs into accessible scores (Ghosh-Hajra et al., 2016). Using a rapid 5 minute auditory sequence to evoke 3 key ERP components, Ghosh-Hajra et al. (2016) confirmed the ERPs at a group and an individual level across two groups, 20-30yrs old and 50-85yrs and demonstrated successful linear transformation to create brain vital sign scores (Ghosh-Hajra et al., 2016). The brain vital signs sequence focused on three well-established ERPs: 1) the N100 (sensory processing), 2) the P300 (attention processing) and 3) the N400 (semantic processing). By comparing the amplitude and latency of each of the 3 ERP components to a normative database, brain vital sign scores for each participant were then generated. Providing scores allows for easily comparable, objective measures over time; individual functional "baselines" of brain health prior to conditions of dysfunction provides effective longitudinal brain health monitoring. Recent findings have demonstrated that the brain vital signs framework has increased sensitivity to cognitive changes due to injury, such as concussions (Fickling, Smith, Pawlowski, & Ghosh-Hajra, 2018).

1.2.1. Brain Vital Signs: Why Auditory to Visual?

Brain vital signs research has shown the value of monitoring brain health with age or injury (Ghosh-Hajra et al., 2016; Fickling, Smith, Pawlowski, & Ghosh-Hajra, 2018) and has great potential in further addressing the need for objective clinical tools to measure and track brain function in wider populations, such as those with hearing impairments, either congenital or due to age or injury (i.e. blast injury). This is of great importance, with Canada's increasing aging population—older adults (65+ year old) now outnumbering youth (<14years old) (Grenier, É. 2017), where 20% of these older adults suffer from hearing loss (Speech-Language & Audiology Canada, www.sac-oac.ca). Initial work with only auditory testing available for older adults proved to be difficult and limited the accessibility. The development of a visual sequence, mirroring the auditory design, is the next step in expanding the reach of brain vital signs. The visual sequence can be designed to target the same key cognitive processes (sensory, attention and

semantic) as in the auditory method. A visual version of brain vital signs will provide a further tool to monitor and track potential risks or impacts on cognitive function.

1.3. Background of brain vital signs components: N100, P300 and N400

1.3.1. Sensory Processing (N100)

Sensory components, such as the N100, known as exogenous, are obligatory responses triggered by external stimuli. The underlying mechanism of basic sensory processing differs across modalities; sound processing occurs in the auditory cortex (temporal lobe) compared to visual processing occurring in the visual cortex (occipital lobe). Conversely, the N100 does reflect similar types of primary sensory processing across modalities, such as selective attention to basic stimulus characteristics, initial selection for later pattern recognition, and intentional discrimination processing (Vogel & Luck, 2000). The N100 also has a similar polarity and ordinal position across modalities (Luck, 2005).

The auditory evoked N100 component has been used as a reliable and objective physiological measure of auditory function (Gawryluk et al., 2010; Martin, Tremblay, & Korczak, 2008). Previous research has typically used an oddball paradigm, containing frequent tones and rare deviant tones to look at discrimination processing, where an N100 response is present to both standard and deviant stimuli but increased amplitudes in response to deviant stimuli (Sculthorpe-Petley et al., 2015). The visual N100 has been evoked using similar paradigm structures with standard and deviant stimuli, where physical features of the visual stimuli are changed. Studies have shown that the N100 amplitude and latency is affected by spatial attention, and certain visual parameters, such as stimulus angularity and luminance (Ito, Sugata, Kuwabara, Wu, & Kojima, 1999; Johannes, Munte, Heinze, & Mangun, 1995). Studies have used increased brightness of stimulus flashes to show shortening N100 peak latencies (Carrillo-de-la-Peña, Rodríguez Holguín, Corral, & Cadaveira, 1999; Johannes, Munte, Heinze, & Mangun, 1995). The visual N100 can also be affected by attention to spatial locations, with greater amplitudes in response to stimuli in attended vs. unattended locations (Luck, Heinze, Mangun, &

Hillyard, 1990). Certain discrimintation tasks, rather than detection tasks have also shown larger amplitude responses (Vogel & Luck, 2000). Other factors, such as age have also shown to influence the visual N100; elderly subjects have exhibited smaller N100s compared to a younger group in a visual counting paradigm with black circle outline as targets and a full black circle as non-targets (standards) on a white background (Knott et al., 2003).

There are at least three sub-components, one anterior and at least two posterior, of the visual N100 associated with current flows from frontal to parietal and occipital scalp areas (Hillyard & Lourdes, 1998; Cadaveira, 1999). Differing latencies have been reported for each N100 visual subcomponent, but generally the N100 found post-stimulus at frontal-central electrode sites has peaked between 70-150ms, and those found at parietal and occipital areas between 150-200ms (Hillyard & Lourdes, 1998; Johannes et al., 1995; Covington & Polich, 1996; Cadaveira, 1999; Huang, Chou, Lo, & Cheng, 2011a; Knott et al., 2003). The lateral occipital N100 subcomponent is typically studied, and appears to reflect discriminative processing (Vogel & Luck, 2000; Hopf et al., 2002). The anterior N100 is less often studied, however has been used in modality comparison studies, measuring similar maximum N100 amplitudes at midline frontal and central electrode sites (Fz and Cz) across auditory and visual modalities (Huang, Chou, Lo, & Cheng, 2011; Knott et al., 2003).

1.3.2. Attention Processing (P300)

The detection of sudden changes in our environment has been key for our survival. This attention-driven neural response to unfamiliar or unexpected stimuli has been linked to the P300 component, first measured by Sutton et al. in 1965 using a paradigm where subjects could not predict whether the next stimulus would be either auditory or visual. A range of processes such as recalling information, recognizing information or stimulus significance, and memory updating have been linked to the P300, but it is most prominently known as overall marking an attentional response (Mccarthy & Donchin, 1981; John Polich & Kok, 1995). Unlike the N100, the P300 is traditionally classified as an endogenous component, meaning it is generated based on internal

individual cognitive processing regardless of the sensory modality input (Katayama & Polich, 1999; Polich, 2007; Squires, Squires, & Hillyard, 1975). The P300 is the most widely studied physiological "window" on attention, and thought to reflect the cognitive process of updating stored neural representation of the current environment; incoming stimuli get evaluated and compared with previous neural representation of the environment, which is then updated and stored in working memory (see review Polich, 2007; John Polich & Comerchero, 2003). The P300 has been widely studied across both auditory and visual modalities in both research and clinical settings (T W Picton, 1992; see review John Polich, 2007; Covington & Polich, 1996; Knott et al., 2003; John Polich & Heine, 1996b).

Overall, P300 generation and processing is thought to be independent of the sensory modality (Katayama & Polich, 1999; Naumann et al., 1992; Polich, 1999; (Barrett, Neshige, & Shibasaki, 1987; Ji, Porjesz, Begleiter, & Chorlian, 1999; John Polich & Criado, 2006; Snyder, Hillyard, & Galambos, 1980). Regardless of modality, factors such as stimulus difficulty, presentation probability, timing, or task relevance, similarly affect the P300 amplitude (Duncan et al., 2009; Patel & Azzam, 2005; Polich, 2007; Jun'ichi Katayama & Polich, 1998; Polich & Kok, 1995; Verleger, 1997). As the probability of the unexpected stimulus decreases, whether globally or locally, the P300 amplitude increases (Duncan-Johnson & Donchin, 1977). Varying levels of task difficulty impacts the amount of processing power/ resources that are used for task performance (Kramer, Schneirder, Fisk, & Donchin, 1986). This in turn affects the P300 amplitude size; P300 amplitude decreases as task difficulty increases during an oddball paradigm regardless of modality or type of motor response. This implies that the P300 amplitude is related to the allocation of attention resources (for review, see Polich, 2007; Bennington & Polich, 1999; Comerchero & Polich, 1998). Latency of the P300 has a large range (300-800ms) and can vary systematically with the duration of stimulus categorization (Marta Kutas & Federmeier, 2011). Generally across modalities, the P300 response is observed over central scalp locations from frontal to parietal electrode sites, with less clear waveforms over the occipital scalp area (Naumann et al., 1992; Bennington & Polich, 1999).

1.3.3. Semantic Processing (N400)

Discovered over 35 years ago, the N400 was first found unexpectedly by Kutas and Hillyard (1980), who designed an experiment to evoke a P300 response by using words as "oddballs" within a sentence. Ever since, the N400 has been the most widely studied language-related component, representing a range of neural functionality mainly in relation to language processing, semantic and recognition memory. More specifically, it has been thought to index the difficulty of retrieving information stored in association to a stimulus, i.e. a word or picture (Duncan et al., 2009; Marta Kutas & Federmeier, 2011). The N400 effect is linked to semantic processing in both reading and speech comprehension, evaluated by comparing the difference between expected and unexpected items (John F Connolly, Phillips, & Forbes, 1995; Ryan C N D'Arcy et al., 2003; Marta Kutas & Federmeier, 2011; M Kutas & Van Petten, 1994; Holcomb & Neville, 1990). This primarily has been observed during language comprehension, using sentences and words, but has also been studied in a wide range of non-linguistic stimuli, differing slightly in response but representing an overall common functionality (Duncan et al., 2009; Kutas & Federmeier, 2011; Bayer & Schacht, 2014). Thus, the N400 is not defined by a localizable neural entity indexing one particular mental operation, but rather a pattern of stimulus-related brain activity, identifiable by its characteristic morphology, timing and pattern of response to certain experimental variables (see review Kutas & Federmeier, 2011).

The N400 effect is typically found within a latency window of 200–700ms post-stimulus, with the peak commonly measured in the 350–650ms interval post stimulus (Ryan C N D'Arcy et al., 2003). The N400 has been found largest at midline centro-parietal scalp sites, with some reports of slightly larger amplitudes over the right hemisphere compared with the left (M. Kutas, Van Petten, & Besson, 1988; Marta Kutas & Federmeier, 2011; Marta Kutas & Hillyard, 1982a; van Petten & Rheinfelder, 1995).

The N400 has been observed using many different paradigms and modalities (e.g. (Bentin et al., 1985b; Holcomb & Neville, 1990; Marta Kutas & Hillyard, 1980; M Kutas et al., 1987; McCallum et al., 1984). Unlike the P300, the N400 was first studied using

visual stimuli, which is still typical for studying this component. The N400 is studied robustly with speech, but it is harder to control timing due to varying spoken word durations. Several studies have shown that the N400 is modality independent, with functional similarities of the N400 observed to words regardless if they are written, spoken or even signed (e.g. Bentin et al., 1985; Holcomb & Neville, 1990; M Kutas & Hillyard, 1980; M Kutas, Neville, & Holcomb, 1987; McCallum, Farmer, & Pocock, 1984; Kutas & Federmeier, 2011). Manipulations such as grammar violations, casing of the letters, or even the truth value of a sentence have not affected the N400 (Kutas & Federmeier, 2011). The N400 can be evoked with or without a response, because a response does not add much value and introduces potential muscle movement artifact to the EEG data collection (Kappenman & Luck, 2012, pp. 397-440). The N400 is well-established and extensively studied in research settings but also has been effectively utilized in clinical assessments in patient populations, such as in schizophrenia patients (Niznikiewicz et al., 1997), traumatic brain injury patients (R. C N D'Arcy & Connolly, 1999, 2000), stroke patients (Ryan C N D'Arcy et al., 2003; Yannick Marchand et al., 2002) and cognitive decline or childhood disorders (see review Duncan et al., 2009).

1.4. EEG Data Analysis Methods

1.4.1. EEG pre-processing

Recorded, continuous EEG data needs to be pre-processed before ERP component analysis can be done. EEG pre-processing tools and methods are used to increase the signal to noise ratio by removing or correcting artifacts.

The following is an example of an EEG and ERP analysis pipeline using established tools and methods:

1. *Down Sampling*. Sampling rate refers to the number of samples taken in a second from the continuous signal. In order to have a discrete time series that will accurately represent the frequency of a sine wave, the number of samples needs to be at least double of the desired frequency, as stated by the *Nyquist's rule* (Steven J. Luck, 2014, p. 178). Typically data is initially sampled at more than twice what is needed for analysis. Down sampling offline for further analysis is beneficial

because it can decrease files size and the computational demand when running following analyses. A down sampling rate for typical ERP studies range from 200-500Hz, which provides more than sufficient precision for latency measures for most components of interest, which mainly contain power below 30Hz.

2. *Channel Inspection.* Visual inspection of all EEG channels for each subject is important in order to remove any channels that contain high frequency noise or no signal.
3. *Re-referencing.* Referencing allows for the subtraction of recorded noise from the signal at all channels, hence reducing the overall noise. EEG systems each have their own initial reference channels, so offline re-referencing is commonly done from a single electrode to, commonly either an average reference or an averaged linked mastoid reference.
4. *Filtering*. Raw EEG data consists of both signal and noise; hence filtering is needed for suppressing noise that contaminates the data. Some noise if sufficiently different in frequency from the data, can be suppressed by attenuation of different frequencies. However, filtering can also distort data such as shifting the phase, which leads to a shifting of timing. Zero phase shift filters are recommended because they minimize phase distortion. Three types of filters are commonly used, high-pass, low-pass and notch filters. Notch filers are used to isolate a narrow band of frequency, such as in North America, the 60Hz electrical line noise is removed. A high-pass filter allows all data frequencies above a cutoff frequency pass and all below removed. A 0.1Hz high-pass on continuous data is recommended to remove low-drifts often caused by sweating or skin conductance (Steven J. Luck, 2014, p. 232). For the N400 component, a high pass of 0.1Hz is recommended with minimal distortion (Tanner, Morgan-Short, & Luck, 2015). A low-pass filter is used to remove high frequency artifacts, such as muscle activity; typically a low pass cutoff between 30-50Hz is used.
5. *Artifact Inspection.* Artifacts can be marked for rejection based on set exclusion criteria, such as gradients set with maximal allowed voltage step or maximal allowed difference of values in intervals. This is meant to catch any infrequent high frequency noise events, potentially due to muscle movement. All artifact rejection can be visually reviewed for each subject and adjusted for optimization if needed. Marked artifacts are excluded from following independent component analysis (ICA) and correction. When data is segmented, the segments that contain marked artifacts are rejected from the averaged data (waveforms). Consistent artifacts, such as blinks and eye saccades are not to be marked at this step because those regular/consistent artifacts are best handled by independent component analysis (ICA) so need to all be left present in the data.
6. *Independent component analysis* (ICA). ICA is the process where an algorithm is used to transform the data from a mixture of signals at each electrode site into

estimated maximally independent individual components (n-1, n= number of channels) (Handy, 2005). This idea is commonly referred to as the "cocktail party problem", where it is assumed that the recorded EEG signals are represented by a limited number of components (or "sources"). The estimated "sources", represented as ICA components, are inspected visually using plotted ICA component waveforms, 2-D component scalp maps and activity spectrum plots. Picking out ICA components pertaining to ocular artifacts, such as blinks or eye saccades takes training but once known, are easily picked out and are removed. The data is then unmixed/reconstructed from component to channel form.

7. *Segmentation and Baseline Correction.* Data is segmented into respective stimulus groups for comparison, typically around 1000ms epochs. Baseline correction refers to focusing on the brain signal of interest by subtracting a control (baseline brain activity) signal, commonly 100-200ms before a stimulus event.
8. *Averaging Epochs*. Once data is cleaned, segments based on stimulus type are averaged together, often referred to as conditional averaging. This allows for the combination of several trials in order to show a pattern of activity, i.e. an ERP waveform.

1.4.2. ERP Analysis

Several established techniques can be used to analyze ERPs, but common methods, such as mean amplitude analysis, adjusted baseline amplitude and peak latency were chosen and outlined below.

1. *Measuring Mean Amplitude.* Mean amplitude is computed through measuring the voltage at each sample point within a selected latency window and computing the average of those measured voltages (Steven J. Luck, 2014, pp. 285-292). This method has several advantages compared to the peak-based measures. A narrower measurement window can be used because it does not matter if the max amplitude falls outside this window for some electrode sites or some subjects. The mean amplitude measure is also less sensitive to high frequency noise than peak amplitude measures, because ranges of points are used instead of a single time point. Lastly, bias is better avoided when comparing amplitude measurements from waveforms that have different noise levels or number of trials. A disadvantage of the mean amplitude technique is that it can be quite sensitive to the problem of overlapping components. Therefore, time windows need to be carefully selected. Latency windows need to be determined by stimulus modality, task conditions, subjects' age, and other factors. Mean amplitude measures are typically used to compare amplitudes across stimulus types. Pre-determined latency windows based from previous literature and visual inspection of data is

recommended (Kappenman & Luck, 2016; Chronaki et al., 2012; Pfabigan et al., 2014).

2. *Adjusted baseline amplitude*. Amplitudes can be measured relative to the adjacent peaks of opposite polarity to account for drift in the waveforms (Ryan C N D'Arcy et al., 2011). The peak of the component, the peak before and the peak after are used to calculate the adjusted baseline measure (see Figure 1.2).

    - *Peak Detection*. Semi-automatic detection, with local maxima searched within specified latency windows is recommended. A priori time windows need to be selected based on previous research. A low pass of 20Hz or 10Hz can be used to help smooth out peaks for peak picking but this may affect the latency values. Peak latencies are defined at the point of max voltage within an a priori latency window for a component.

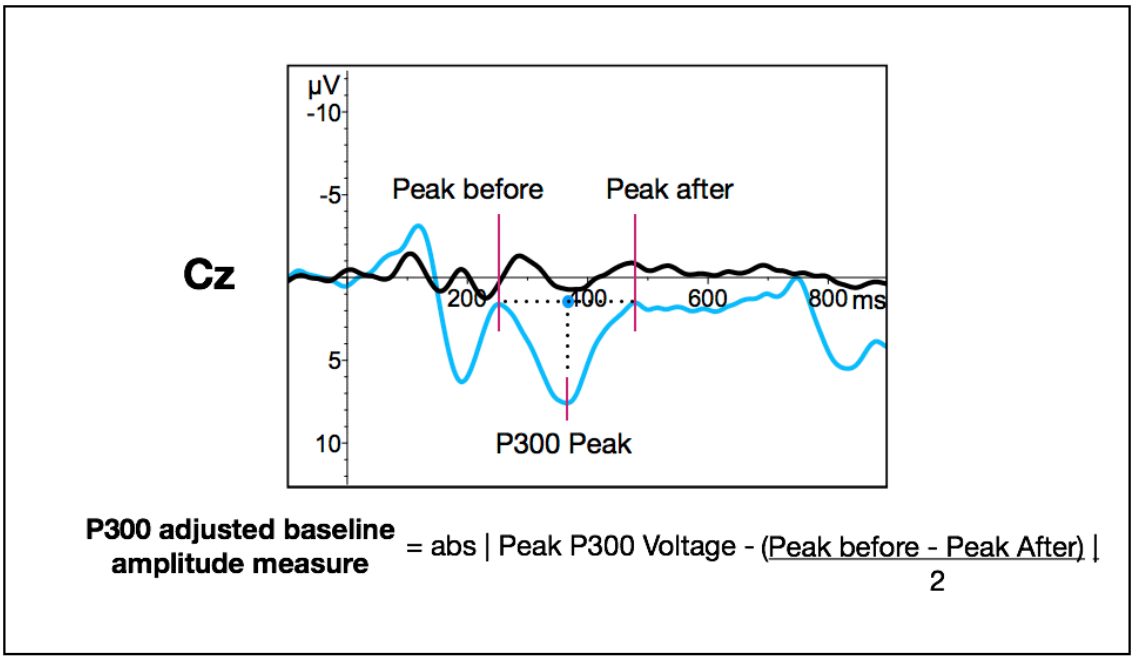

Figure 1.2. Process of taking adjusted baseline measure of ERP component.

1.4.3. Calculating Elemental Brain Scores (EBS)

Once the amplitude and latencies values of the components are measured, they can be translated into accessible scores within the brain vital signs framework. Adjusted baseline amplitude and peak latency ERP values are linearly transformed into 6 Elemental Brain Scores (EBSs) for each participant (3 components x 2 measures). Participants' scores are generated by normalizing the amplitude and latency values against the best possible outcome within a group and translating into scores from 0 to

100. Mathematically, EBS measures can be expressed as shown in equations 1 and 2 below:

$$Score = 100 - abs\left(\frac{M - best}{max - min}\right) \quad (1)$$

$$Score = 100 - abs\left(\frac{best - M}{max - min}\right) \quad (2)$$

The M represents the mean value of either the amplitude or latency. The max and min are the maximum value and the minimum value, respectively. The best variable is the "ideal" value that should be achieved, which can either be the max or the min value depending on whether the lowest or the highest value represents the ideal situation. For instance, an "ideal" value for latency is generally shorter because it represents faster (better) processing, whereas for amplitude values, depending on the targeted ERP component, the highest positive value or lowest negative value is thought to represent "ideal" processing (Ghosh-Hajra et al., 2016). Both larger amplitudes and shorter latencies translate to higher EBS scores. Equation (1) is utilized for N100 and N400 amplitude and latency as well as P300 latency, whereas Equation (2) is used for P300 amplitude.

1.5. Summary

As outlined in this chapter, EEG and ERPs are tools that have been extensively studied and used in research, only more recently emerging to clinical applications. Building on our previous research and utilizing these established tools, we aim to further expand the potential application of the brain vital signs framework to include visual brain vital signs. There are some known differences across modalities, therefore the translation from an auditory based sequence to a visual one will have some expected differences in the ERPs recorded, but overall similar levels of the each cognitive process is being aimed for across modalities. The following chapter outlines the study carried out to develop and validate a new visual based brain vital signs sequence. This study is the initial crucial step in developing, extracting, and characterizing visual ERPs as brain vital signs, essential

for subsequent translational use, such as the evaluation of cognitive function in populations with hearing impairments and potential dysfunction in conditions like mild cognitive impairment or dementia.

Chapter 2.

Brain Vital Signs: Auditory to Visual Translation

2.1. Background

The need for objective, standardized tests to monitor brain health is rising due to increasing awareness of effects from injury, disease or aging on cognitive function. Currently, subjective tests are still mainly used to evaluate patients, lacking accuracy due to the reliance on behavioural or verbal responses from patients (J F Connolly & D'Arcy, 2000). Established research tools such as Electroencephalography (EEG), provides a way to address the growing need for physiological, unbiased measures to monitor cognitive function, with the benefits of being low-cost, non-invasive, easily accessible, and particularly well-suited for clinical and point-of-care applications (Gawryluk et al., 2010; Giacino et al., 2014; John F Connolly, Phillips, & Forbes, 1995; D'Arcy et al., 2003; Sculthorpe-Petley et al., 2015). A range of cognitive functioning, from low-sensory to higher-level cognitive processing can be evaluated with EEG. The translation of EEG research into clinical neurophysiological assessment applications has been demonstrated with rapid non-invasive tools, such as the Halifax Consciousness Scanner (HCS; D'Arcy et al., 2011) and more recently, the brain vital signs framework (Ghosh-Hajra et al., 2016). The HCS was an early implementation of a rapid, auditory sequence used for monitoring and tracking cognitive functioning across healthy, stroke and brain injury patients, as well as levels of consciousness in comatose patients (HCS; D'Arcy, Hajra, Liu, Sculthorpe, & Weaver, 2011; Fleck-Prediger, Hajra, Dick, & Gray, 2015; Sculthorpe-Petley, Liu, Hajra, et al., 2015). The brain vital signs framework has shown age-related differences (Ghosh-Hajra et al., 2016) and demonstrated increased sensitivity to the potential effects of repetitive subconcussive head impacts (Fickling et al., 2018). These applications thus far are auditory-based tests, but with the increasing demand for accessible, objective testing of cognitive function across the lifespan, there is a need to expand the capabilities of such tests to wider populations, such as those that have congenital hearing loss or hearing impairments due to injury or aging. Hence the aim of

this study is to translate the established brain vital signs auditory sequence to a visual sequence.

2.1.1. Overview and utilization of ERPs in brain vital signs

The brain vital signs framework assesses brain health through three cognitive processes: one low-level process (sensory), and two higher-level cognitive processes (attention and language). Sensory and cognitive processes can be evoked by stimuli, evoking certain neural responses, which are recorded as voltage fluctuations on the scalp. These recorded voltages (EEG signal) are time-locked to certain stimuli, allowing for segmentation and averaging, resulting in event-related potentials (ERPs). Conventionally, some ERPs are named based on their polarity (negative or positive) and their approximate timing (milliseconds), and identified based on their morphology, timing, and behaviour under certain experimental manipulations. For brain vital signs three well established ERPs were selected: N100, P300 and N400, reflecting sensory, attention and language responses, respectively.

An interlaced design for the sequence was developed to isolate the three specific ERPs in parallel, avoiding the typical lengthy serial testing time (Ghosh-Hajra et al., 2016; Kappenman & Luck, 2012). The auditory stimulus sequence consists of a passive auditory oddball task and spoken word pairs, which are presented through insert earphones. The oddball task includes tones divided into standard and deviant conditions. The N100 and P300 components are derived from this oddball task. Word pairs are divided into prime and congruent target pairs, and prime and incongruent target pairs. The N400 is derived from the incongruent prime word pairs. The tones and word pairs are interlaced, optimizing the number of trials per unit time (e.g., 5s/cycle * 72 cycles = 6 minutes) (see figure 2.1).

The brain vital signs framework not only looks at the presence or absence of the three ERP components, but rather at individuals' ERPs properties (amplitude and latency) compared to a normative dataset, to form Elemental Brain Scores (EBS) (Ghosh-Hajra et al., 2016). Amplitude and peak latency for each ERP component are ranked against the best possible outcome, linearly transforming the measures into 6 EBS scores, each from 0

to 100 (for detailed breakdown see Ghosh-Hajra et al., 2016). Larger amplitudes and faster latencies result in higher scores, where as decreased amplitudes and slower latencies equate to lower scores.

By providing this framework, where complex ERP data can be captured rapidly, and translated into accessible scores, brain vital signs offers effective longitudinal monitoring of brain function. A "baseline" of healthy cognitive function can be established and used for comparison after a condition of dysfunction occurs (i.e. injury or disease). This has allowed our research to address the essential gap in translating ERP research into a clinically accessible framework and has shown the value of monitoring brain health (Ghosh-Hajra et al., 2016; Fickling et al., 2018). Recent findings have further demonstrated that brain vital sign measures have increased sensitivity to cognitive changes compared to other measures; despite no diagnosed concussions over a hockey season, athletes showed significant changes in brain vital sign measures between baselines to post-season. The decreased amplitude and increased latency scores observed indicated the negative effects of concussions and potential negative effects of repetitive subconcussive head impacts (Fickling et al., 2018).

The applications of this essential technology and framework has expanded from the evaluation of strokes, traumatic brain injury, to concussions, and is now aiming to study the effects of aging, mild cognitive impairment and dementia as well. However, 20% of adults over the age of 65, 40% over 75, and 80% of nursing home residents experience hearing loss (Speech-Language & Audiology Canada, https://www.sac-oac.ca/seniors). In order to better reach such populations, as well as others who suffer from hearing loss, congenitally or due to injury, visual assessment can be done. As done with auditory stimuli, sensory (N100), attention (P300) and semantic (N400) processing can be evoked using visual stimuli. There are some known differences within the components between auditory and visual, however they are mostly modality independent.

Sensory Processing (N100)

Basic sensory processing differs in the initial pathways across modalities; sound processing occurs through our ears to the auditory cortex (temporal lobe) compared to

visual processing occurring from our eyes, optic nerves to the visual cortex (occipital lobe). The initial cortex response time is shorter to auditory stimuli (15ms) compared to visual (40-60ms) (T.W. Picton, Stuss, Champagne, & Nelson, 1984). Despite these differences, the N100 is considered an exogenous response, largely dependent on the physical parameters of the stimulus rather than internal cognitive states. In both auditory and visual processing, the N100 is thought to reflect similar selective attention responses to basic physical stimulus characteristics and intentional discrimination, such as noticing the loudness of an auditory stimulus or brightness of a visual stimulus (Vogel & Luck, 2000). The N100 also has a similar polarity and ordinal position across modalities (Luck, 2005).

There are several methods to evoke the N100. Changing location of stimuli in the visual field has been used, where the N100 was larger if a stimulus was presented in a location that was attended versus unattended (Luck and Hillyard 1995; Doallo et al., 2005). However, having varying locations for visual stimuli introduces increased eye movement artifact into the EEG data. Within the auditory brain vital sign sequence, differing tone intensity stimuli (standard and rare/deviant) are used to elicit the N100 and measure auditory sensory processing (Ghosh-Hajra et al., 2016). Visual paradigms can utilize a similar structure with rare, visual characteristics to evoke the visual N100, such as with differing brightness, colours or shapes (Johannes et al., 1995). When comparing detection tasks (i.e. brightness/colour) to discrimination task (i.e. shapes), the later requires more attentional processes (Luck and Hillyard 1995). This can be a concern because the more attention resources used for initial sensory processing from a discrimination task, may reduce the following visual P300 amplitude due to multiple areas of the cortex being employed to gather attentional resources especially when further effort is required (Lavoie, Johnston, Leclerc, Lassonde, & Dupuis, 2004). Therefore, a simple visual detection task is needed in the visual brain vital signs sequence. Previous studies have successfully utilized a simple detection task using brightness of stimuli to evoke a visual N100 response (Johannes et al., 1995; Polich, Ellerson, & Cohen, 1996; Carrillo-De-La-Peña et al., 1999). A more recent study used both an active (counting) and passive (no counting) task to evoke and record a frontal-central N100 (Huang et al., 2011a). The anterior N100 subcomponent occurs around 80 to 150ms and is best

recorded at frontal and central electrode sites (Fz and Cz), similar to the auditory N100 (Vogel and Luck, 2000; Huang et al., 2011; Knott et al., 2003). Therefore the visual anterior N100 was chosen for comparison to the auditory evoked N100, at frontal-central midline electrodes.

Attention Processing (P300)

The P300 has been most commonly studied in relation to attention processing by utilizing the oddball paradigm, across both auditory and visual modalities. An oddball paradigm is where stimulus probability and task relevance is varied; rare, unpredictable target stimuli are spread amongst known/expected stimuli (Steven J. Luck, 2014, p. 8; Pritchard, 1981). Auditory oddball paradigms have been the preferred method for evaluating the P300 in both lab and clinical settings, primarily because parameters (i.e. tone, frequency, duration, rise/decay time, intensity etc.) have been easy to produce, replicate and systematically assess (Picton, 1992; Polich, 1998; Luck, 2005). Deviant tones denoted by different frequency and lower probability compared to the standard tones, evoke a significantly larger P300 amplitude (Ghosh-Hajra et al., 2016; Sculthorpe-Petley et al., 2015). Within the visual modality, oddball sequences have often consisted of deviant stimuli with certain visual characteristics being changed, such as: checkerboard sizing, colours, shapes, letters, words, or pictures (see review Bernat, Shevrin, & Snodgrass, 2001; Bledowski, 2004; Cano, Class, & Polich, 2009; Duncan et al., 2009; V Knott et al., 2003; Bennington & Polich, 1999; Mertens & Polich, 1997; Stevens, Skudlarski, Gatenby, & Gore, 2000; Comerchero & Polich, 1998; Luck and Kappenman, 2012, pp.159-180).

The P300 is mostly modality independent, however, there are some modality specific differences (Luck, 2005). Early comparison studies have shown enhanced and/or later P300 amplitudes in the visual modality as compared to auditory (Johnson, 1989; Jun'ichi Katayama & Polich, 1998; T.W. Picton et al., 1984; John Polich & Heine, 1996a). These visual oddball paradigms are often active tasks, requiring a response, which can introduce noise (motor movement artifact) or compliance issues with certain patient populations (i.e. dementia or patients lacking motor capacity) (Patel & Azzam, 2005). Therefore, a passive oddball task is preferable, such as the current auditory brain

vital signs task. A passive task refers to one that does not require a response. The P300 latency has been found stable in visual oddball tasks across active and passive tasks (Patel & Azzam, 2005). However, the P300 has been found to be easier to evoke within auditory versus visual modality in passive tasks (Bennington & Polich, 1999; Halgren, Marinkovic, & Chauvel, 1998). Despite the smaller P300 responses to a visual passive oddball task, detectable increases in amplitude for rare visual stimuli have been observed (Bernat et al., 2001)**.** In order to ensure a robust attention response is evoked in the visual brain vital sequence, a particularly relevant and salient stimulus, such as a subject's own name (SON), can be utilized within an oddball design (see review of SON paradigms: Berlad & Pratt, 1995). When presented with low probability, the recognition of one's own name is associated with a P300 response (Perrin, García-Larrea, Mauguière, & Bastuji, 1999; F Perrin et al., 2006). However, when presented with high probability, the SON is associated with an early negative enhancement (ENE) which occurs around the latency of N100 and P200 (Sculthorpe-Petley et al., 2015).

Presented aurally in both passive and active paradigms, responses to SON have shown larger P300 amplitudes compared to other names and words (Berlad & Pratt, 1995; Fischer, Dailler, & Morlet, 2008; Holeckova, Fischer, Giard, Delpuech, & Morlet, 2006; Müller & Kutas, 1996; Fabien Perrin et al., 2005). When presented visually, the SON response have shown similar results– an enhanced P300 response compared to other similar or differing stimuli within a 350–850ms interval at central electrodes (Tacikowski & Nowicka, 2010; Zhao et al., 2009; Zhao, Wu, Zimmer, & Fu, 2011; Cygan, Tacikowski, Ostaszewski, Chojnicka, & Nowicka, 2014). Several others have used a SON in oddball paradigms to study responses in brain-injured patients (Cavinato et al., 2011; Fischer et al., 2008; Fischer, Luaute, & Morlet, 2010; F Perrin et al., 2006; see review Demertzi et al., 2008; Sculthorpe-Petley et al., 2015).

Besides being particularly salient, SON paradigms also have benefits for a rapid, visual sequence, because it has been found to be particularly resistant to repetition blindness during rapid serial visual presentations (RSVP) (Arnell, 2006; Tacikowski & Nowicka, 2010).

Semantic Processing (N400)

The N400 is typically seen in response to violations of semantic expectancies in both auditory and visual modalities (Kutas & Hillyard, 1982; M Kutas & Hillyard, 1980; M Kutas & Van Petten, 1994; John F. Connolly, Major, Allen, & D'Arcy, 1999). This is commonly achieved in experimental paradigms with either sentences (semantic-anomaly) or word pairs (semantic-priming) typically (Bentin et al., 1985b). In both paradigms, the expectation created by the sematic context can be violated with a non-suitable word, evoking a N400 response. The semantic-anomaly paradigm involves presenting words sequentially from a sentence, where a certain target word is set as congruent or incongruent with the preceding sentential context, such as, 'I like my sandwich with peanut butter and jam/rocks' (Lau, Phillips, & Poeppel, 2008). Word pair paradigms (semantic-priming) evoke a similar N400 response but allow for faster testing times compared to sentence paradigms, which was utilized in the auditory brain vital signs sequence (Ghosh-Hajra et al., 2016; Marta Kutas, 1993). The semantic priming paradigm uses sequential word pairs presented centrally on a screen, where the priming word is considered the 'context' into which the target word must be integrated. The expectancy (the degree of semantic congruency) between the prime and target word affects the N400 amplitude, reflecting the amount of processing power used to access the meaning of that word after the full input (if your priming was correct or not) (reviewed in M Kutas & Petten, 1988; Marta Kutas & Federmeier, 2011). The N400 amplitude is reduced to words that match- when the target is semantically related to the prime word (i.e. 'romeo-juliet'). The N400 amplitude is larger for when the prime word doesn't match--it is unrelated/incongruent to the target (i.e. 'romeo-coffee') (Brown & Hagoort, 1993; Brown, Hagoort, & Chwilla, 2000; Chwilla, Hagoort, & Brown, 1998; Rugg, 1985; Ghosh-Hajra et al., 2016; Lau et al., 2008). Although the effects of sentential context on the N400 response tend to be larger in amplitude, the latency and spatial distribution of evoked N400 from both paradigms are similar, and are assumed to represent the same underlying functional response (Bentin et al., 1985a; Marta Kutas, 1993; Marta Kutas & Federmeier, 2011).

When directly compared, the auditory and visual modality showed no differences of N400 responses between healthy subjects (Balconi & Pozzoli, 2005; Niznikiewicz et al., 1997). However, other studies have shown some latency and duration differences between the audiotry and visual modality. Auditory-presented stimuli have been reported to have earlier onset latencies compared to visually presented stimuli for the N400, but only to natural speech, not when speech was presented at a fixed rate (reviewed in Marta Kutas & Federmeier, 2011; M Kutas & Van Petten, 1994). Auditory N400 also tend to have longer durations (i.e. 400ms) compared to the visual N400 (i.e. 300ms) (Luck, 2005; Marta Kutas & Federmeier, 2011). Irrespective of the modality, the N400 is typically found between 200–600ms post-stimulus (Marta Kutas & Federmeier, 2011), with maximal amplitudes at midline central or parietal sites and noticeably smaller amplitudes at prefrontal and lateral frontal sites (Duncan et al., 2009).

Translating the auditory sequence into a visual sequence is simplest for semantic processing (N400), with the same word pairs easily adapted from the auditory to the visual modality. Overall, the differences across modalities for the N400 are reportedly minimal, with only some differences in latency and duration.

Summary and Sequence Considerations

Overall, there are some known systematic differences across modalities within each component (i.e. latency differences or duration). Therefore, the translation from an auditory based sequence, to a visual one will have some expected group differences in the properties of the ERPs recorded, but the overall aim is for similar average levels of cognitive processing is evoked from both modalities and correlated relationship across modalities within individuals. As outlined above, past research demonstrated viable paradigms to evoke the targeted ERPs that can be adapted and combined into a rapid visual sequence while mirroring the interlaced structure of the established auditory sequence.

However, developing a rapid visual sequence presents some challenges. The level of intensity and difficulty of the two sequences needs to be matched because such factors can affect the amplitude and latency of components, particularly the P300 in a passive

task. A response does not add much value for the N100 (sensory processing) and N400 (sematic processing) (Luck and Kappenman, 2012, pp. 397-440) but does affect the P300 (attention processing). When compared to active tasks, the passive oddball paradigm in both modalities has shown reduced amplitudes and differing latencies and scalp topographies (Bennington & Polich, 1999). Nonetheless, passive paradigms have still shown highly comparable and reliable P300 responses (John Polich & McIsaac, 1994). A passive task is preferred for patient populations that may struggle with responses or demanding tasks, such as young children or dementia patients. Past research has confirmed the viability of attaining all the targeted ERP responses under passive conditions in both healthy and patients populations (Ghosh-Hajra et al., 2016; Y Marchand, D'Arcy, & Connolly, 2002; Fabien Perrin et al., 1999; Sculthorpe-Petley et al., 2015; Huang et al., 2011a). Based on past research, choosing a more salient passive visual task, such as contrast flip and SON, should ensure a N100 response and a robust visual P300 response. Another advantage of a passive task is that is requires much less time than an active task which requires time for a response, and also greatly reduces the potential for unnecessary muscle movement artifact to the EEG data collection.

In order to further reduce movement and muscle artifact, particularly eye movement and blinking artifact, visual stimuli should be presented serially in the center of the screen. This also allows for bilateral processing. If a stimulus is presented laterally, the N100 has been reported to be larger and earlier, but appear contralateral to the visual field of the stimulus (Wascher, Hoffmann, Sänger, & Grosjean, 2009). Whereas, a centrally presented stimulus causes the N100 to present bilaterally, which is needed when focusing on the midline and central electrode sites.

Visual ERPs are also sensitive to rapid serial visual presentation (RSVP), which can cause repetition blindness, habituation, and potential entrainment of alpha rhythm with the stimulus timing (Steven J. Luck, 2014, pp. 203-204; Ravden & Polich, 1998). These factors can affect the amplitude and/or latency of components and quality of the data (Steven J. Luck, 2014, pp. 203-204). Avoiding set or predictable timing by incorporating variable time intervals (a jitter) into the inter-stimulus-interval (ISI) and in the inter-block interval (IBI) helps to avoid these effects (Ravden & Polich, 1998).

A sequential order at a rate of 500ms (300ms per word, with at least an inter-stimulus interval of 200ms) has been recommended (Luck and Kappenman, 2012, p. 430), but longer durations and ISIs, particularly for oddball paradigms, have been used and recommended with patient populations (Knott et al., 2003; Duncan, 2009; Polich, J., 1991), This is an important factor to consider for future applications of the visual brain vital signs sequence within patient populations. However, this is in contradiction to developing a rapid visual sequence. Adapting the interlaced structure of the auditory brain vital signs sequence, where the oddball is interlaced between the word pairs, aids with extending the time between paradigms.

Overall, overcoming come challenges and the goal of a rapid, passive visual brain vital signs sequence is possible. The N100 and P300 pose more difficulty in adapting across modalities, whereas the N400 is the easiest, with the same word pairs easily adapted and presented in the visual modality. Considerations in the development of the sequence were made for planned future portable application in patient populations.

2.1.2. Objectives

This study aims to address the important gap of having more tools accessible for brain health monitoring, particularly in populations with auditory impairments due to injury or aging. We plan to do this by expanding the brain vital signs framework to include a visual sequence. As outlined above, the targeted cognitive processes within the auditory-based brain vital signs framework can also be evoked through the visual modality. Building from previous research and the established auditory sequence, we plan to accomplish this, though two main objectives:

1. Translate the interlaced, rapid auditory sequence into a visual sequence and validate it by assessing if the targeted EPRs (N100, P300, and N400) are successfully evoked; and

2. Compare the raw and normalized magnitudes (amplitudes) and speeds (latencies) of the targeted ERPs across modalities. Then evaluate the relationship between modalities within individuals.

In order to evaluate objective 1, we have two hypotheses:

i. There is a significant difference in mean amplitude values between standard and deviant stimuli at midline electrodes;

ii. There is a significant difference in mean amplitude values between congruent and incongruent word pairs at midline electrodes;

These hypothesises will enable an unbiased approach for us to determine the presence or absence of the three targeted ERPs (N100, P300 and N400) at a group-level at the midline electrode sites. The results will indicate whether the developed visual brain vital signs sequence was successful. In order to evaluate our second objective, we have three hypotheses:

iii. There are non-significant differences in average amplitudes between modalities for the 3 ERPs;

iv. There are peak latency differences between modalities, with later peak latencies for visual (compared to auditory) for N100 and P300;

v. Any absolute differences between modalities are normalized when peak amplitude and latency values are linearly translated into the Elemental brain scores (EBS); and

vi. There are significant correlations in peak amplitude and latency values between modalities within subjects.

These hypothesises will confirm some known differences between modalities (i.e. latencies), further demonstrate EBS capabilities, and show if relatively similar magnitude and/or speed of sensory (N100), attention (P300) and semantic (N400) processing is occurring within individuals across modalities. As done by previous brain vital studies and others that clinically applied ERPs, the present study focused on three midline scalp electrodes (frontal (Fz), central (Cz), and parietal (Pz)) (Ryan C N D'Arcy et al., 2011; Fischer et al., 2008; Ghosh-Hajra et al., 2016; Kotchoubey et al., 2005; Sculthorpe-Petley et al., 2015).

2.2. Methods

2.2.1. Experimental Design

Each participant had four EEG recordings: two of each visual and auditory stimulus sequences. The order of the stimulus sequences and probability conditions were counter-balanced across subjects. Only the first run was used for analysis in this study.

2.2.2. Sequence Structures

Both auditory and visual sequences followed a similar interlaced design, with an oddball paradigm occurring between word pair presentation. A global oddball design was used, where not every block, containing an oddball stimulus and word pair, had a deviant oddball stimulus. Overall both sequences had 24 deviant stimuli for the oddball paradigm and 72 word pairs (36 congruent and 36 incongruent). Both sequences were passive tasks (no response required).

Auditory Sequence

The auditory stimulus sequence was adapted from previous brain vital signs studies (see Ghosh-Hajra et al., 2016 and Fickling et al., 2018). The auditory sequence consisted of tones (250ms duration) and spoken word pairs (~1000ms duration) stimuli. An oddball paradigm was used for the tones, split into 67% standard (75 dB) and 33% deviant (100 dB), with the N100 and the P300 derived from the deviant condition. The 72-paired spoken words were divided into congruent prime pairs (e.g., romeo-juliet, 50%) and incongruent prime pairs (romeo-coffee, 50%). The N400 was derived from the incongruent words condition. The interlacing of tones and word pair stimuli enabled full optimization of near maximum trials per unit time (e.g., ~5s /stimulus block × 72 blocks = ~ 5 min) (see figure 2.1).

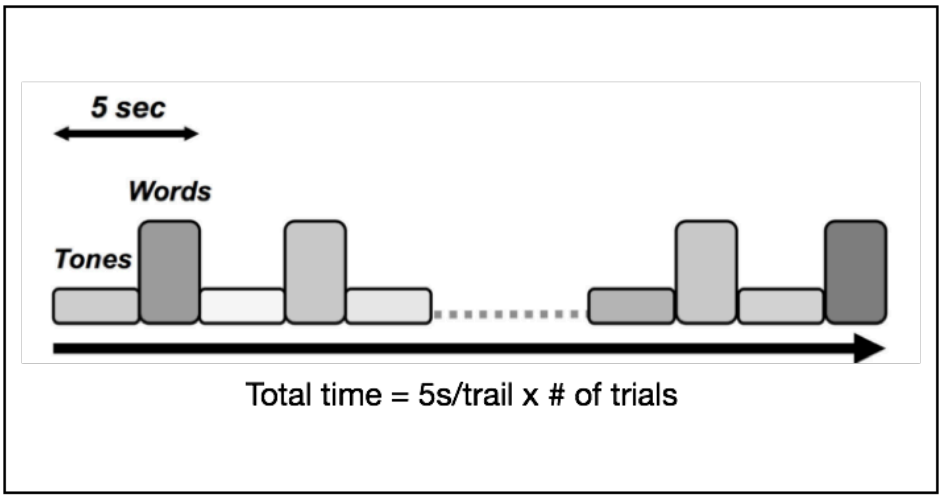

Figure 2.1. Schematic illustration of auditory stimulus sequence consisting of words and tones (from Ghosh-Hajra et al., 2016 (Licensed CC-BY)).

Visual Sequence

The interlaced structure of the visual stimulus was similar to that of the auditory sequence; an approximately 4.6 min inter-laced oddball and word pair sequence (see figure 2.2). All visual stimuli were presented serially in the center of the screen. The words were presented in white font (Sans serif, size 56) on black background. The standard ("ready") or deviant (SON in inverse contrast) had a duration of 600ms followed by the prime and target words pairs, duration of 300ms each. The oddball was also divided into standard (67%) and deviant (33%) conditions, with the N100 and P300 derived from the deviant condition. The same 72 word pairs were used as in the auditory sequence. A jitter was incorporated into the inter-stimulus-interval (ISI) (800ms ± 100ms) and in the inter-block interval (IBI) (1000ms ± 100ms).

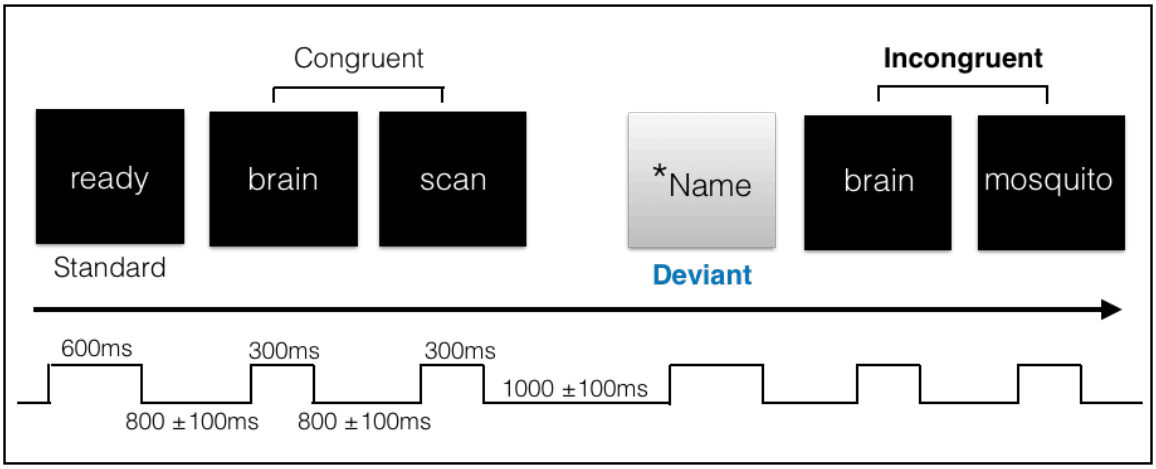

Figure 2.2. Schematic illustration of the visual stimulus sequence, containing the subjects' name, and word pairs. Total sequence is ~5 minutes in length.

2.2.3. Participants

All participants were 18+ years of age, right-handed, fluent in English, with normal or corrected-to-normal vision. Participants with a history of any condition affecting brain function were excluded from the study. Thirty-four participants ranging from 19 to 66 years of age were recruited (33 ± 14 years, 16 females). One participant was excluded due to equipment issues where all channels were very noisy (subject 12). Three other participants (10,18 and 45) were excluded due to non-compliance with task or exceeding the a priori inclusion threshold of <25% of total trials lost due to artifact (see section 2.2.6). Participant characteristics are presented in Table 2.1.

Table 2.1. Sample characteristics.

Sample size	30
Age (years)	33 ± 14
Sex (M: F)	8:7

2.2.4. Informed Consent and Safety

The Research Ethics Boards of Simon Fraser University and Fraser Health Authority approved this research, and written informed consent was obtained from each participant prior to data acquisition. The investigators explained the purposes and

methods of the study and went through the consent form with each participant. Those who chose to participate were asked to sign the consent form, formerly approved by ethics. This study involved a non-invasive procedure that is considered “minimal risk”. The only potential risk to participants was a minor chance of skin irritation and/or infection due to the application of the EEG electrodes and conductive, water-soluble gel. All participant information collected from the study was de-identified. The data and signed consent forms are securely stored at the Surrey NeuroTech Lab (an SFU Lab embedded in Surrey Memorial Hospital).

2.2.5. EEG Acquisition

The participant was fitted with an elastic cap with attached electrodes (BrainAmp 64-channel system actiCAP). Each of the 64 Silver/Silver Chloride (Ag/AgCl) electrodes were injected with gGAMMAsys electrode gel for conductivity, aiming for <20kΩ impendence at each electrode. FP1 and AF7 electrode sites within the 64-channel cap, which are located on the supra-orbital ridge and outer canthus of the left eye, were used as the vertical and horizontal electrooculographic (EOG) channels. Visual stimuli were delivered through a computer monitor that was centered 75cm in front of the participant in a dim lit room (Marchand et al., 2002). Acoustic stimuli were delivered binaurally through insert headphones. Participants were instructed to sit still and pay attention to the visual sequence or the auditory stimuli. During the auditory sequence, participants were asked to maintain visual fixation on a cross displayed in the center of the screen. Raw EEG data was recorded by BrainVision Recorder (Version 1.20.0801 Brain Products GmbH) while the participants were instructed to sit still and either listen or view the stimulus sequence. Both the auditory and visual sequences were delivered using Presentation® software (Version 18.0, Neurobehavioral Systems, Inc., Berkeley, CA, www.neurobs.com). Uncontrolled variations in neural activity, such as arousal level, time since last meal, phase of circadian cycle, etc., were minimized by instructing participants to refrain from caffeine, alcohol, extraneous exercise or lack of sleep in the preceding 24hrs to data collection.

2.2.6. EEG Pre-processing analysis

EEG analysis was done using Brain Vision Analyzer® software, version 2.03 (Brain Products, Gilching, Germany). EEG data was down-sampled from 1000Hz to 500Hz. All 64- channels were inspected for noise and re-referenced offline from FCz to the average of the two mastoids (electrodes TP9 and TP10). A 0.1Hz- 50Hz zero phase-shift, 4^{th} order Butterworth bandpass filter and 60Hz notch filter was applied to the data. Artifacts were marked for rejection based on the following exclusion criteria: gradients set with maximal allowed voltage step of 10 uV/ms and maximal allowed difference of values in intervals of 100uV. All artifact rejection was visually reviewed for each subject and adjusted for optimization if needed. Blinks and saccades were not included in artifact rejection in order to run artifact correction using independent component analysis (ICA). The Infomax (gradient restricted) ICA algorithm was used to identify and remove eye blinks and saccades components. The data were epoched relative to the onset of the auditory or visual stimulus (-100 to 900ms) and baseline corrected (-100 to 0ms). Within each modality, and for each participant, trials were averaged based on their respective stimulus type (standard, deviant, congruent or incongruent). Averaged epochs did not include segments that contained artifacts (as marked with artifact rejection step). A priori threshold of rejected segments was set; any subject for whom 25% or more of segments were rejected (collapsed across all trial types) were excluded from further analysis (Steven J. Luck, 2014, pp. 209-210). Three subjects were excluded for this reason in the present study.

2.2.7. ERP Analysis

Mean amplitude

After artifact correction, data was exported to MATLAB for mean amplitude analysis using ERPLAB, an open-source Matlab package for analyzing ERP data (Lopez-Calderon & Luck, 2014). The mean amplitude measures were calculated for each stimulus type for each individual at 3 midline electrode sites (Fz, Cz and Pz) due to previous brain vital signs studies and to assess feasibility of future visual applications utilizing a portable EEG system, limited to midline and EOG electrodes. Different

durations of time windows for each component were used. The N100 was indexed by differential activity within a 50ms window, as recommended for early components (Vogel & Luck, 2000; Steven J. Luck, 2014, pp. 286-287). The P300 was measured over a 200ms window (Cano et al., 2009; Wood, Potts, Hall, Ulanday, & Netsiri, 2006). The N400 was measured over a shorter latency for visual (400ms) than auditory (500ms), because the visual N400 is typically shorter in duration compared to the auditory N400 (Marta Kutas & Federmeier, 2011; M Kutas & Van Petten, 1994). Each latency window was guided by past literature recommendations and visual inspection of the grand average (GA) waveforms (Chronaki et al., 2012; Pfabigan et al., 2014). Mean amplitudes were calculated over the following latency windows for the auditory data: 114-164ms (N100), 250-450ms (P300) and 200–700ms (N400). The indexed windows chosen for measuring mean amplitudes in the visual data were: 87-137ms (N100), 300-500ms (P300) and 200-600ms (N400).

Adjusted baseline amplitude and peak latency

Adjusted baseline amplitude and peak latency were measured for all 3 components in both modalities. Adjusted baseline amplitude measures were calculated at Cz from peak amplitudes relative to the two adjacent peaks of opposite polarity (D'Arcy et al., 2011; Ghosh-Hajra, 2016) (see Figure 1.2). A 20Hz low-pass filter (4^{th} order zero phase shift Butterworth filter) was applied to ERP waveforms for local peak picking and GA waveforms. All peaks were obtained with a semi-automatic process using Brain Vision Analyzer, within expected latency windows, identifying local peak amplitudes (as defined by Steven J. Luck, 2014, pp. 285) of expected polarity (Y Marchand et al., 2002). Latency windows vary across studies, depending on stimulus types, task conditions, subject age, etc. (Cano et al., 2009; J. Polich, 1997; John Polich & Kok, 1995). Hence it is recommended to choose latency windows based on both literature and visual inspection of the GA waveforms (Cassidy, Robertson, & O'Connell, 2012; Chronaki et al., 2012; López Zunini et al., 2016; Pfabigan et al., 2014). Due to the wide range of age (19-66yrs) and two modalities within this study, latency windows for each component were chosen according to several previous studies. For both modalities, the N100 peak, was measured between 75-200ms (Niznikiewicz et al., 1997; Hillyard & Lourdes, 1998; Johannes et

al., 1995; Covington & Polich, 1996; Cadaveira, 1999; Huang, Chou, Lo, & Cheng, 2011a; Knott et al., 2003). Shorter latencies were expected for P300 in auditory (250-500ms) compared to visual (250-600ms) (Campanella, Delle-Vigne, Kornreich, & Verbanck, 2012; Cano et al., 2009; Verner Knott et al., 2003; Bernat et al., 2001; Tacikowski & Nowicka, 2010; Comerchero & Polich, 1998). The latency window for N400 peaks was 300-650ms for auditory and visual (Y Marchand et al., 2002; Ryan C N D'Arcy et al., 2003; Marta Kutas & Federmeier, 2011).

Elemental Brain Scores (EBS)

The 6 total (3 components x 2 measures) ERP measures for each modality were linearly transformed into the brain vital sign framework, generating the 6 EBSs for each participant between 0 and 100. The EBSs are generated by normalizing the amplitude and latency values against the best and worst possible outcomes using the group mean value and ± 3 standard deviations (for more details, see Chapter 1, section 1.4.3, or Ghosh-Hajra et al., 2016). This translation allows for complex ERP data to become accessible metrics, while preserving the underlying ERP results. This technique also will enable normalization within modalities to account for the known differences while preserving the relationship across modalities.

2.2.8. Statistical Analysis

Statistical analysis was performed using JMP (JMP®, Version *12.2.0* SAS Institute Inc., Cary, NC). Normality was assessed using the Shapiro-Wilk W test. To assess the difference between stimulus type, a repeated-measures ANOVA was used with the mean amplitude values for each component within each modality. The within subject repeated measures ANOVA had two factors: stimulus (standard vs. deviant or congruent vs. incongruent) and electrode site (Fz, Cz and/or Pz). The number of levels for site was specific to each component; frontal-central channels (Fz and Cz) were chosen for N100, three (Fz, Cz and Pz) were chosen for P300 and central-parietal (Cz and Pz) for the N400. The Greenhouse-Geisser adjusted values were used for any violations of sphericity assumptions. Student t-tests or Tukey-Kramer correction for multiple comparisons was

applied for all post-hoc comparisons to adjust alpha levels. Results are presented as mean (± standard deviation).

Adjusted baseline amplitude and peak latency values, as well as EBS values were compared at the group-level across modalities. Normality was assessed using the Shapiro-Wilk W test. Only the measures for visual P300 amplitude did not pass the normality test, therefore the Wilcoxon test was used for comparison. All others were compared using matched pairs t-test. Results are presented as mean ± SD.

Pearson correlation coefficient (Pearson r) was used to evaluate the relationship of individual values across modalities. This statistic assumes a linear relationship and is confirmed by inspection of the r value, associated p-value and scatter plot. Pearson R correlation analysis was used for all except P300 amplitude values. The visual P300 amplitude values failed the Shapiro-Wilk test of normality (i.e. non-parametric distribution) so Spearman rho was used for correlation analysis.

2.3. Results

2.3.1. Targeted ERP Responses (Hypothesis i and ii)

Figure 2.3 shows the targeted N100 and P300 components evoked using oddball paradigms within the auditory and visual sequences. Figure 2.4 shows the targeted N400 component evoked by the word pair paradigm within the auditory and visual sequences.

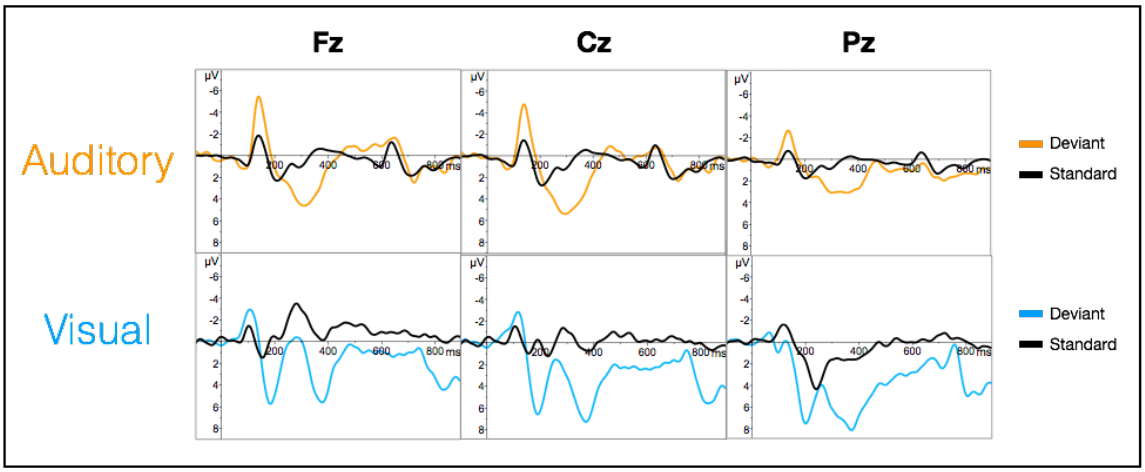

Figure 2.3. **Grand averaged waveforms from oddball paradigm (standard vs deviant stimuli) in both modalities. The N100 and P300 components are visible in both modalities. Waveforms are filtered at 20Hz.**

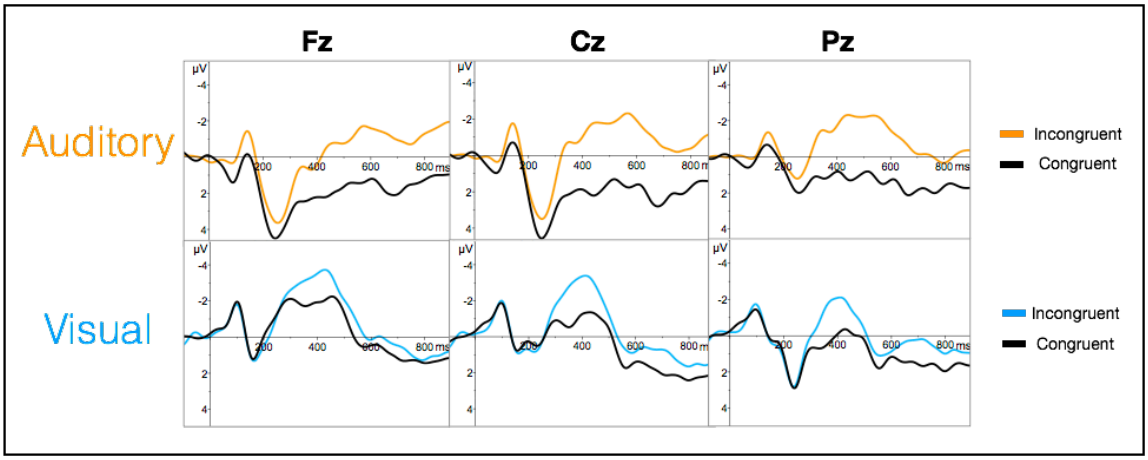

Figure 2.4. **Grand averaged waveforms from the auditory and visual word pair paradigms (congruent vs incongruent word primes). The N400 component is visible in both modalities. Waveforms are filtered at 10Hz for this figure.**

Mean amplitudes were measured for each component for each stimulus condition. ANOVAs for the mean amplitudes within each modality revealed main effects for stimulus type across all three components. Across all components in each modality, no interaction effects were found. Quantitative mean amplitude measures for group-level N100 and P300 are shown in Table 2.2 and for N400 see Table 2.3. A summary of effects tests is shown in Table 2.4.

Due to noise and electrode function, Fz was missing from three participants for the N100 analysis. The ANOVA analysis for the auditory N100 revealed a main effect of

stimulus between standard and deviant stimuli, F (1, 27) = 78.466, p < 0.0001. On average larger negative N100 amplitudes were observed for the auditory deviant condition (M = -3.75μV, SE = 0.33) compared to standard (M = -1.22μV, SE = 0.33). The estimated mean difference found was 2.54μV (SE=0.29). No effect of electrode site (channel) was found for either the auditory or visual N100. The stimulus condition also had a main effect on mean amplitude of the visual N100, F (1, 27) = 29.838, p < 0.001, with an estimated mean difference of 1.33μV (SE=0.24). On average larger negative amplitudes were observed for the deviant condition (M= -2.20μV SE = 0.44) compared to standard (M = -0.87μV, SE = 0.44) in the visual modality.

For the auditory P300, there was a main effect of stimulus, F (1, 29) = 137.042, p < 0.0001). An estimated mean difference of 2.73μV (SE= 0.23) was found, with an estimated mean of 2.87μV (SE = 0.22) for the deviant condition and 0.14μV (SE = 0.22) for the standard condition. There was no evidence of a channel effect found.

For the visual P300 we found strong evidence (F (1, 29) = 138.844, p < 0.0001) of an effect of stimulus between standard (M = -0.12μV, SE = 0.52) and deviant (M = 4.36μV, SE = 0.52) conditions, with an estimated mean difference of 4.48μV (SE = 0.38). Evidence of a channel main effect was found, F(1, 29) = 17.278, p < 0.0001, with on average larger mean amplitudes found at Pz (M= 3.41μV, SE=0.55) and Cz (M = 2.31μV, SE=0.55) compared to Fz (M=0.65μV, SE= 0.56). Further post-hoc (Tukey Honest Significant Difference) was done to look where the potential differences lie. The largest estimated difference between stimulus conditions means was found at Pz, followed by Cz and Fz. Comparison was done of all channels' estimated means with each other, revealing a maximum estimated difference of 2.76μV (SE =0.47), p< 0.0001 between Pz and Fz. We also found evidence of an effect between the Cz and Fz channels (p =0.0017) with an estimated difference of 1.66μV (SE=0.47). There was no evidence of a difference between Pz and Cz (p=0.0574) with an estimated mean difference of 1.10μV (SE= 0.46). Further post-hoc (Tukey HSD) showed that the estimated mean difference between stimulus conditions at Pz was 4.80μV (SE=0.65), at Cz was 4.86μV (SE=0.65), and at Fz was 3.79μV (SE=0.67). All were found significant, with p <0.0001.

Table 2.2. Summary Statistics: Mean amplitude measures for group-level N100 and P300 (μV).

ERP	Channel	Auditory Oddball Stimulus (μV)		Visual Oddball Stimulus (μV)	
		Standard	Deviant	Standard	Deviant
N100	Fz	-1.46 ± 1.84	-4.09 ± 2.69	-0.90 ± 2.12	-2.60 ± 2.63
	Cz	-0.97 ± 1.45	-3.42 ± 2.29	-1.05 ± 2.20	-2.27 ± 2.44
P300	Fz	0.01 ± 1.06	2.81 ± 2.50	-1.22 ± 3.03	2.57 ± 4.62
	Cz	0.22 ± 0.94	3.40 ± 2.34	-0.12 ± 3.02	4.74 ± 4.28
	Pz	0.21 ± 0.64	2.42 ± 2.15	1.01 ± 2.10	5.81 ± 3.61

Mean ± SD.

Stimulus type (congruent-incongruent) had an effect of mean amplitude for the auditory N400, $F(1, 29) = 86.301$, $p<0.0001$, with an estimated mean difference of 5.0μV (SE= 0.54) was found. On average larger negative amplitudes for the incongruent word primes (M = -1.72μV SE = 0.62) compared to congruent primes (M = 3.28 μV, SE = 0.67) were found. A channel main effect was found, $F(1, 29) = 8.133$, $p = 0.0054$, with an estimated mean difference of 1.54μV (SE= 0.54). On average larger mean amplitudes were found at Cz (M =1.55μV, SE = 0.62) compared to Pz (M= 0.02μV, SE = 0.62). Further post-hoc (Tukey HSD) showed the estimated mean differences between stimulus conditions at Cz was 5.41μV (SE=0.76), and at Pz was 4.59μV (SE=0.76).

Visually presented word pairs showed a main effect of stimulus type (congruent vs. incongruent condition), $F(1, 29) = 6.848$, $p = 0.0105$, with an estimated mean difference of 1.71μV (SE=0.65). On average larger negative mean amplitudes were found for incongruent (M = -1.56μV, SE = 1.09) compared to congruent (M = 0.15μV, SE = 1.09) stimulus conditions. There was a channel effect, $F(1, 29) = 17.635$, $p < 0.0001$, with an estimated mean difference of 2.75μV (SE=0.65). On average larger negative amplitudes were observed at Cz (M= -2.08 μV, SE = 1.09) compared to Pz (M= 0.67μV, SE = 1.09). Further post-hoc (Tukey HSD) showed the estimated mean difference between stimulus conditions at Cz was 1.59μV (SE=0.26), and at Pz was 1.83μV (SE=0.26). Quantitative mean amplitude measures for group-level N400 between congruent and incongruent word primes is shown in Table 2.3.

Table 2.3 Summary Statistics: Mean amplitude measures for group-level N400 (μV).

ERP	Channel	Auditory Word Pair Stimulus (μV)		Visual Word Pair Stimulus (μV)	
		Congruent	Incongruent	Congruent	Incongruent
N400	Cz	4.26 ± 4.47	-1.15 ± 4.62	-1.28 ± 6.92	-2.88 ± 7.04
	Pz	2.31 ± 3.18	-2.27 ± 3.45	1.58 ± 5.67	-0.25 ± 6.13

Mean ± SD.

Table 2.4 Summary of the Effects Tests: F-ratio and p-values of all the main effects and interaction effects of mean amplitude ANOVAs.

ERP	Source	Auditory		Visual	
		F Ratio	Prob > F	F Ratio	Prob > F
N100	Stimulus	**78.4661**	**<0.0001**	**29.8380**	**<0.0001**
	Channel	3.8962	0.0516	1.0253	0.3142
	Stimulus* Channel	0.0907	0.7640	1.3884	0.2420
P300	Stimulus	**137.0415**	**<0.0001**	**138.8442**	**<0.0001**
	Channel	1.7835	0.1717	**17.2778**	**<0.0001**
	Stimulus* Channel	1.4747	0.2323	0.8177	0.4435
N400	Stimulus	**86.3009**	**<0.0001**	**6.8476**	**0.0105**
	Channel	**8.1326**	**0.0054**	**17.6354**	**<0.0001**
	Stimulus* Channel	0.5831	0.4471	0.0327	0.8570

A main effect of stimulus condition was found regardless of electrode site for all the targeted ERPs. Only visual P300 and N400, and auditory N400 had evidence of a channel effect, however all showed an estimated mean difference of stimulus condition at Cz. Hence, Cz, being the central and overlapping site across all components, and the site used in our previous brain vital signs studies (Ghosh-Hajra, 2016; Fickling et al., 2018), it was chosen for adjusted baseline amplitude and peak latency measures and EBS values for comparison analysis.

2.3.2. Comparison of auditory and visual sequences (Hypotheses iii, iv, v and vi)

The adjusted baseline amplitude and peak latency measures for the 3 components across modalities were measured at Cz electrode site, which were used to compare amplitudes and latencies across modalities using matched paired t-tests. The Wilcoxon test was used for values that did not pass the Shapiro-Wilk W test for normality. Adjusted baseline amplitude and peak latency measures were translated into EBSs and compared via matched pairs t-tests to show the normalization of differences within modalities. Lastly, correlation analysis was done to evaluate the relationship between modalities using the Pearson *r* correlation, and Spearman rho for non-parametric data.

Adjusted baseline and peak latency measures

The group averaged adjusted baseline amplitude and peak latency measures for the 3 components across modalities are shown in Table 2.5. The N100 adjusted baseline amplitude measures were non-significantly different across modalities: auditory (-9.17 ± 3.12 μV) and visual (-8.80 ± 3.26μV) (p=0.8089). However, N100 peak latencies were significantly different across modalities (mean difference= 16.20, SE = 4.37, p = 0.0009), with an average latency of 139.33 ± 10.60ms for auditory and 123.13 ± 21.43ms for visual. The Wilcoxon Signed-Test showed that the P300 adjusted baseline amplitude measure was non-significantly different across modalities: auditory (8.06 ± 3.79μV) and visual (8.87 ± 2.63μV) (p =0.5040). The auditory P300 peak latency (309.0 ± 42.82ms) was on average significantly earlier compared to visual (369.07 ± 58.56ms), estimated mean difference = 60.07, SE= 9.41, p < 0.0001. The N400 differed significantly within adjusted baseline amplitude and peak latency measures across modalities; auditory N400 amplitude (-5.82 ± 2.11μV) was smaller compared to the visual N400 (-6.82 ± 1.80μV) (p = 0.0061) and auditory N400 latency (488.73 ± 58.97ms) was later compared to the visual N400 (414.40 ± 30.47ms), mean difference = 74.33, SE=11.14 p < 0.0001. All components were present in all participants.

Table 2.5. Summary Statistics: Adjusted baseline amplitude and peak latency measures for group-level ERP characteristics at Cz.

ERP	Measure	Auditory	Visual	p- value
N100	Amplitude (μV)	-9.17 ± 3.12	-8.80 ± 3.26	0. 8089
	Latency (ms)	**139.33 ± 10.60**	**123.13 ± 21.43**	**0.0009**
P300	Amplitude (μV)	8.06 ± 3.79	8.87 ± 2.63	0.5040
	Latency (ms)	**309.00 ± 42.82**	**369.07 ± 58.56**	**p < 0.0001**
N400	Amplitude (μV)	**-5.82 ± 2.11**	**-6.82 ± 1.80**	**0.0061**
	Latency (ms)	**488.73 ± 58.97**	**414.40 ± 30.47**	**p < 0.0001**

Mean ± SD.

Elemental Brain Scores (EBS)

All mean EBS and matched pairs t-test statistical results are shown in Table 2.6. Only the measures for visual P300 amplitude did not pass the normality test, therefore the Wilcoxon test was used for comparison. All normalized EBS measures showed no significant differences between modalities. Figure 2.5 shows auditory and visual group EBS in all 6 measures.

Table 2.6. Elemental Brain Scores (EBS) measures for group-level ERP characteristics.

ERP	Measure	Auditory Scores	Visual Scores
N100	Amplitude (μV)	51.78 ± 16.63	49.16 ± 16.67
	Latency (ms)	49.48 ± 16.67	49.12 ±16.67
P300	Amplitude (μV)	53.32 ± 16.67	56.29 ± 16.67
	Latency (ms)	46.17 ± 16.31	49.71 ± 16.64
N400	Amplitude (μV)	51.60 ±16.67	46.68 ± 16.67
	Latency (ms)	52.55 ± 16.67	49.51 ± 16.67

Mean ± SD within-subject elemental brain scores across modalities and * denotes significance at $p < 0.05$.

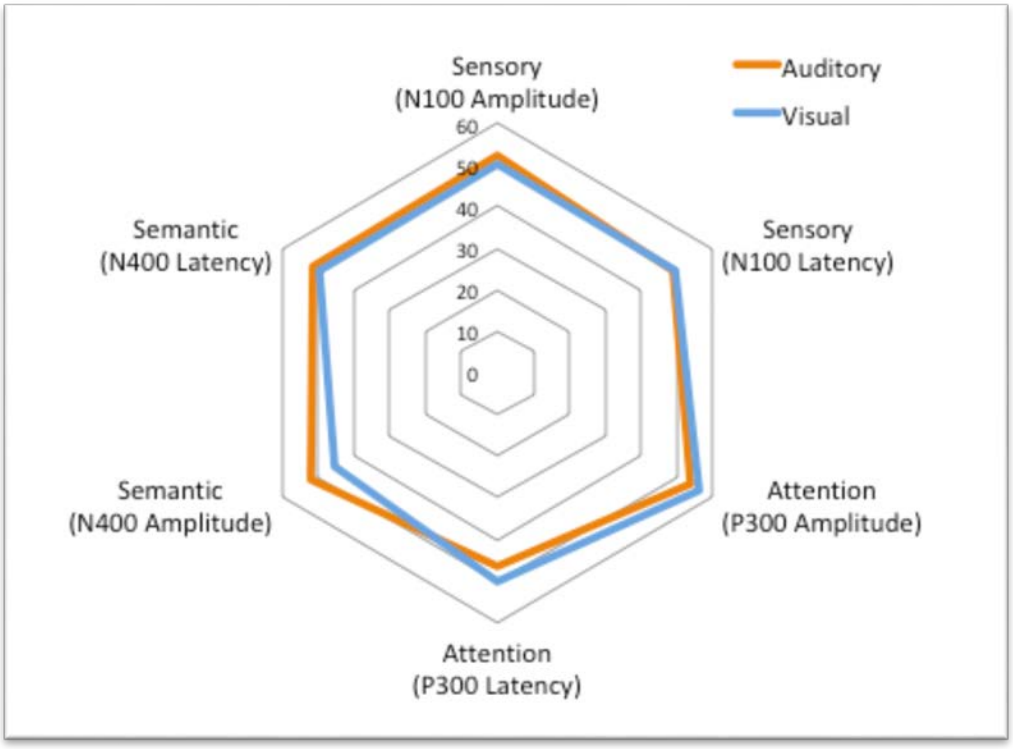

Figure 2.5. Radial Plot of amplitude and latency EBS values for both modalities across all 3 ERP components.

Correlation Analysis

See Table 2.7 for all correlations and figures 2.6 and 2.7 for amplitude and latency scatter plots. Moderate to high correlations were found across modalities in amplitude for P300 (rho = 0.7, p =0.0001) and N400 (r = 0.6, p = 0.0012) and P300 latency (r =0.5, p = 0.0033). The N100 amplitude and latency, and N400 latency showed no significant correlations.

Table 2.7. Correlations of amplitude and latency measures at Cz.

ERP	Measure	Correlation (r)	p- value
N100	Amplitude (μV)	0.3	0.1737
	Latency (ms)	0.04	0.8470
P300	Amplitude (μV)	**0.7***	**0.0001**
	Latency (ms)	**0.5**	**0.0033**
N400	Amplitude (μV)	**0.6**	**0.0012**
	Latency (ms)	0.2	0.3135

Pearson r correlation coefficient used for all normally distributed data and Spearman rho used

for non-parametric data, P300 amplitude*.

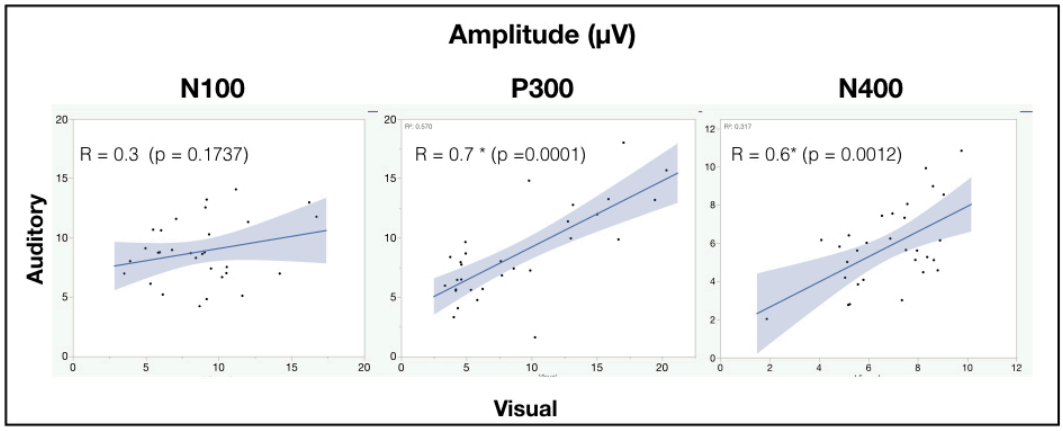

Figure 2.6. Correlation analysis between auditory and visual adjusted baseline amplitude values for each subject. Significance of <0.05 is denoted with *.

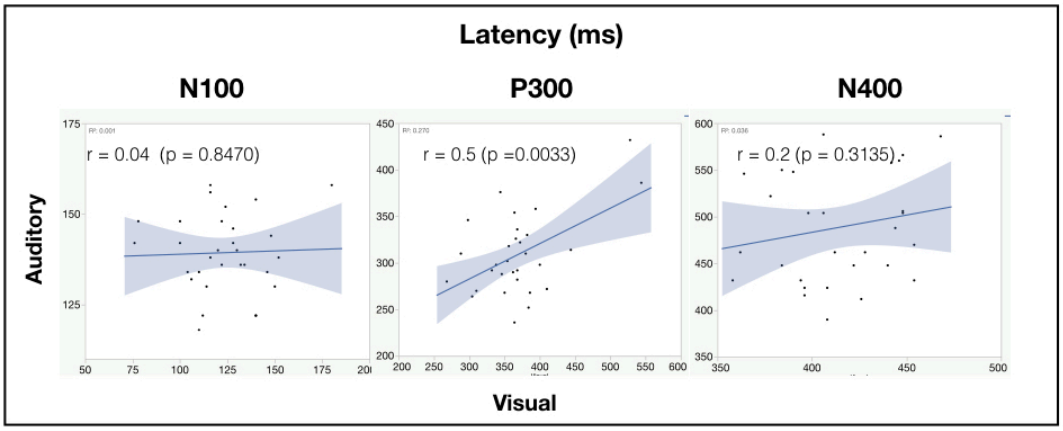

Figure 2.7. Correlation analysis between auditory and visual peak amplitude values for each subject. Significance of <0.05 is denoted with *.

2.4. Discussion

The current study had two objectives to: 1) translate the interlaced, rapid auditory sequence into a visual sequence and validate it by assessing if the targeted EPRs (N100, P300, and N400) are successfully evoked; and 2) compare the raw and normalized

magnitudes (amplitudes) and speeds (latencies) of the targeted ERPs across modalities, and evaluate the relationship between modalities within individuals. The results demonstrated that the targeted ERPs (N100, P300, and N400) were evoked and detectable by comparing mean amplitudes for each stimulus conditions in the visual modality at a group-level (Hypothesis i and ii; see Table 2.2, 2.3 and 2.4). For evaluating objective 2, we first found no differences in group-level average adjusted baseline amplitude measures between modalities for sensory (N100) and attention (P300) processing, however significant differences were found for semantic (N400) processing (hypothesis iii). Projected later peak latencies for the visual modality were found in attention (P300), but opposite in sensory (N100) processing (hypothesis iv). Semantic (N400) processing also revealed faster latencies for visual compared to auditory. However, as expected, the normalization EBS technique successfully eliminated all the relative modality differences found (hypothesis v; see Table 2.6 and Figure 2.5). Lastly, correlation analysis within-subjects, across modalities revealed moderate to strong significant correlations for attention (P300) levels (amplitude) and speed (latency) as well as for semantic (N400) amplitude, (hypothesis vi; see Table 2.7 and Figures 2.6 and 2.7). Overall, this study showed the viability of the developed rapid, interlaced brain vital signs visual sequence, which successfully evoked the targeted ERPs and provided the first step towards understanding the relationship between the auditory and visual brain vital signs sequences. Further discussion of the two objectives and results for each ERP are discussed below.

2.4.1. Targeted ERP Responses (Objective 1)

Mean amplitude measures were used in order to avoid selection bias when first establishing the sequence (Steven J. Luck, 2014, pp. 285-290). This method is also advantageous because conditions with differing number of trials (i.e. standard and deviant) or noise levels (i.e. artifacts) do not affect the results, allowing for all trials to be kept, providing greater statistical power (reducing Type I error rate).

The mean amplitude results revealed that the 3-targeted ERPs were detectable at a group-level in the visual and auditory modality. As expected, a significant difference

between standard and deviant conditions was found, with on average larger negative N100 amplitudes and on average larger positive P300 amplitudes evoked from the deviant conditions within both modalities (see Tables 2.2 and 2.4). These increased amplitudes for the deviant conditions indicate the predicted presence of the N100 and P300 components, marking increased sensory and attention processing, respectively, to the tone intensity deviants (within the auditory sequence), as well as to the SON and contrast flip deviant stimuli (within the visual sequence) compared to the standard stimuli. Within auditory, finding increased N100 and P300 amplitudes to tone intensity deviants is consistent with our past brain vital signs study (Ghosh-Hajra et al., 2016; Fickling et al., 2018) as well as many other auditory oddball paradigm studies (N100: Ryan C N D'Arcy et al., 2011; Sculthorpe-Petley et al., 2015; Vogel & Luck, 2000; P300: Comerchero & Polich, 1998; Terence W. Picton, 1992; John Polich, 2007; Sculthorpe-Petley et al., 2015). Within the visual modality, the increased N100 amplitude to the contrast flip is consistent with past studies using this method (Carrillo-de-la-Peña et al., 1999; Covington & Polich, 1996; Dustman, Shearer, & Snyder, 1982; Johannes, Munte, Heinze, & Mangun, 1995b). The increased positive amplitude (marked by the P300) to seeing one's own name is consistent with several previous studies findings (Tacikowski & Nowicka, 2010; Zhao et al., 2009, 2011; Cygan, Tacikowski, Ostaszewski, Chojnicka, & Nowicka, 2014; Müller & Kutas, 1996; Fabien Perrin et al., 2005). Our results are in line with the interpretation that the P300 amplitude reflects the allocation of information processing resources associated with the attentional system and memory, where an increased P300 amplitude reflects an increased attentional response to particularly self-relevant information, such as one's own name (Cygan et al., 2014; Herzmann & Sommer, 2007; Tacikowski & Nowicka, 2010; Polich, 2007; Herzmann, Schweinberger, Sommer, & Jentzsch, 2004; Zhao et al., 2011).

In general, the P300 scalp distribution of amplitude has been reported to increase in magnitude from frontal to parietal electrode sites (Johnson, 1993) regardless of modality (John Polich, 2007; John Polich et al., 1996). This study's results revealed similar differences across the three electrode sites (channels) for the visually evoked P300 response. A main effect of channel was found ($p<0.0001$), showing the largest estimated means at the parietal electrode site (Pz), followed by central (Cz) and frontal

(Fz). Both Cz and Pz differed from Fz, with the largest estimated mean difference between frontal (Fz) and parietal (Pz) electrodes (2.76μV, SE =0.47, $p < 0.0001$). Studies utilizing visual SON paradigms have reflected this pattern, with larger amplitudes found at central-parietal sites compared to frontal (Gray, Ambady, Lowenthal, & Deldin, 2004; Tacikowski & Nowicka, 2010). However, regardless of electrode, the P300 response (significant difference between standard and deviant conditions) was observed. Post-hoc analysis revealed that all three electrodes still showed a significant difference ($p<0.0001$) between stimulus conditions, with Cz (4.86μV (SE=0.65)) and Pz (4.80μV (SE=0.65)) showing larger estimated differences compared to Fz (3.79μV (SE=0.67)). Therefore, the attention (P300) response to the visual SON paradigm was observed at all three electrodes. This is in line with past literature, where the P300 has commonly been observed over central (midline) scalp locations from frontal to parietal electrode sites (Naumann et al., 1992; Bennington & Polich, 1999; Marta Kutas & Federmeier, 2011). Studies using SON, in particular, have also measured larger P300 responses at central-parietal electrodes compared to frontal (Tacikowski & Nowicka, 2010; Cygan, Tacikowski, Ostaszewski, Chojnicka, & Nowicka, 2014; Zhao et al., 2009, 2011; Fischer et al., 2008).

The overall small negative amplitudes observed in both modalities for the incongruent stimuli condition was not a concern because the N400 is also not always negative in absolute terms; hence a comparison of congruent versus incongruent word pairs conditions, as initially done in this study, is typically done to confirm the N400 effect (Marta Kutas & Federmeier, 2011). Across both modalities, on average larger negative amplitudes were found for incongruent word stimuli, compared to congruent word stimuli (see Tables 2.3 and 2.4). These results indicate the presence of the N400 response as expected due to increased processing in response to violations of semantic expectancies (C. Brown & Hagoort, 1993; Colin M. Brown, Hagoort, & Chwilla, 2000; Chwilla et al., 1998; Ghosh-Hajra et al., 2016; Marta Kutas & Federmeier, 2011; Lau et al., 2008; Osterhout & Holcomb, 1996; Rugg, 1985).

Effects of channel location differed across the two modalities for the N400 response. On average larger mean amplitudes were found at Cz compared to Pz for the

auditory presented words ($p = 0.0054$, estimated mean difference= 1.54µV (SE= 0.54)). Whereas for the visually presented words, slightly larger estimated means were found at Pz compared to Cz ($p < 0.0001$, estimated mean difference= 2.75µV (SE=0.65)). Despite the on average larger mean amplitudes measured at Pz for visual words across stimulus conditions, the difference between congruent and incongruent conditions is of interest when establishing the N400 effect. Further post-hoc analysis showed the estimated mean difference between stimulus conditions at the two electrodes was only slightly larger at Pz (1.83µV, SE=0.26) compared to Cz (1.59µV, SE=0.26). Despite the small difference between Cz and Pz, the N400 effect was still measurable at Cz, which is the site used in past brain vital signs research and the site chosen for modality comparison in this study (Ghosh-Hajra et al., 2016; Fickling et al., 2018). The results are in line with previous literature, with the N400 effect typically being measured at midline centro-parietal scalp sites (M. Kutas et al., 1988; Marta Kutas & Federmeier, 2011; Marta Kutas & Hillyard, 1982a; van Petten & Rheinfelder, 1995).

Overall, the auditory mean amplitude results confirm and extend previous studies that utilized the passive, rapid, auditory sequence to evoke the three-targeted ERPs (Ghosh-Hajra et al., 2016; Ficking et al., 2018). The visual results overall indicate the presence of the visual sensory (N100), attention (P300) and semantic (N400) processing components at a group-level in response to the passive, rapid, visual brain vital signs sequence developed (hypotheses i and ii).

2.4.2. Comparison of auditory and visual sequences (Objective 2)

Sensory (N100) and attention (P300) amplitudes revealed no group-level differences in average levels of activation across modalities at the central location (Cz), however semantic processing (N400) did (see Table 2.5). Peak latency measures showed shorter N400 latencies for visual, and expected longer latencies in the P300; however, the visually evoked N100 was faster compared to auditory evoked sensory processing (see Table 2.5). The conversion into EBS allowed for normalization of all absolute differences found, showing no significant relative differences between modalities (see Figure 2.5 and Table 2.6). The translation into EBS, however, did not affect the correlation across

modalities within individuals because the linear translation from ERP measures to EBS are calculated only relative to the normative database (N=30) within each modality separately, therefore not affecting the relationship across modalities. Correlations done with EBS and ERP measures were identical. Correlation analysis showed significant, moderate to strong (0.5 to 0.7) correlations for amplitude measures for P300 amplitude and latency as well as N400 amplitude across modalities (see Table 2.7 and Figures 2.6 and 2.7). The combination of all these results and comparison between modalities across the targeted ERP components is further discussed in the following sections.

N100

Translating and comparing the auditory sequence to visual proved most difficult for the N100 component, as reflected in the results; no significant correlations in either amplitude or latency were found between the modality sequences. While we found no difference in group-level N100 amplitudes, the lack of correlation implies similar levels of overall activation at a group-level may be occurring, however not consistently within individuals across modalities. The N100 can be evoked in the absence of attention, but can also be influenced by attention to a small extent (Woldorff et al., 1993) therefore, one modality may capture a bit more attentional resources than the other, varying across participants. For instance, some people may have paid more attention, resulting in a larger reaction (amplitude) to the visual stimuli (contrast change) compared to the auditory stimuli (tone intensity change).

Both the auditory and visual anterior N100 are typically measured in frontal-central electrodes, although this study focused primarily on the central site (Cz) as an overlapping site and marker of viability for future applications in a portable EEG system. Mean amplitude analysis revealed that both auditory and visual modalities showed no effect of channel location between frontal (Fz) and central (Cz) electrodes. Further post-hoc analysis revealed a non-significant but slightly larger mean amplitude difference between stimulus conditions at Fz (2.62μV, SE=0.41) compared to Cz (2.45μV, SE= 0.40). However, further correlation analysis of adjusted peak amplitude measures at Fz showed a low but significant correlation (0.4, p= 0.0318; see Appendix Table A.2) not found at Cz (see Table 2.7). The lack of correlation between the auditory and visual N100

amplitudes at Cz possibly reflects that inconsistent levels of sensory processing was being evoked by the auditory and visual stimuli within individuals, however, perhaps Fz should have been chosen as the primary site for comparison. The difference in results could also be due to individual variations of max amplitude across participants. Further analysis of the location of the max N100 amplitude for each modality is needed.

Significant group-level differences and non-significant correlations for sensory (N100) latencies between modalities suggest that speed in sensory processing differs and is not predictive within individuals across modalities. Overall differing latency results were expected due to the known different sensory processing pathways and mechanisms across modalities. Typically earlier latency windows are found for the auditory evoked N100 responses compared to the visually evoked N100 responses (Knott et al., 2003; Niznikiewicz et al., 1997). However, we found the opposite, with on average shorter peak latencies for the visual N100 compared to the auditory N100. Increasing levels of intensity have been reported to shorten the N100 latency, specifically with increased brightness of stimulus flashes (Carrillo-de-la-Peña et al., 1999; Dustman et al., 1982). Hence, perhaps due to the intensity of the contrast from black background (standard stimuli) to the white background (deviant stimuli), we observed a faster reaction compared to the rare deviant tone (100dB vs. standard (75 dB)), within the auditory sequence. Non-significant correlation of the N100 latency implies that auditory sensory processing and visual sensory processing speed are not predicative of one another; speed (shorter latency) in one does not indicate sensory processing speed in the other.

P300

The aim of the visual oddball paradigm within the sequence was to ensure a similar attentional response (P300) was evoked as the one evoked from the established auditory brain vital signs stimulus. This was a challenge because despite the P300 typically being found independent of external factors like modality, other factors to consider such as task difficulty, effort or relevance could affect aspects of P300 generation (Duncan et al., 2009; Patel & Azzam, 2005; Polich, 2007; Jun'ichi Katayama & Polich, 1998; Polich & Kok, 1995; Verleger, 1997). The more effort devoted to a task, the larger the P300 amplitude, which can be attributed as a measure of resource

allocation, yet increased difficulty of a task can cause potential uncertainty and smaller P300 amplitudes (Kramer, Schneirder, Fisk, & Donchin, 1986; for review, see Polich, 2007; Bennington & Polich, 1999; Comerchero & Polich, 1998). Conversely, simple passive oddball paradigms in the visual modality have shown reduced amplitudes, more so in the visual modality than auditory (Bennington & Polich, 1999; Halgren, Marinkovic, & Chauvel, 1998). Therefore, we aimed to develop a passive visual paradigm with a similar difficulty level of detection as the auditory sequence, but still one that was salient enough to evoke a robust P300 response in a passive task. One study (Naumann et al., 1992) used user ratings to quantity level of difficulty across modalities, however both the auditory and visual paradigms are simple, passive and interlaced with the rest of the sequence, so this was not a reliable method for assessing the difficulty of the embedded oddball paradigm.

The visual oddball paradigm used appeared to be evoking similar levels of attentional responses as the auditory paradigm within individuals; no significant difference at the group-level and a strong correlation of adjusted baseline amplitude between modalities was found (rho=0.7, p=0.0001; table 2.7). These results imply that similar levels of attention allocation (marked by P300 activation) were being evoked in subjects from either sequence despite the different oddball approaches. The salient visual oddball paradigm included a subject's own name (SON) with a changed contrast (black background with white writing to white background with black writing) stimulus. The contrast change from black background to white was primarily used to evoke a sensory response (N100), however it was presented in combination with the SON. This confounding stimulus may have affected the P300, however, such a change in brightness has been documented to elicit an early N100 response and a P200 prior to the P300 (see Figure 2. 3; Hruby & Marsalek, 2003; Carrillo-de-la-Peña et al., 1999; Dustman et al., 1982). These early visual sensory (N100-P200) responses often occur with P300 components in visual oddball paradigms and should not have interfered with the P300 evoked from participants recognizing their own names. The stimulus was presented for 600ms, allowing plenty of time for participants to react and adjust to the contrast change and recognize their names. The change in contrast may have caused participants to increase their engagement in the task and level of attention to when their names were

presented, in turn potentially affecting the magnitude (amplitude) of the P300 response to the SON. The deviant condition is therefore a potential confounding stimulus for the P300, however, it was chosen in order to reach our first objective of developing a passive visual sequence that successfully evokes the targeted ERP responses. Designing a passive visual oddball paradigm that evokes a robust P300 was a challenge, hence based on pilot data and extensive literature review, a salient visual stimulus was developed, which reflected a measurable P300, similar in size as the one evoked from the auditory sequence at a group-level and correlated across individuals.

Overall, the non-differing and correlated P300 amplitude responses arose from two very different manipulations (tone oddball paradigm, and visual contrast flip and SON) and yet they both reflected a similar overarching P300 response, produced by a distributed network of brain processes associated with attention and memory operations (Polich, 2007). Within auditory, finding increased attentional responses (P300 amplitudes) to tone intensity deviants is consistent with past brain vital signs studies (Ghosh-Hajra et al., 2016; Fickling et al., 2018) as well as many other auditory oddball paradigm studies (N100: Ryan C N D'Arcy et al., 2011; Sculthorpe-Petley et al., 2015; Vogel & Luck, 2000; P300: Comerchero & Polich, 1998; Terence W. Picton, 1992; John Polich, 2007; Sculthorpe-Petley et al., 2015). The increased positive amplitude (marked by the P300) to seeing one's own name is consistent with this interpretation that P300 amplitude reflects the allocation of information processing resources associated with the attentional system and memory, where an increased P300 amplitude reflects an increased attentional response to particularly self-relevant information, such as one's own name (Cygan et al., 2014; Herzmann & Sommer, 2007; Tacikowski & Nowicka, 2010; Polich, 2007; Herzmann, Schweinberger, Sommer, & Jentzsch, 2004; Zhao et al., 2011).

The speed of attentional processing, reflected by the P300 latency, is thought to index mental classification speed (detection and evaluation of target stimulus), where shorter latencies are related to better cognitive performance (Magliero, Bashore, Coles, & Donchin, 1984; Pelosi et al., 1992; John Polich, Howard, & Starr, 1983). Correlation of latency ($r=0.5$; $p=0.0033$) was also found, however the peak latencies across modalities differed ($p < 0.0001$), with on average shorter latencies observed in the auditory P300

(308.80 ± 41.32ms) compared to visual (365.07 ± 60.55ms). There is "general consensus in the field is that stimulus modality has no significant effect on the P300 amplitude and latency" (Key, Dove, & Maguire, 2005). However, varying results leave the issue of modality effects on the P300 not very clear with some findings suggesting that P300 characteristics are not identical across various modalities (e.g., Johnson, 1989; Key, Dove, & Maguire, 2005). For instance, in line with our results, several studies have reported shorter P300 latencies for auditory stimuli compared to visual in a traditional oddball paradigms (Key et al., 2005; T.W. Picton et al., 1984; Katayama and Polich 1999) as well as from a three-stimulus oddball paradigm (Jun'ichi Katayama & Polich, 1996). Picton 1984 suggested such differences might be due to the differences in stimulus intensity and discriminability between modalities. More recent studies have reported processing time (the P300 latency) to be sensitive to variables involved in stimulus evaluation (i.e. how complex the stimulus is) (Duncan et al., 2009). Therefore the more complex the stimulus, the more time needed to evaluate (process) the target stimulus, the longer the latency of P300 (Donchin & Coles, 1988; Duncan et al., 2009; John Polich, 2007). The visual deviant stimulus used may have been a more complex task (i.e. reading your name after a contrast change) compared to the detection of an auditory deviant tone, therefore causing us to find later visual P300 latencies. Several visual SON paradigms have also reported generally later P300 latencies, between 350–850ms (Tacikowski & Nowicka, 2010; Zhao, 2011). The latency differences may also be partially accounted for by the basic differences in initial pathways of processing across modalities; initial response time in the auditory cortex is approximately 15ms, whereas initial response in the visual cortex occurs around 40-60ms (T.W. Picton et al., 1984). Our results potentially reflect some of this modality difference, with on average longer latencies found for the visual P300 compared to the auditory P300 ($p<0.0001$), by approximately 60.07 ± 9.41ms. Overall, the differences between auditory and visual P300 latencies may reflect a combination of a slightly more complex visual stimulus compared to the auditory as well as basic speed differences of sensory pathways. Based on past literature and the correlated but differing group-level peak latencies found, it can be concluded that similar functional processes of attention were evoked with a possible systematic difference of modalities, where the visual deviant stimulus requires slightly longer time

for detection and processing compared to the auditory deviant stimulus. The correlation also implies that the individual relative speed of detection and classification of the deviant stimuli was similar across modalities; reflecting that attention processing speed within an individual is similar regardless of the stimulus modality.

N400

Designing the visual word pair paradigm in order to elicit the semantic (N400) response was the simplest task from the three components within the brain vital signs framework; the 72 word pairs used in the auditory paradigm were directly translated into the visual paradigm, also presented serially. Utilizing the same word pairs permitted control over factors that may affect the N400 such as word difficulty or frequency of occurrence in the language (Osterhout & Holcomb, 1996). Despite being established as modality independent and reflecting the same functional categorization and overall pattern of semantic processing, small elements of the N400 component have been found to differ across visual and auditory processing of words (Bentin et al., 1985b; Holcomb & Neville, 1990; M Kutas & Hillyard, 1980; M Kutas et al., 1987; Marta Kutas & Federmeier, 2011; McCallum et al., 1984). For instance auditory-presented stimuli tend to elicit longer N400 durations compared to visually evoked N400 response (Marta Kutas & Federmeier, 2011). This is reflected in our results, with the same word pairs used across modalities, yet larger amplitudes ($p = 0.0061$) and shorter latencies ($p < 0.0001$) were found for the visual N400 compared to the auditory N400.

The differing peak amplitudes can partially be accounted for by the known differences in N400 morphology between modalities, however it could imply different levels of processing. Smaller amplitudes at a physiological level may reflect the same group of neurons with smaller post-synaptic potentials (PSPs), fewer neurons activated in the population, and/or less synchronized timing between the groups of neurons (Marta Kutas & Federmeier, 2011). Therefore, the auditory word pairs may be evoking a response that requires or causes less processing (smaller PSPs or fewer neurons) than visual word pairs. This may be a result of reading being a more attention-grabbing task compared to speech comprehension of the word pairs; visual stimuli tend to coerce the utilization of attentional resources more than auditory because of the dominance of the

visual input on attentional processes (Geisler & Polich, 1994). The N400 can be evoked without attention (Relander, Rämä, & Kujala, 2009; Perrin et al., 2002), or with impairments such as in brain injury patients (D'Arcy et al., 2003; Marchand et al., 2002), however, attention can affect the N400 amplitude (Marta Kutas & Federmeier, 2011). Nevertheless, the elimination of the N400 amplitude difference between modalities through the linear translation to EBS, paired with the significant moderate correlation of amplitude ($r = 0.6$, $p = 0.0012$), implies that the modality amplitude difference is possibly systematic. Hence a similar level of semantic processing relative to each modality is being evoked within individuals across modality paradigms.

Emerging neuroimaging technologies have allowed for further investigation into theories of early word processing and recognition (Carreiras, Armstrong, Perea, & Frost, 2014). Competing theories still debate on the precise initial recognition process of printed and spoken words, however data shows that both reading and listening are incremental and largely a serial processes (Rayner, Clifton, & Clifton Jr, 2009; review by Carreiras, Armstrong, Perea, & Frost, 2014). Nevertheless, reading (visual linguistic processing) is faster than listening (auditory linguistic processing) (Breznitz & Berman, 2003), with reading able to reach relatively high speeds (250-350 wpm for most skilled readers) not thought achievable for listening comprehension (Rayner, Clifton, & Clifton Jr, 2009). This difference in speed between reading and listening processing is reflected in ERP studies, with shorter latencies and durations typical of a visual N400 relative to an auditory N400 (Holcomb et al., 1992; Marta Kutas & Federmeier, 2011; Steven J. Luck, 2005). This may account for the differing latencies found across modalities. Furthermore, the lack of correlation in latency also implies that fast reading ability is not predicative of fast speech comprehension and vice versa. Individual differences may have been a factor; for instance some participants may have stronger reading skills than auditory comprehension skills. Some of this variation in the data may be accounted for by varying English language skills; processing speeds have shown to differ between native and secondary language groups (Anurova & Immonen, 2017). All participants were fluent in English; however, some may have been bilingual with English potentially as a second language, as the pool of participants was from a diverse group. For bilinguals, the N400 effect have been found in both their languages, but with language proficiency and age of

acquisition impacting the timing (and sometimes amplitude), showing later and smaller N400 effects for less well-learned languages (Marta Kutas & Federmeier, 2011).

A potential limiting factor of this analysis could be the electrode location chosen for analysis, Cz. The word pair-evoked N400 has commonly been measured and found to be largest at midline centro-parietal (Cz-Pz) scalp sites (M. Kutas et al., 1988; Marta Kutas & Federmeier, 2011; Marta Kutas & Hillyard, 1982a; van Petten & Rheinfelder, 1995). The auditory mean amplitude analysis showed an effect of electrode location, with on average larger mean amplitudes at Cz compared to Pz, with larger mean differences between congruent and incongruent stimuli also found at Cz. Within the visual modality, however, on average larger N400 mean amplitudes were found at Pz compared to Cz, with also slightly larger mean differences between congruent and incongruent stimuli also found at Pz. As such, utilizing Cz, rather than Pz for comparisons of adjusted baseline amplitudes and correlation analysis may not have fully captured the visual N400 response. This may have affected the results, and suggest that Pz may be the site to focus on in future N400 analysis for this visual sequence. Despite this possibility, the presence of the N400 was confirmed with the mean amplitude analysis at both Cz and Pz and correlations of adjusted baseline amplitude were found at Cz (see table 2. 7). Topographic differences in the past were often thought to suggest different processors, however, more modern views in the field hold more "…distributed and interactive views, where distributional differences are…treated in a graded rather than categorical fashion" (Marta Kutas & Federmeier, 2011). Therefore, despite some small scalp topography differences across modalities, the same underlying functional semantic processing is thought to be reflected from both the auditory and visually evoked N400.

Summary

The developed, passive, interlaced and rapid visual sequence successfully evoked the targeted cognitive processes (ERPs) at a group-level (Objective 1: hypothesis i and ii). All three components were measurable at central electrode locations, showing potential for portable EEG application in the future, as done with previous brain vital signs studies (Ghosh-Hajra et al., 2016; Fickling et al., 2018). Overall modality comparison analysis at the central electrode site (Cz) revealed that primarily attention

(P300), as well as semantic (N400) processing, are potentially transferrable and comparable across modalities, however sensory (N100) processing is not (Objective 2). Sensory processing levels did not differ at a group-level, however lacked correlation implying overall levels were potentially achieved with the two modalities, but inconsistently evoked across modalities within individuals. Sensory processing speeds were significantly different across modalities before EBS normalization and also lacked significant correlation. Initial group-level differences in attention processing speeds and sematic processing levels, paired with normalization and correlations across modalities, indicated potential modality systematic differences in attention processing speeds and levels of semantic processing activation for visual stimuli. The significant correlation of attention latencies but not sensory or semantic implies perhaps only attention processing speed is similar and predictive in an individual across modalities, but speeds in sensory perception and language comprehension are unrelated across modalities. While some modality differences were revealed, more importantly, the developed visual sequence successfully evoked the targeted ERPs, establishing an initial visual sequence in the brain vital signs framework.

Chapter 3.

Conclusion

3.1. Future Directions

The main goal of this study was to translate and develop a visual tool within the brain vital signs framework that successfully evokes sensory (N100), attention (P300) and semantic (N400) processing. The expected cognitive processes (marked by the targeted ERPs) were confirmed at a group-level in this study, demonstrating that the developed visual sequence successfully evoked all the targeted responses using a rapid, passive sequence design. Overall, this study is the initial step towards utilizing a visual based tool that can expand the capability of the brain vital signs framework by providing an alternative objective, standardized tool to monitor cognitive changes in populations that suffer from hearing loss or impairments. Once adapted to a portable system, similar to the auditory version, the visual brain vital signs sequence could be utilized to monitor the impacts of many different factors on brain function. Such a tool is beneficial for tracking how interventions (i.e. medications, rehabilitation) or activities (i.e. physical activity) impact brain function. For instance, altered visual-spatial attention (N100) has been associated with falls risk in older adults (Handy, T., 2013). Other studies have shown the value of measuring cognitive components, such as tracking pathological changes of the P300 in relation to cholinergic-based theories of dementia (V Knott et al., 2003), Alzheimer's disease (AD), Parkinson's disease, schizophrenia or depression (Hruby & Marsalek, 2003; Landa, Krpoun, Kolarova, & Kasparek, 2014). Research in cholinergic –based drug impacts on cognitive function has also shown differing impacts to the visual and auditory attention processing in both healthy and AD patients (Knott, V., 2013). Therefore, this visual tool may also provide further insight, complementary to the auditory sequence for monitoring brain function in the future. Comparing the visual sequence to the existing auditory sequence provides an interesting insight into inter-modal comparisons and unique methodology for examining cognitive changes underlying cognitive changes over the lifespan, examining changes with age, injury or disease.

Further investigation into individual variability of ERPs' characteristics across time of day, different days, and weeks is currently investigated for the auditory brain vital signs framework and can be adapted in the future to the visual ERPs. A growing normative database also allows for classifying normal, average individual variation in ERP characteristics within the brain vital signs framework.

Future application of the visual brain vital signs will encounter some challenges, such as controlling environmental factors when viewing the sequence. Potential solution for this would be to utilize technologies such as virtual reality (VR) goggles to help control factors, such as luminance, which affects the visual sensory response (N100) (Johannes, 1995). VR goggles may also help ensure that participants are in fact focusing on the visual stimuli presented. However, EOG channels can also be used to track and monitor eye movements (eye saccades) or eye trackers can also be used. Lastly, potential future clinical application will require comparison to established measures of health, such as the neuropsychological assessments or more recent methods such as blood biomarkers.

Alternatively to future applications of the translated brain vital signs sequence, more research into individual-level analysis and the particular mechanisms of the cognitive processes between modalities could be investigated.

Further validation: individual level analysis

A critical next step for the visual brain vital signs is validation at an individual level. The current study provides the initial validation step of a visual sequence within the brain vital signs framework, confirming the targeted visual ERPs at a group-level. It has been shown that ERPs can be used to index cognition reliably at the individual subject level (John F. Connolly et al., 1999; Ghosh-Hajra et al., 2016; Parvar, et al., 2014). Therefore, further validation can be done to confirm the targeted visual ERPs at an individual-level by using machine learning methods, such as support vector machine (SVM), which allows for the training of two category classifiers used to distinguish between stimulus conditions (Parvar et al., 2014). This method, paired with permutation analysis to verify the accuracy of the SVM solution was previously done to confirm ERPs at an individual level with 100 healthy subjects (Sculthorpe-Petley et al., 2015) and

between two age groups (Ghosh-Hajra et al., 2016). A trained SVM classifier provides an expert- independent method to identify response differences, for instance for the P300, comparing standard and deviant conditions.

Characterizing the visual oddball paradigm

Further investigation into the developed visual oddball paradigm could be done by breaking apart the contrast flip from the SON. The contrast flip paired with the SON was used because pilot work confirmed that commonly used stimuli in a passive task caused a reduced P300 response (Polich, 2007). Several more recent studies showed how SON was a reliable method for evoking a robust P300 response (Müller & Kutas, 1996; Fabien Perrin et al., 2005; Tacikowski et al., 2014; Tacikowski & Nowicka, 2010). In order to also evoke an N100 response, the combined stimulus was chosen. However, the contrast flip may have caused participants to blink. Correlation of the timing of blinks throughout the trials and the N100 response could be done in order to see if they coincide, potentially affecting the N100 and subsequent components, such as the P300. Independent component analysis was used to remove any components of eye artifact and still significant N100 and P300 responses were found. The SON was displayed for 600ms and the average blink lasts ~150–300ms in duration (Manning, Riggs, & Komenda, 1983; Riggs, Volkmann, & Moore, 1981), so even if a blink had occurred, the participants would still have time to recognize and read their own name. However, if blinks had consistently occurred to the contrast flip, the amplitude of the N100 could have been affected and the timing of the SON recognition, marked by the P300 latency, may have been increased. Therefore, further investigation into blink rate and timing with the SON and contrast flip could be done.

Modality Differences: lateralization of activity

This study followed the methods of previous brain vital signs studies in order to test the viability of future portable application; hence midline electrodes were utilized. The P300 and N400 were both successfully measured at the midline in both modalities. Lateralization effects for both attention (P300) and semantic (N400) processing have

been found in other studies. Future work on potential lateralization effects between modalities could be done with the data from this study.

The P300 is one of the most widely studied components in ERP research, being evoked in various ways but considered the same attentional response. Many studies have claimed there is no difference between auditory and visual evoked P300 responses with oddball paradigms, however, a recent study argues that there may be some differences in specific neuronal generators of the P300 between modalities; previous studies have failed to detect such potential modality differences reflected in scalp topographies, arguably due to low-density EEG systems (Dreo et al., 2017). Dreo et al (2017) used a 128- channel system, an auditory and visual 3-stimulus oddball paradigm and a normalization technique to study the whole-scalp topographical distribution across modalities by comparing brain-surface distribution as calculated via the Current Source Density (CSD) interpolation method, also know as the spherical spline Laplacian (SSL) method. This method replaces the voltage values at electrodes with current source density ($\mu V/m^2$), by taking the known voltages at the distributed electrodes and applying the spherical spline interpolation method to calculate the entire voltage distribution (BrainVision Analyzer User Manual 2.1.0; Perrin et al, 1990). Dreo et al. (2017) concluded that there is some underlying sensory modality difference in the neuronal generators of the P300 because they found a significant difference between visual and auditory evoked P300 topographies from the target and distractor stimuli, however, not from the target minus frequent or distractor minus frequent comparisons. A couple other studies have reported more specific differing lateralization patterns of P300 amplitude in response to visually presented SON or faces (Tacikowski et al., 2014; Zhao et al., 2011). To further explore the potential for modality specific P300 topographies, CSD maps from this study's data showed some differing activation patterns (see Appendix for P300 CSD maps) but statistical analysis is needed in order to investigate any potential significant modality differences of the P300 scalp topography.

Language processing likewise has some reported lateralization. Several studies have reported lateralization irrespective of the modality (Atchley & Kwasny, 2003; Holcomb, Coffey, & Neville, 1992), whereas others have reported differing lateralization

(left vs. right) across modalities (M Kutas & Petten, 1988; Marta Kutas & Federmeier, 2011; Marta Kutas & Hillyard, 1982a; McCallum et al., 1984; van Petten & Rheinfelder, 1995). There is a large overlap in word processing that occurs in each modality but these processes are not identical. Potential differences have been reflected in N400 studies where visually presented word pairs have shown slightly larger N400 amplitudes over the right hemisphere, whereas auditory presented word pairs have shown slightly larger amplitudes over the left hemisphere at temporal-parietal electrodes (Holcomb & Neville, 1990; M. Kutas et al., 1988). Future analysis in this 64-channel study could be done to potentially investigate any differences of language activation patterns across modalities (see Appendix for N400 CSD maps).

Modality differences: Age Analysis

The current dataset contains a wide age range (19-66yrs old); therefore further analysis into the effects of age can be investigated. Appendix Table A.3 and A.4 show positive correlation with age and latency for P300 in both modalities; higher age, longer latency. These results are in line with previous reports that show age-related P300 latency delays (Braverman & Blum, 2003; Ghosh-Hajra et al., 2016). The previous BVS found increased P300 latencies for the elderly group (50-85 years old) compared to the young group (20-30 years old) (Ghosh-Hajra et al., 2016). Similar future work, selecting differing age groups, with the visual brain vital sequence can be done to evaluate the sensitivity of the visual components to factors such as age. Some studies previously reported that P300 latency age differences were more apparent when evoked with visual rather than with auditory stimuli (Ford & Pfefferbaum, 1991; V Knott et al., 2003). However others have shown remarkably similar results generated by either modality, showing decrease in amplitude and increase in latency with age (Polich, 1991; J. Polich, 1997). Further comparison of the auditory and visual brain vital signs results will provide more insight into the sensitivity of certain cognitive function changes.

3.2. Significance

This study has investigated some of the differences found between auditory and visual modalities, but more crucially translated the established auditory brain vital signs sequence into a visual brain vital signs sequence. The developed rapid, passive, and interlaced, visual 5-minute assessment successfully evoked the 3 targeted cognitive processes, each derived from well-established event-related potentials (ERPs): N100 (sensation); P300 (attention); and N400 (semantic processing). This aids in expanding the reach of the brain vitals signs framework, by providing an additional tool to evaluating brain function with objective, physiological measures. Previous ERP and brain vital signs research has demonstrated the value in evaluating brain function with objective, physiological measures, through monitoring changes in age, concussions, traumatic brain injury and/or disease. The visual brain vital signs sequence has potential future application in populations that have hearing loss or impairments.

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Appendix.

LS Means Plots for mean amplitude ANOVA analysis.

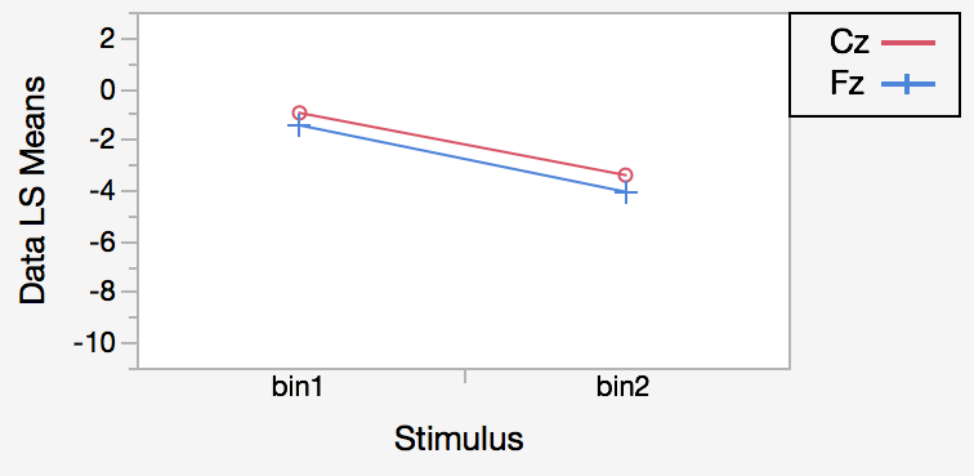


Figure A.1. **LS Means plot for auditory N100 analysis. Bin1 represents standard stimuli and bin2 represents deviant stimuli.**

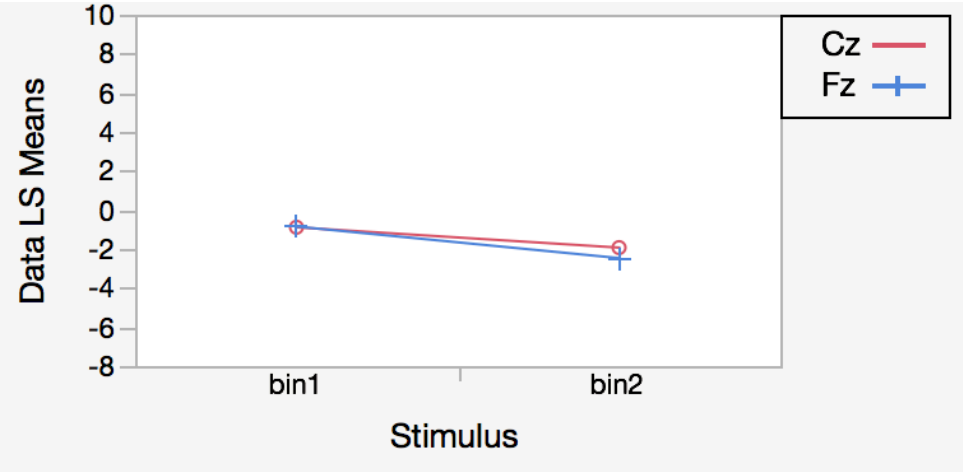


Figure A.2. **LS Means plot for visual N100 analysis. Bin1 represents standard stimuli and bin2 represents deviant stimuli.**

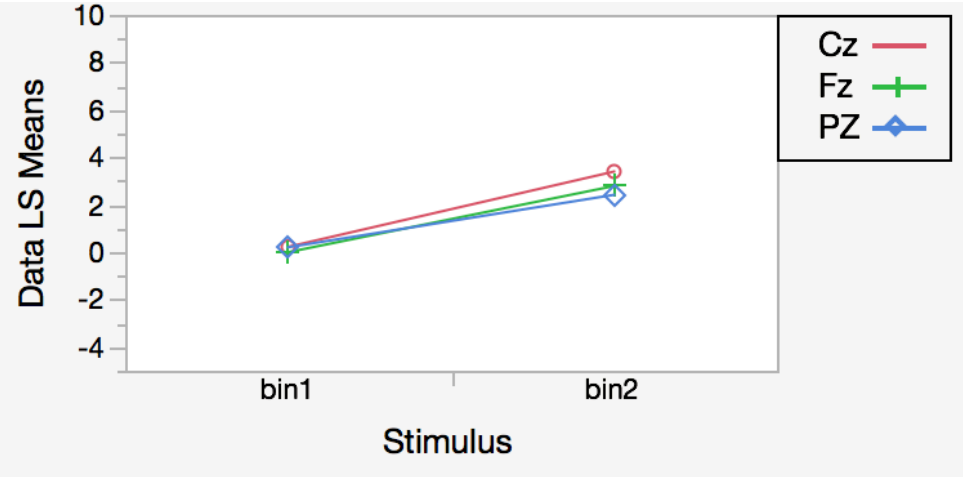


Figure A.3. **LS Means plot for auditory P300 analysis. Bin1 represents standard stimuli and bin2 represents deviant stimuli.**

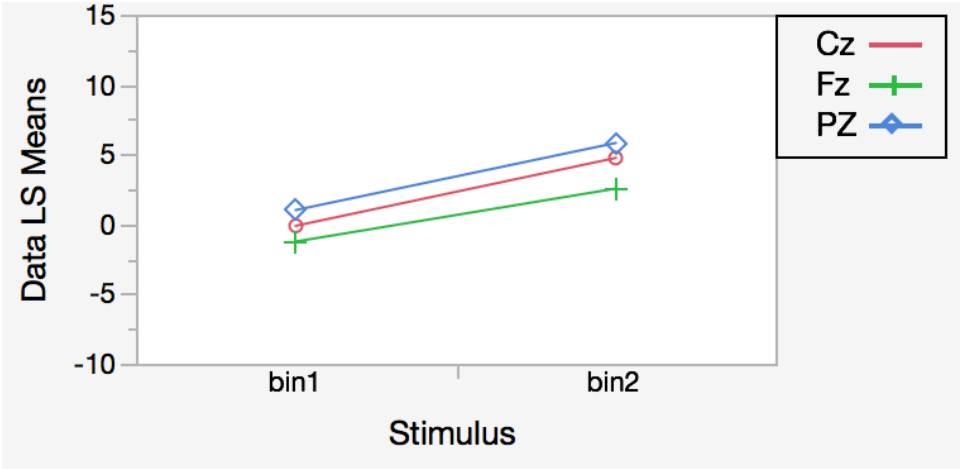


Figure A.4. **LS Means plot for visual P300 analysis. Bin1 represents standard stimuli and bin2 represents deviant stimuli.**

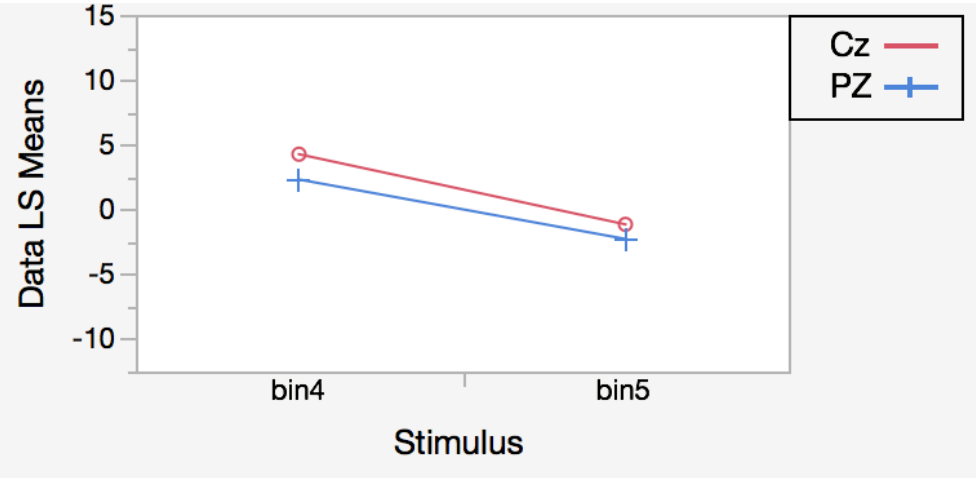


Figure A.5. **LS Means plot for auditory N400 analysis. Bin4 represents congruent stimuli and bin5 represents incongruent stimuli.**

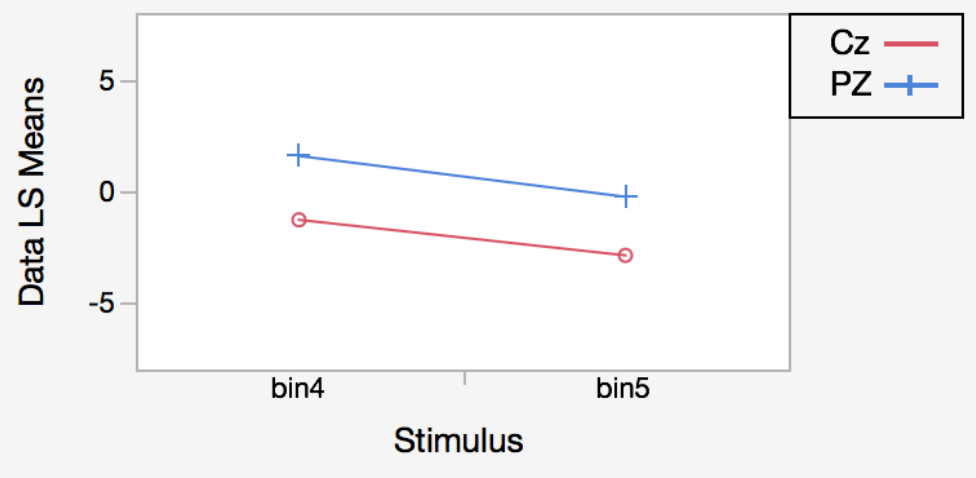


Figure A.6. **LS Means plot for visual N400 analysis. Bin4 represents congruent stimuli and bin5 represents incongruent stimuli.**

Box Plots for mean amplitude ANOVA analysis

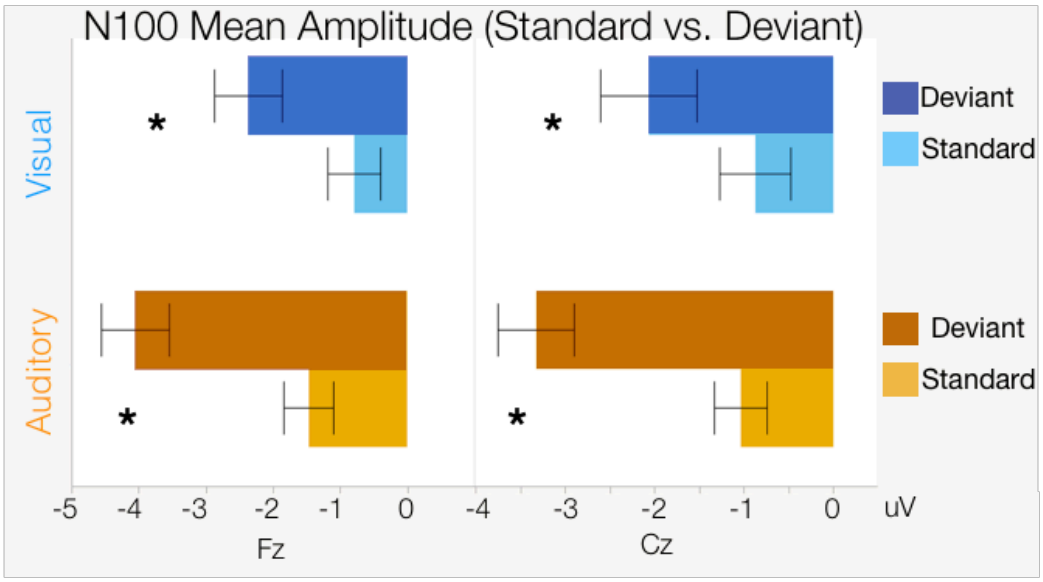


Figure A.7. **Auditory and visual N100 mean amplitude ANOVA analysis, showing the difference between standard and deviant stimuli conditions. *denotes significance, p < 0.05.**

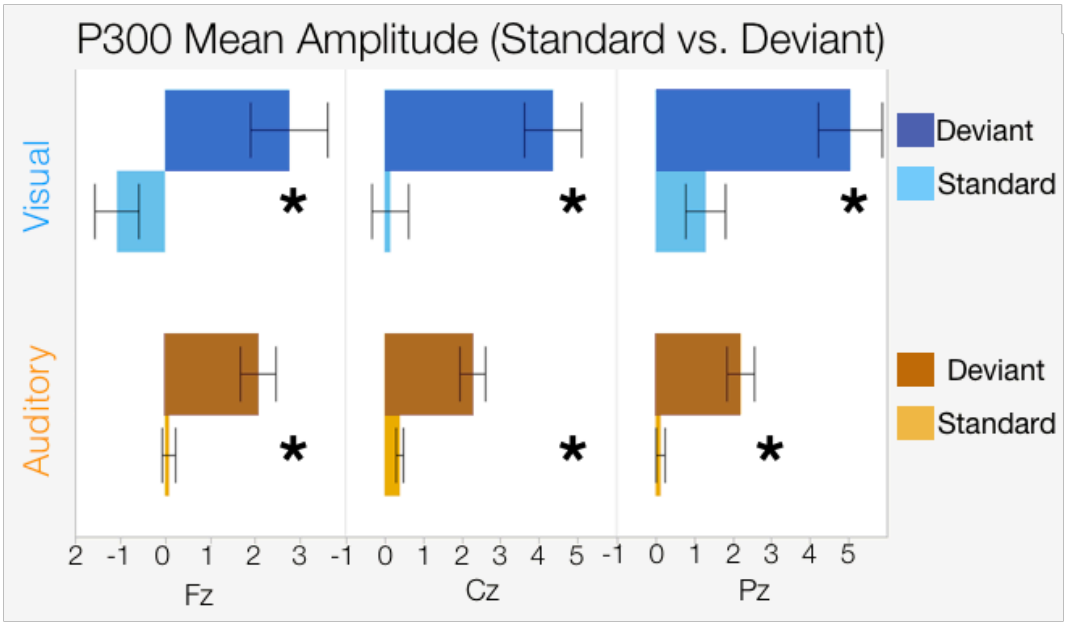


Figure A.8. **Auditory and visual P300 mean amplitude ANOVA analysis, showing the difference between standard and deviant stimuli conditions. *denotes significance, p < 0.05.**

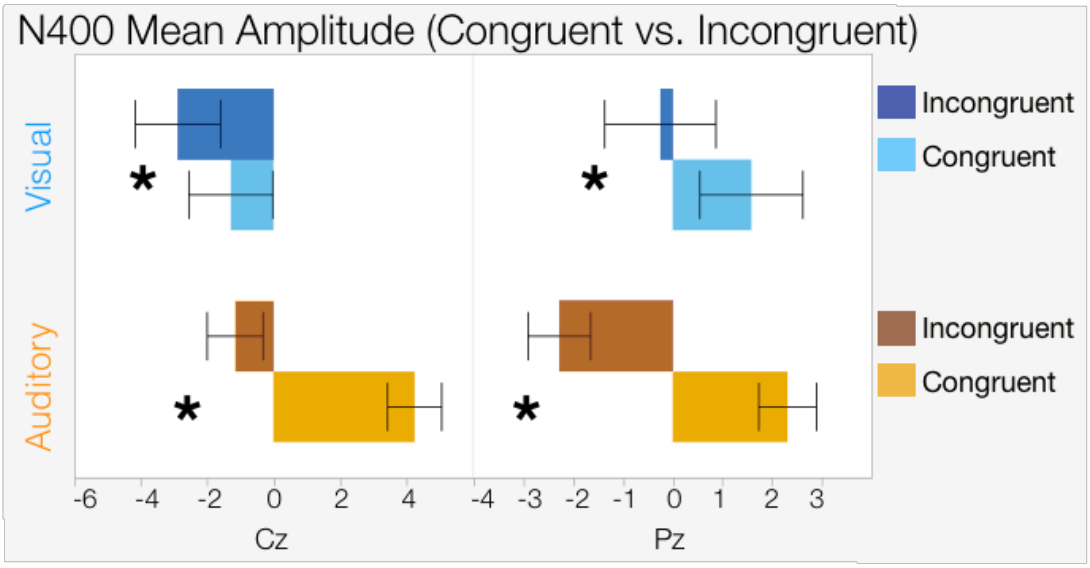


Figure A.9. Auditory and visual N400 mean amplitude ANOVA analysis, showing the difference between congruent and incongruent word pair stimuli conditions. *denotes significance, $p < 0.05$.

Pairwise comparisons (matched pairs t-tests) for adjusted baseline and peak latency measures

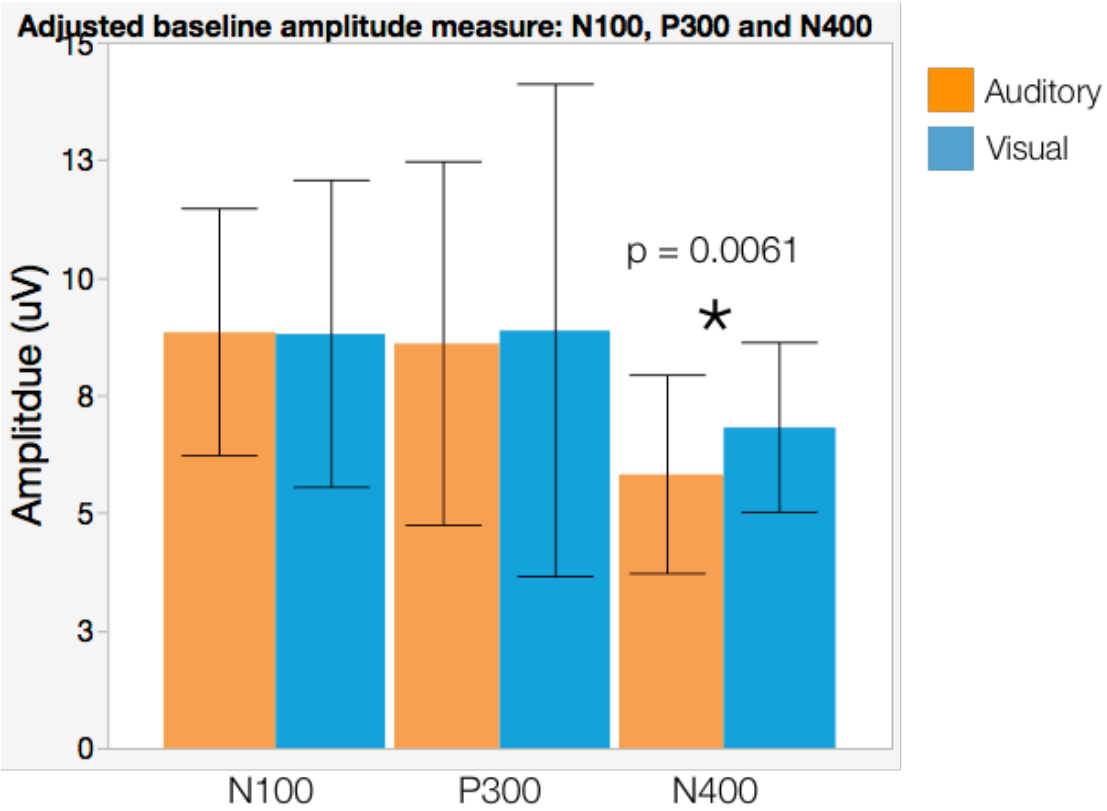


Figure A.10. Auditory and visual adjusted baseline amplitdue matched pairs t-test analysis, showing the difference between modalities. *denotes significance, $p < 0.05$.

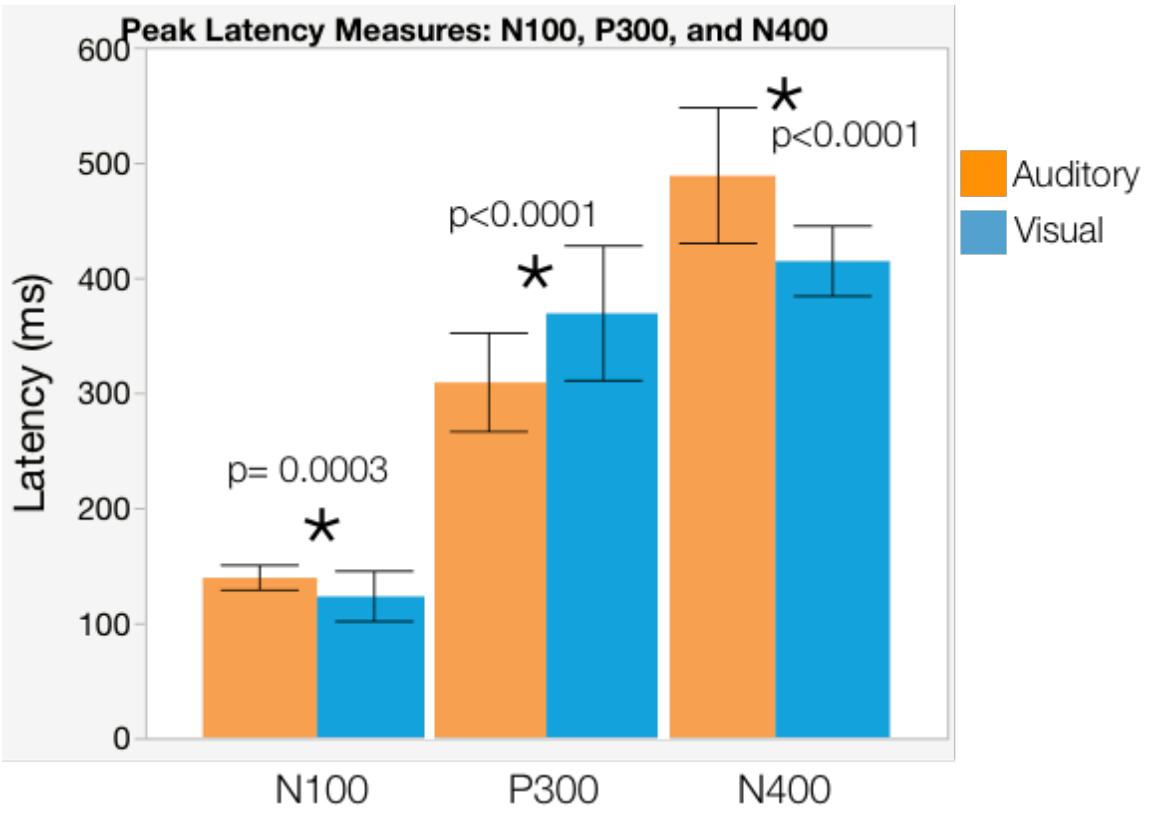


Figure A.11. Auditory and visual latency matched pairs t-test analysis, showing the difference between modalities. *denotes significance, p < 0.05.

Further pairwise comparisons (matched t-tests) and correlation analysis across modalities and age

Table A.1. Adjusted baseline amplitude and peak latency measures for group-level ERP characteristics.

ERP	Measure	Channel	Auditory	Visual	p- value
N100	Amplitude (μV)	Fz	9.20 ± 3.07	9.24 ± 3.62	0.9473
		Cz	-9.17 ± 3.12	-8.80 ± 3.26	0.8089
	Latency (ms)	Fz	142.00 ± 10.48	118.86 ± 24.03	**<0.0001**
		Cz	139.33 ± 10.60	123.13±21.43	**0.0009**
P300	Amplitude (μV)	Cz	8.60 ± 3.79	8.87±2.63	0.5040
		Pz	6.09 ± 3.82	7.12±3.99	0.1186
	Latency (ms)	Cz	308.80 ± 41.32	365.07 ± 60.55	**p < 0.0001**
		Pz	309.00 ± 42.82	369.07 ± 58.56	**p<0.0050**
N400	Amplitude (μV)	Cz	-5.82 ± 2.11	-6.82 ± 1.80	**0.0061**
		Pz	-4.66 ± 2.06	-5.95 ± 1.76	**p<0.0007**
	Latency (ms)	Cz	488.73 ± 58.97	414.40 ± 30.47	**p < 0.0001**
		Pz	481.80 ± 49.80	409.67±31.37	**p <0.0001**

Mean ± SD.

Table A.2. Pairwise Correlations of adjusted baseline amplitude and peak latency measures between the auditory and visual modality.

ERP	Measure	Channel	Pearson r	p- value
N100	Amplitude (μV)	Fz	**0.4***	**0.0318**
		Cz	0.3	0.1737
	Latency (ms)	Fz	0.2	0.4320
		Cz	0.04	0.8470
P300	Amplitude (μV)	Cz	**0.6***	**0.0001**
		Pz	**0.6**	**0.0006**
	Latency (ms)	Cz	**0.5**	**0.0033**
		Pz	0.2	0.2026
N400	Amplitude (μV)	Cz	**0.5***	**0.0011**
		Pz	**0.5***	**0.0028**
	Latency (ms)	Cz	0.2	0.1845
		Pz	0.2	0.3114

Mean ± SD.

Table A.3. Pairwise Correlations of <u>age</u> and <u>auditory</u> adjusted baseline amplitude or latency measures at Cz.

ERP	Measure	Correlation (r)	p- value
N100	Amplitude (μV)	-0.2	0.2893
	Latency (ms)	0.1	0.4644
P300	Amplitude (μV)	-0.3	0.1606
	Latency (ms)	**0.5****	**0.0026**
N400	Amplitude (μV)	-0.2	0.3015
	Latency (ms)	-0.07	0.7070

Pearson r correlation coefficient used for all normally distributed data and Spearman rho used for non-parametric data, P300 amplitude. * denotes significance at $p < 0.05$ and ** denotes $p < 0.01$.

Table A.4. Pairwise correlation of age and visual adjusted baseline amplitude or latency measures at Cz.

ERP	Measure	Correlation (r)	p- value
N100	Amplitude (μV)	-0.01	0.9575
	Latency (ms)	0.1	0.5186
P300	Amplitude (μV)	-0.01	0.9575
	Latency (ms)	**0.50****	**0.0056**
N400	Amplitude (μV)	-0.1	0.5179
	Latency (ms)	-0.1	0.5624

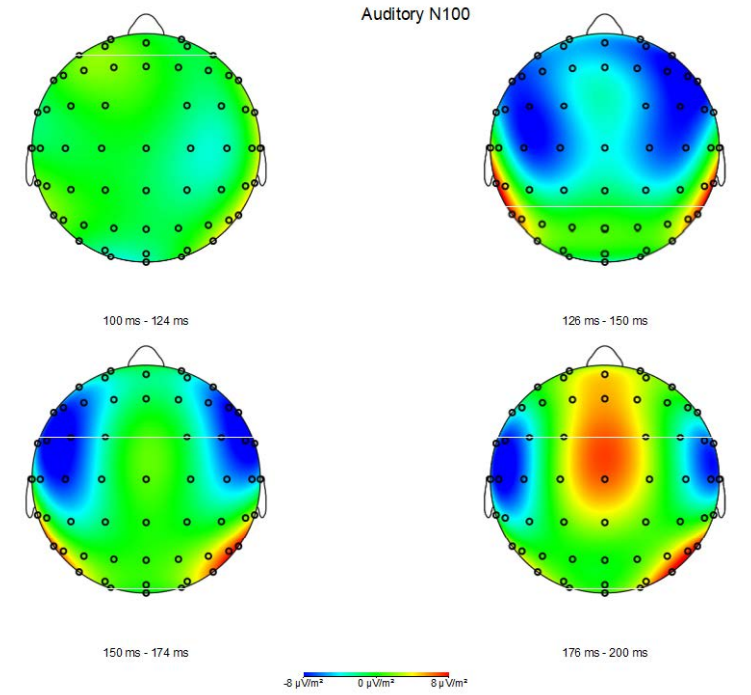
Pearson r correlation coefficient used for all normally distributed data and Spearman rho used for non-parametric data, P300 amplitude. * denotes significance at $p < 0.05$ and ** denotes $p < 0.01$.

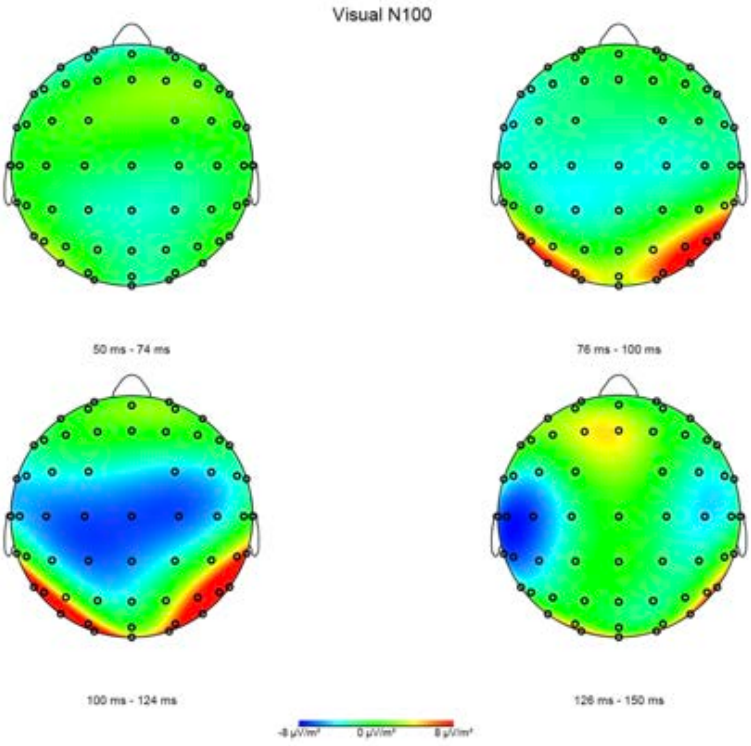
Table A.5. Partial Correlation: Age was taken out as a covariate (control).

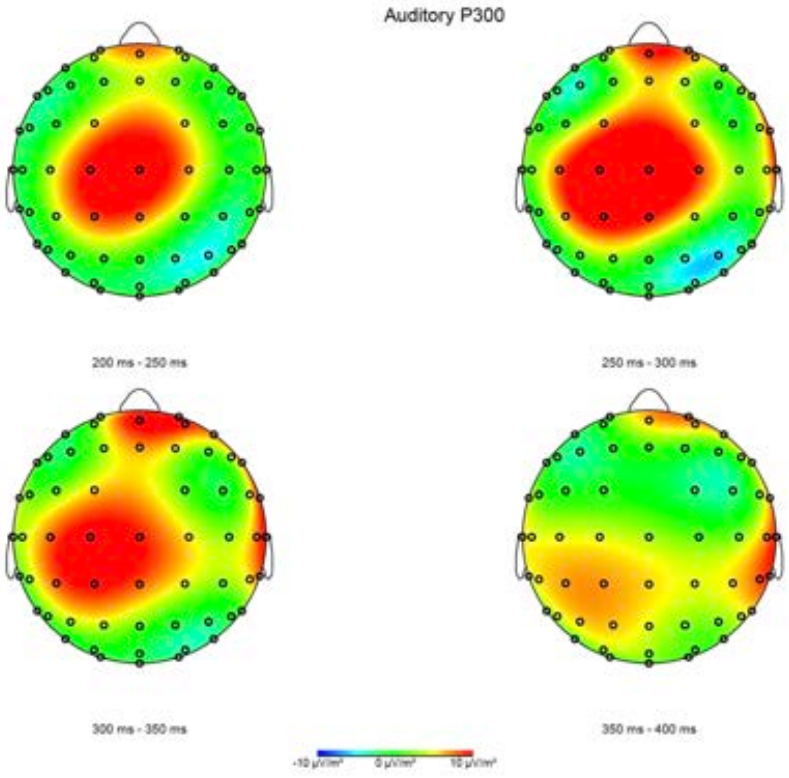
ERP	Measure	Correlation (r)	p- value
P300	Latency (ms)	**0.4**	**0.013**

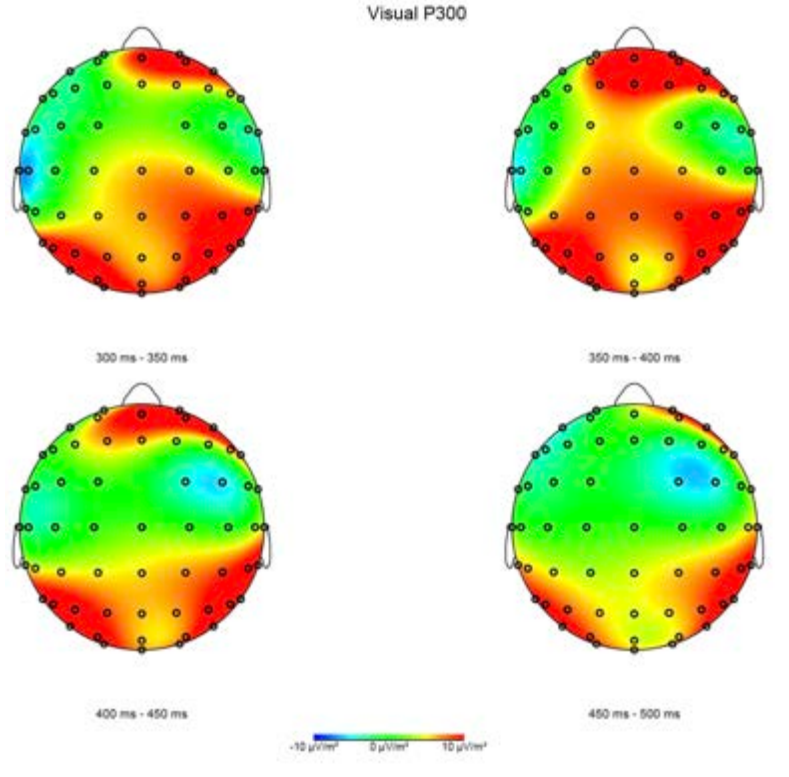
Pearson r correlation coefficient used.

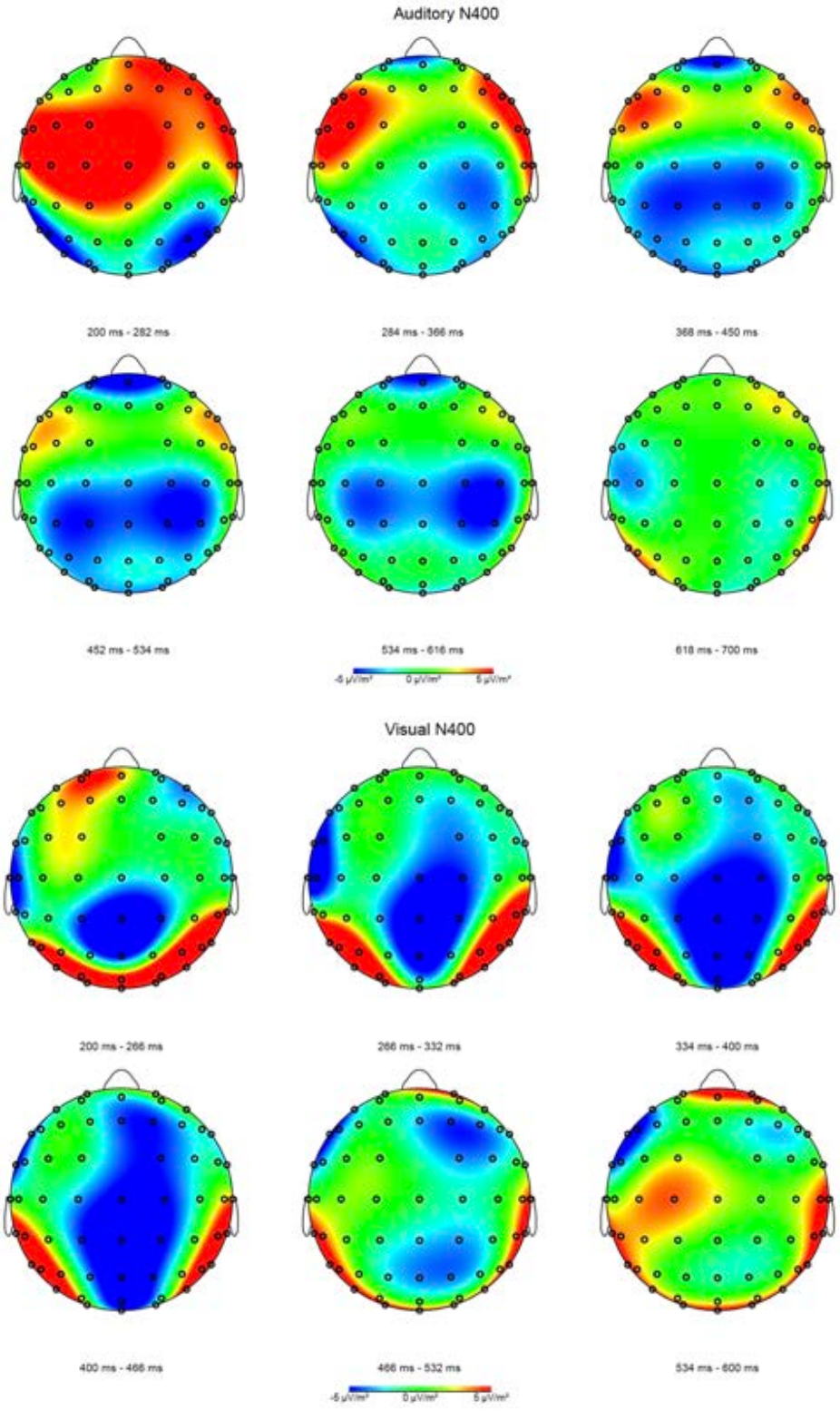
CSD Maps: The order of splines was 4, with a max legendre polynomial degree of 10, based on a default lambda of 1e-5.






Auditory P300
200 ms - 250 ms
250 ms - 300 ms
300 ms - 350 ms
350 ms - 400 ms
-10 µV/m²
0 µV/m²
10 µV/m²


Visual P300
300 ms - 350 ms
350 ms - 400 ms
400 ms - 450 ms
450 ms - 500 ms
-10 µV/m²
0 µV/m²
10 µV/m²


Auditory N400
200 ms - 282 ms
284 ms - 366 ms
368 ms - 450 ms
452 ms - 534 ms
534 ms - 616 ms
618 ms - 700 ms
-5 µV/m²
0 µV/m²
5 µV/m²
Visual N400
200 ms - 266 ms
266 ms - 332 ms
334 ms - 400 ms
400 ms - 466 ms
466 ms - 532 ms
534 ms - 600 ms
-5 µV/m²
0 µV/m²
5 µV/m²

Average versus Linked Mastoid Reference

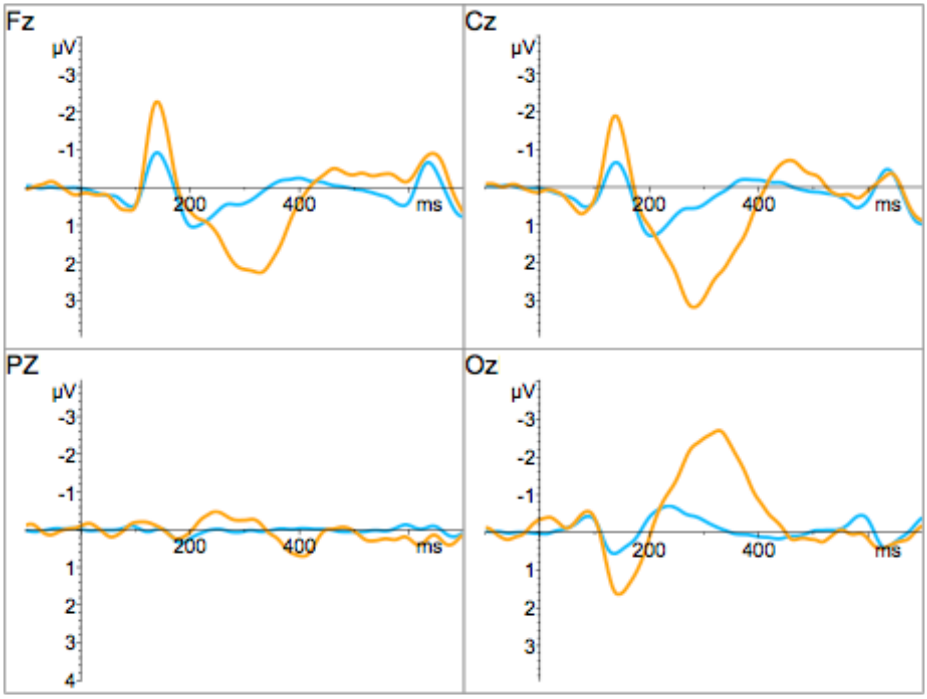


Figure A.12. Auditory grand average with average reference.

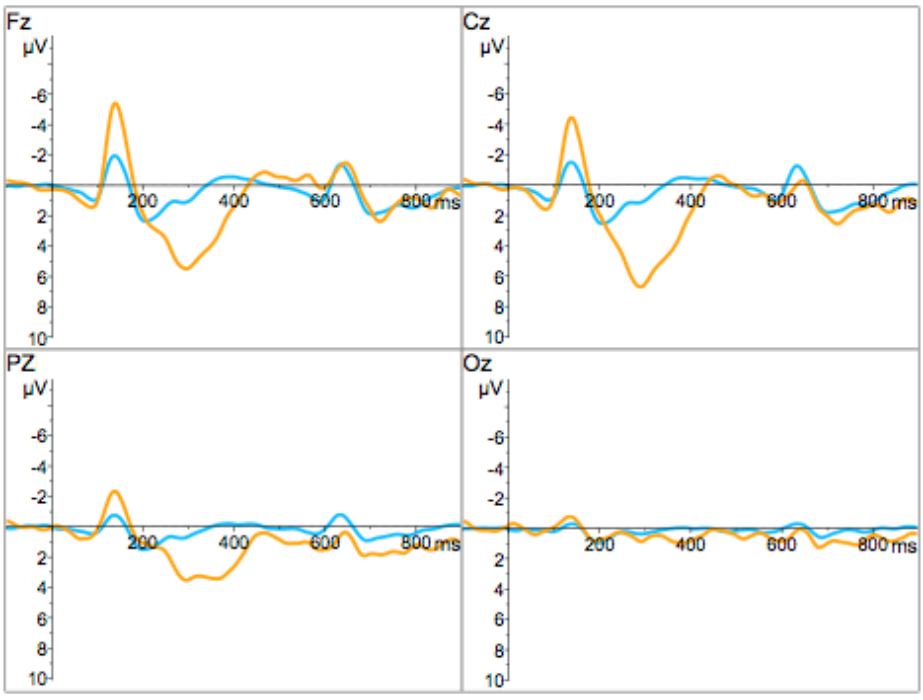


Figure A.13. Auditory grand average with linked mastoid reference.

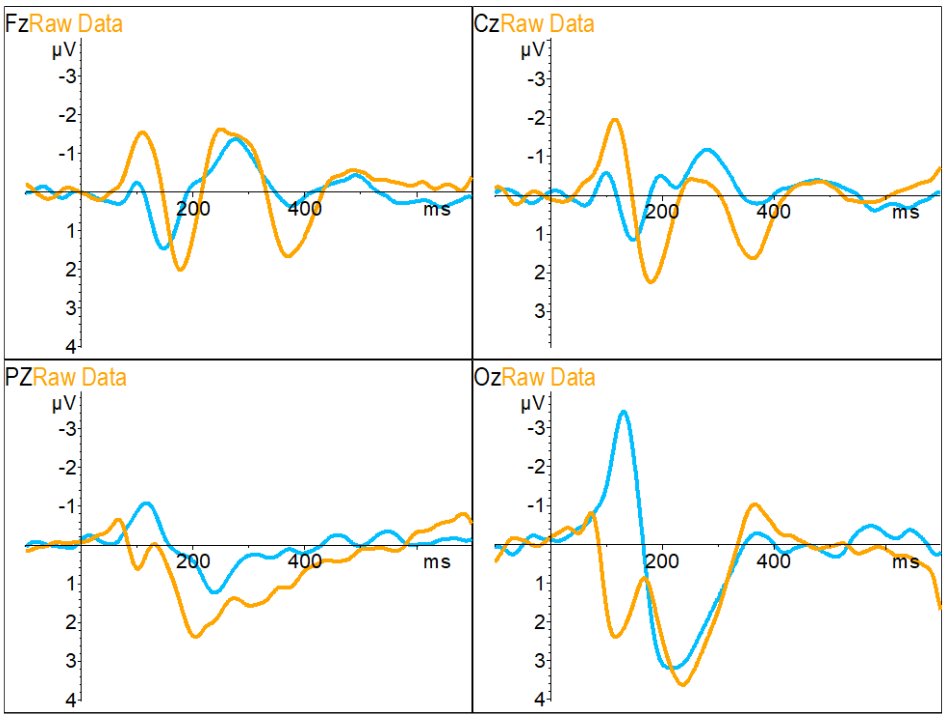


Figure A.14. Visual grand average with an average reference.

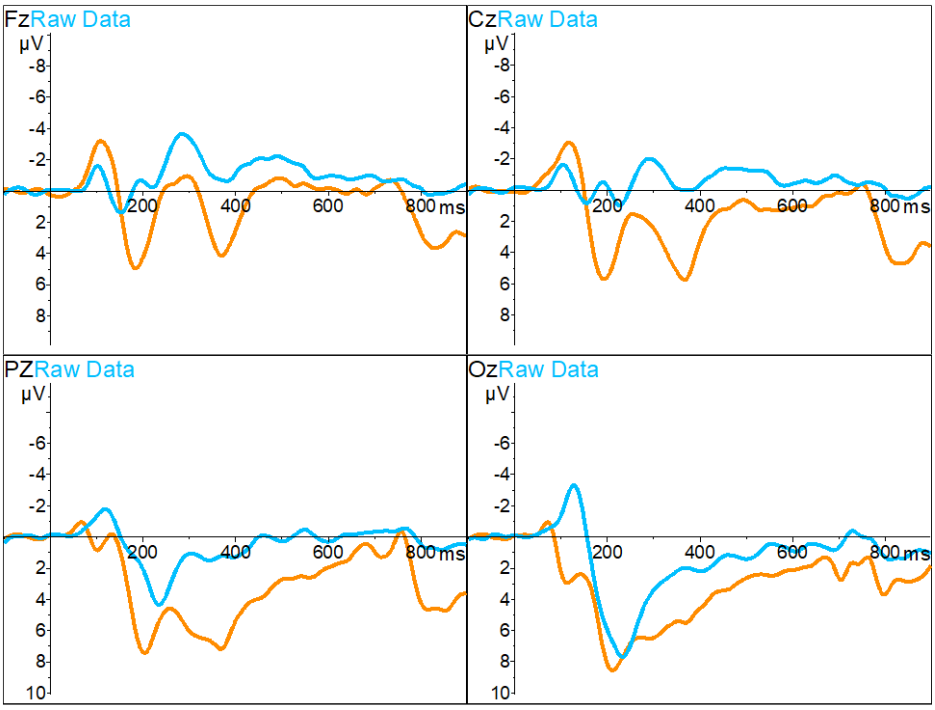


Figure A.15. Visual grand average with a linked mastoid reference.