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Changes in Cortical Processing Following Unilateral Visual Cortex Deafferentation

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Changes in Cortical Processing Following Unilateral Visual Cortex Deafferentation

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by

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ABSTRACT

After the loss of inputs, cells in visual cortex adapt and begin representing space beyond their classical receptive fields. This ability for functional reorganization is a phenomenon known as neuroplasticity. Homonymous hemianopia is a unique case of this scenario that results from hemispheric deafferentation, or when all visual inputs in to one hemisphere of the brain are lost. This condition occurs due to unilateral damage of the post-chiasmatic geniculo-striate pathway, the network that carries visual information from one side of visual space to the visual cortex for processing. Damage to this pathway causes perceptual blindness in the side of space that it represents. In two experiments, this dissertation investigates the changes in neural response properties immediately following hemispheric deafferentation using event-related potentials (ERPs) and psychophysics. Hemianopia was simulated in healthy adults with the use of an eye-tracker to produce a gaze-contingent display on a computer screen. Results of the ERP study indicate a significant difference in the state of cortical excitability after deafferentation. The complementary psychophysics experiment demonstrated a significant reduction in contrast thresholds for the deafferented hemisphere. These results are consistent with a model of short-term neuroplasticity known as disinhibition and extend our understanding of neuroplasticity to cases of hemispheric deafferentation.

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CHAPTER 1

INTRODUCTION

Until the latter half of the 20th century the consensus among the scientific community was that the brain was largely an unmalleable, static organ that was incapable of reorganization after childhood. However, it is now well known that adult cortex possesses the ability to functionally change its neural representations, a property often referred to as neuroplasticity.

Neuroplasticity can readily be thought about in cases of deafferentation, or a loss of inputs to the central nervous system, especially in the somatosensory cortex. For example, when a digit is amputated, the cortical regions that previously represented this digit are not silenced but become responsive to stimulation of adjacent digits (Rasmusson, 1982). Somatosensory cortex, like the other sensory cortices, is organized topographically. That is, sensory representations are mapped on to the cortical surface in an orderly fashion with nearby body parts being represented nearby one another. When the cortical representation of a body part loses its inputs, the area will reorganize to become responsive to the to the inputs of the surrounding regions of cortex. This phenomenon is not restricted to the somatosensory domain, however, but has been described in auditory (Robertson & Irvine, 1989), motor (Sanes et al., 1988) and visual (Kaas et al., 1990) cortices. This dissertation will examine plasticity within the visual system following the loss of inputs representing one side of visual space.

Neuroplasticity in the visual system is classically described following partial retinal damage where a circumscribed lesion to the retina leads to the deprivation of a small zone within visual cortex of sensory input (Gilbert & Wiesel, 1992). Despite the loss of visual input, these deafferented regions of sensory cortex are not silenced but instead become responsive to stimulus representations well beyond their classical boundaries. Such long-term sensory

neuroplasticity has been studied in animal models (Kaas et al., 1990) and has been further documented in human patients suffering from retinal degeneration (Baker et al., 2008). The study of such large-scale visual reorganization has provided critical insights into neuroplasticity; however, the time scales involved (months to years) prohibit the short-term dynamics of neuroplasticity from being investigated. Changes in visual cortical organization are observable within minutes to seconds of deafferentation and these short-term alterations of visual response properties clearly demonstrate that reorganization is driven by functional changes to existing neural circuits rather than large-scale structural changes (Calford et al., 2000). Investigation into the immediate drivers of this plasticity is critical for advances in treatments for degenerative diseases of the visual system and can serve as a model for understanding plasticity in other cortical systems (sensori-motor, auditory, etc.).

Studying neuroplasticity in humans is often accomplished with the use of electroencephalography (EEG). Scalp-recorded potentials provide excellent temporal resolution of cortical processing, although spatial resolution is quite poor. However, components of the visual-evoked potential (VEP) have been reportedly been localized with a fair degree of certainty (Di Russo et al., 2001, 2003). The first component of the canonical VEP wave, the C1, reflects the first initial afferent processing in primary visual cortex (V1) and peaks around 50-70 ms in occipital electrodes. Later components, the P1 and N1, reflect processing in extrastriate visual areas (Di Russo et al., 2001). Dipole modeling suggests each of these components may be localized to areas near the middle occipital gyrus, although the spatial resolution is too low for a precise visual area to be determined. Both the P1 and N1 are observed maximally in electrodes contralateral to the visual stimulus, with the P1 peaking between 90-130 ms and the N1 between 170-200 ms. Research on the P1 and N1 components have repeatedly found them to be

modulated by top-down attention (Di Russo et al., 2003; Hillyard et al., 1998; Luck, 1995) and changes in cortical excitability (Lunghi et al., 2015; Gannon et al., 2017; Parks & Corballis, 2012).

A number of experiments in humans have found changes in the excitability of visual cortex after reversible deafferentation (Borrojerdi et al., 2000; Lunghi et al., 2015; Parks & Corballis, 2012). After monocular deprivation, visual probes to the deprived eye exhibit increased activity in V1 (Lunghi et al., 2015). In this study one eye of participants were deprived of visual inputs for a period of 150 minutes and then EEG was measured while subjects visual stimuli were displayed to each eye, independently. After this period, probes to the deprived eye showed a significant increase in excitability, while probes to the non-deprived eye had a significant decrease.

A similar study showed that complete light deprivation increases excitability in visual cortex, as well (Borrojerdi et al., 2000). Here, subjects were completely deprived of all visual inputs and then cortical excitability was tested with the use of transcranial magnetic stimulation (TMS). Single-pulse TMS is used to index cortical excitability in visual cortex by determining the minimum intensity needed to elicit a 'phosphene'. A phosphene is an illusory flash of light that is perceived due to direct stimulation of visual cortex by the TMS pulse. Reductions in the intensity needed to elicit a phosphene is explained as an increase in cortical excitability. This experiment found significant reductions in phosphene threshold after a visual deprivation of 180 minutes.

Another method of reversible deafferentation is the artificial scotoma paradigm. Here participants view a dynamic background of white noise with an overlaid gray disk is the periphery. The gray disk effectively restricts visual inputs from the circumscribed region of

space to mimic a visual scotoma. Measuring EEG while a visual stimulus probes the visual space within the artificial scotoma leads to potentiation of VEP amplitudes, a marker of increased excitation (Parks & Corballis, 2012). These studies indicate that, at least in specific instances, deafferentation of portions of visual cortex results in measurable increases in cortical excitability. The increase in excitability in typical deafferentation experiments are thought to be driven by disinhibition of local inputs, as well as by feedback from higher visual areas, both of which rely on intact visual inputs to the hemisphere where the deafferentation has taken place (Masuda, et al., 2008).

Hemispheric deafferentation

There has been less examination, however, of the cortical response after visual inputs are restricted from an entire hemisphere. Some evidence suggests that the transcallosal pathway interconnecting visual areas of two hemispheres has a primarily inhibitory role (Bocci et al., 2011; Kinsbourne, 1987). In one experiment, low-frequency repetitive transcranial magnetic stimulation (rTMS) was performed over one hemisphere of visual cortex. Low frequency rTMS has been demonstrated to have an inhibitory effect by dampening cortical excitability (Chen et al, 1997; Wasserman & Lisanby, 2001). Bocci and colleagues (2011) found that when applied over one visual cortex hemisphere this inhibitory rTMS protocol resulted in an increase of excitability in the contralateral hemisphere. This suggests that suppression of activity in one hemisphere can alter the balance of excitation between and have a disinhibitory effect on the contralateral hemisphere. This pattern of results is consistent to findings with patients with parietal cortex damage. A common symptom of patients with parietal cortex damage is unilateral visuo-spatial neglect. The cause of this neglect has been attributed to increased inhibition being

exerted on the damaged hemisphere by the intact hemisphere, which was ameliorated by inhibitory rTMS over undamaged hemisphere (Fectaeau et al., 2006, Fierro et al., 2006).

Other studies have found interhemispheric connections to be predominantly excitatory in nature (for review, Conti & Mazoni, 1994). Recent single-cell recording studies in cat visual cortex have shown that most neurons show a significant decrease in activity after deactivation of the contralateral hemisphere (Wunderle et al., 2012, 2015). In these studies, one hemisphere of cat visual cortex was reversibly deactivated with thermal cooling and cortical activity measured in the contralateral hemisphere. Controlling the inputs over the interhemispheric network had a mixture of effects on individual neurons. One of the effects was the dampening of the overall responsiveness of cells, indicating that the interhemispheric network plays a role in response gain. The other effect was on the contrast sensitivity of cells, indicating that the interhemispheric network plays a role in contrast gain. The authors conclude that these separate effects demonstrate that interhemispheric connections shape contralateral cell's activity through both input and output gain modulation.

The contradictory results of the above research on the interhemispheric network could potentially be explained by the differing methodologies. Both of these studies showed that the balance of excitation and inhibition is upset when the processing of one hemisphere is disrupted. Neither of these studies, however, used a method of controlling inputs in to one hemisphere and measuring the resultant changes in contralateral hemisphere. The functional effects that this imbalance would have on the response properties of each hemisphere is not yet clear.

Homonymous Hemianopia

Brain damage to the geniculo-striate visual pathway leads to various types of visual impairments. When damage is lateralized to one hemisphere, as can be the case in strokes, trauma, and tumors, the visual deficits that result manifest as a blindness of the visual space contralateral to the damaged hemisphere; a condition known as homonymous hemianopia (HH). Stroke is the leading cause of hemianopia, accounting for more than 60% of cases, with 8%-10% of stroke victims developing the condition (Zhang, et al., 2006). Patients with hemianopia suffer from a myriad of behavioral deficits including difficulties reading (Zihl, 1995), navigating their environment (Mueller, et al., 2003), and driving (Bowers, et al., 2009; Elgin, et al., 2010), producing significant impairments in their daily life and limiting their independence. These behavioral deficits are caused, not only from the lack of conscious vision in one visual field, but also due to deficiencies in compensatory eye movements to the impacted side of space (Zihl, 1995). Stroke is the leading cause of serious long-term disability, with nearly 800,000 stroke cases in the United States per year (Benjamin, et al., 2017). Additionally, risks of stroke vary by demographics with older, black, and low socioeconomic individuals having the highest risks (Benjamin, et al., 2017). This makes impairments due to stroke, such as hemianopia, not just a public health and economic issue, but an issue of diversity, as well.

Among the tested rehabilitative options is a therapy that uses audio-visual stimuli to improve visual detection and orientation to the blinded hemifield (Frassinetti et al., 2005; Passamonti et al., 2009). In this paradigm, a visual stimulus is presented coincident with an auditory stimulus emanating from the same spatial location. In the first study of this kind, Frassinetti and colleagues (2005) demonstrated that patients with hemianopia were able to detect the presence of a visual stimulus in their blind hemifield significantly more often when it was

accompanied with an auditory stimulus from the same position. Interestingly, this effect was not observed when the auditory stimulus was presented at a disparate spatial location, suggesting that general arousal was not the primary driver of the effect. Other studies have shown audio-visual training to be effective in improving oculomotor behavior in visual exploration tasks (Bolognini, et al., 2005, Passamonti, et al., 2009). Here, patients demonstrated improved saccade and fixation profiles during visual search and reading tasks after the training regime, improvements that remained stable at a 1-year follow-up.

Role of retino-colliculo-extrastriate pathway

There is evidence that some individuals with hemianopia due to cortical damage retain some visual behaviors that operate outside of their conscious experience. The term "blindsight" was coined to describe these functional abilities such as above chance detection of a flashed stimulus (Weiskrantz et al., 1974) and even the ability to detect the emotional content of faces (termed affective blindsight) (de Gelder et al., 1999; 2001). It has been proposed that the retino-collicular-extrastriate pathway subserves these residual visual abilities (Barbur et al., 1980; Weiskrantz et al., 1974). This pathway that bypasses V1 often remains intact in patients with hemianopia and, as such, is the subject of investigation for potential therapies.

Investigations into the mechanism by which audio-visual training facilitates these improvements have again pointed towards the involvement of the superior colliculus (SC) and the retino-collicular-extrastriate pathway. The superior colliculus is a midbrain structure that cues a rapid motor response orienting an organism towards sensory stimuli (Wurtz & Albano, 1980). Multisensory properties of the SC have been known since the seminal work of Meredith and Stein (1983) that demonstrated that individual cells in cat SC were responsive to both visual

and auditory sensory stimuli, and the responsiveness of these cells could be enhanced or suppressed superadditively when stimulated with multisensory inputs.

Further work elucidated the principles that governed the responsiveness of these cells, namely that the greatest enhancement occurred when visual and auditory stimuli were presented coincident in both time and space, and when both stimuli are relatively weak in strength (Meredith and Stein, 1986a,b). In this work, the visual and auditory receptive fields of neurons in superior colliculus were mapped by single-cell recordings. The receptive fields of the separate modalities overlapped for a given cell, with the auditory receptive field being larger than the visual receptive field. When an auditory and visual stimulus were both presented within the overlapping receptive field region, i.e. in close proximity, the cell exhibited a multiplicative response enhancement. However, if one stimulus fell outside of the overlapping receptive field, there would be a suppression of the cells response. The presentation of the two stimuli also had to be in close time proximity to create the enhanced response. Additionally, the greatest enhancement occurred when each stimulus was weak in strength. For a unisensory stimulus that would evoke a minimal response from a SC neuron, the addition of a second modality stimulus showed the greatest response enhancement. This has been termed the ‘inverse effectiveness rule’.

In humans, SC is also important for integrating multisensory stimuli. Neuroimaging studies have provided evidence of multisensory gains in BOLD signal during an audio-visual task (Calvert et al., 2001). Similar to the animal electrophysiology studies, the enhanced BOLD signal was superadditive when the auditory and visual stimuli were presented in spatial and temporal coincidence. More recent work using stimuli that are either visible or invisible to SC has been able to show it plays a causal role in audio-visual (Leo et al.,2008) and visuo-motor integration (Tamietto et al., 2009). Neuroanatomical studies have demonstrated that SC does not

receive projections from short-wavelength-sensitive S cones (Marrocco & Li, 1977) and therefore, stimuli that selectively activate S cones are invisible to SC. Taking advantage of this fact, it was found coincident auditory stimuli facilitated response time is a reaction time task when paired with red, long-wavelength stimuli, but not purple, short-wavelength stimuli (Leo et al., 2008). Orienting motor responses and SC BOLD activation have also been demonstrated to be compromised with short wavelength visual stimuli (Tamietto et al., 2009). In patients with unilateral V1 damage, nonconscious orienting towards stimuli in the blind field of vision was impaired for short wavelength stimuli as compared to achromatic stimuli. Reductions of activity in SC and extrastriate visual cortex also accompanied the reduction in orienting behavior.

Extrastriate, temporo-parietal areas such as the superior temporal sulcus and gyrus, and inferior parietal cortex also show enhanced responding to multisensory stimuli (Calvert et al., 2000; 2001). These areas, like SC, respond greatest when auditory and visual stimuli are spatially and temporally coincident (Bertini et al., 2010; Laurienti et al., 2005).

CHAPTER 2

DISSERTATION HYPOTHESES AND METHOD

It is known that extrastriate cortex in the damaged hemisphere is able to become activated through interhemispheric connections from undamaged hemisphere (Kavcic, et al., 2015), as well as from inputs from superior colliculus, via pulvinar, and from lateral geniculate nucleus that bypass V1 (Ajina, et al., 2015). These activations are thought to underlie the blind sight phenomenon and are considered a target for possible vision restoration therapies (Jobke et al., 2009). A promising strategy for visual rehabilitation in patients with hemianopia, recently in use (Frassinetti et al., 2005; Passamonti et al., 2009), has been using concurrent audio-visual stimulation. With this in mind, I further investigate the state of deafferented visual cortex, as in hemianopia, to advance our current understanding with respect to possible recovery strategies. Simulating the effects of hemianopia in healthy adults, I investigated 1) the immediate changes in the response properties of deafferented cortex, and 2) the interactive effect auditory stimulation has on deafferented visual cortex. As described previously, disinhibition of cortical areas has been shown to occurs after deafferentation. Consistent with these previous results, in Experiment 1 this prediction would be demonstrated as increased amplitudes of the P1 and N1 VEP components compared to baseline. Disinhibition would also predict signatures of multisensory processing to be potentiated after cortical deafferentation. In Experiment 2, disinhibition predicts a reduction in contrast thresholds for deafferented cortex and the largest benefit occurring with the coincident presence of an auditory stimulus.

General Method

Two experiments were conducted to assess changes in the response properties of visual cortex due to hemispheric deafferentation. Stimuli and methods were adapted from previous research (Gannon et al., 2017; Parks and Corballis, 2012) using artificial scotoma paradigms that limit visual inputs to circumscribed regions of the visual field. Here, eye-tracking was used to produce a gaze-contingent display to restrict visual inputs to one half of the subjects' visual field, simulating the effects of homonymous hemianopia. This paradigm has been previously shown to induce the behavioral effects experienced by patients with hemianopia (Mitra et al., 2010; Schuett et al., 2009). For each subject, half of the blocks of trials used this simulated hemianopia paradigm and half of the blocks did not restrict stimulation across the visual field. These non-restrictive blocks were used as a control condition. Participants performed a 2 alternative-forced-choice task (2AFC) discriminating the tilt of a gabor stimulus which appeared peripherally in either the 'sighted' or 'blinded' hemifield. In each experiment a coincident auditory stimulus was produced with the visual probe on half of trials to examine the interactive effect that auditory inputs have on the changing visual cortex response properties.

In the following two studies, the terminology I have used for the conditions are Control, Hemianopia – Blind, and Hemianopia – Not blind. Here, the Control condition refers to data from the blocks that did not restrict any visual inputs, while Hemianopia – Blind refers to trials that visually stimulated the visually-restricted hemifield of the simulated hemianopia condition and Hemianopia – Not blind refers to stimulation of the visual hemifield that was not restricted. Additionally, trials in which there was no auditory stimulus coincident with the visual stimulus are referred to as Visual-only and trials in which the auditory stimulus was present is referred to as Simultaneous stimulation.

CHAPTER 3

EXPERIMENT 1

Experiment 1 examined changes in cortical excitability following hemispheric deafferentation. Visual probes were used to elicit visual-evoked potentials (VEPs) in Control, Hemianopia – Blind, and Hemianopia – Not blind conditions. Additionally, on half of trials a coincident auditory stimulus was also presented with the visual target. Planned analyses of VEP waveforms elicited on Visual-only trials examined changes in the visual P1 and N1 components. Each of these components reflect processing in extrastriate visual areas (Di Russo et al., 2001) and have been shown to index cortical excitability (Hillyard, et al., 1998, Martinez, et al., 2001a, b). Analysis of multisensory trials was used to determine an interaction effect of multisensory processing on deafferented cortex.

Method

Subjects

Twenty-four naïve participants (20 females, 87.5% Caucasian) were recruited by email from the University of Arkansas undergraduate population (mean age = 21.8, SD = 2.7). All subjects had normal or corrected to normal vision. Experimentation was approved by the University of Arkansas Institutional Review Board and with the informed consent of each participant. Subjects were compensated with class extra-credit for their participation.

Stimuli and Procedure

Experimentation took place in a darkened room with subjects positioned at a viewing distance of 57 cm from the stimulus computer monitor (refresh rate 60 Hz, 1024 x 768

resolution). Presentation (Neurobehavioral Systems, Albany, CA) was used for stimulus display and all experimental control, while eye-tracking was performed and saved to a separate computer. Task stimuli were Gabor patches 2.0 degrees in diameter with spatial frequencies of .3, 1.25, and 5.0 cycles per degree at 90% contrast (Figure 1.). Gabor patches were tilted 5˚ clockwise or counterclockwise from vertical. Auditory stimuli were a pink-noise tone of 70 db emitted through desktop speakers on either side of the monitor.

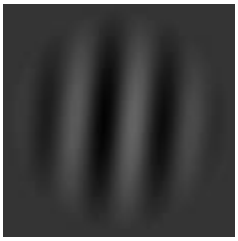

Figure 1. Example of task stimulus with a tilt of 5 degrees

Participants performed a 2AFC task discriminating the tilt of a Gabor (left or right), flashed for 50ms, 10 degrees in the periphery while maintaining fixation on a central fixation dot. Each experimental session consisted of 16 blocks of 48 trials. Experimental sessions contained eight experimental blocks that simulated hemianopia and eight control blocks, and the Gabor stimulus was equally likely to appear in either visual hemifield in both condition types. The visual field that was 'blinded' in the Hemianopia condition was counter-balanced across participants but remained consistent within a subject's session. That is, the simulated hemianopia blocks would restrict inputs from the same side of space (right or left) during a participant's entire session. The order of block conditions was randomized for each participant. An additional manipulation was the presence or absence of an auditory tone, coincident with the visual

stimulus. This auditory tone was present on half of trials and always emanated from the same side of space as the visual stimulus.

During experimentation, participants maintained fixation while viewing a dynamic background consisting of 1600 white squares (0.2˚ × 0.2˚) for a period of 5.0 seconds. Each white square was randomly repositioned every 50 ms (20 Hz), a procedure that provides a background of "white noise." Following this conditioning phase the background of white squares offset for a random interval between 100 and 300ms prior to the onset of the visual task probe and coincident auditory stimulus. After the task stimuli were flashed, the fixation point turned in to a question mark ('?') which prompted the participants response. A graphical representation of the task procedure can be seen in Figure 2.

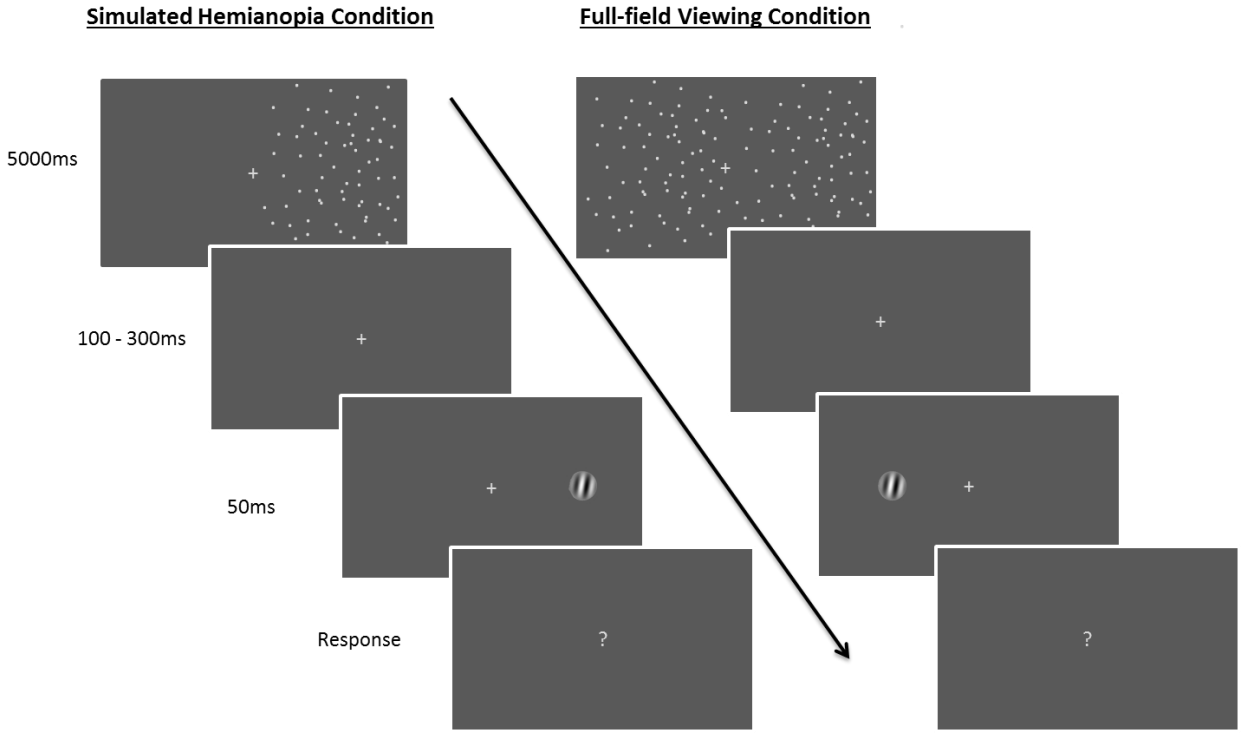

Figure 2. Task stimuli and procedure. Each trial began with a five second conditioning period, with a 100 – 300 ms random delay before the onset of the visual task stimulus.

Gabor onset also served as the visual probe to which visual-evoked potentials (VEPs) were time-locked. Separate VEPs were constructed for condition (hemianopia and control), hemifield of stimulation in hemianopia condition (blind and not blind), and auditory stimulus (present and absent). Additionally, four auditory-only probes were also presented randomly throughout each block of the experiment to elicit auditory-evoked potentials (AEPs). These AEP waveforms were added to the Visual-only waveforms to create a summed Visual and Auditory stimulus waveform. The summed waveforms were used to compare to the waveforms of ERPs elicited by the simultaneous presentation of visual and auditory stimuli. Differences between the summed and simultaneous waveforms can be attributed to multisensory interactions. This method is often used in bi-modal paradigms to analyze interaction effects between sensory modalities (Molholm, et al., 2002).

Electroencephalography and Data Analysis

EEG was recorded with a 64-channel BrainAmp DC (Brain Products, Munich, Germany) using Ag/AgCl electrodes placed according to the 10-10 system at positions AF3/4, AF7/8, Fz, F1/2, F3/4, F5/6, F7/8, FCz, FC1/2, FC3/4, FC5/6, FT7/8, Cz, C1/2, C3/4, C5/6, CPz, CP1/2, CP3/4, CP5/6, T7/8, TP7/8, Pz, P1/2, P3/4, P5/6, P7/8, POz, PO3/4, PO7/8, PO9/10, Oz, O1/2, and M1/2. Electrode impedance was kept below 10 kΩ. Continuous EEG was referenced to electrode FPz during recording and re-referenced offline to an arithmetic average of the left and right mastoids. Electrode pairs above and below the left eye and on the outer canthus of each eye recorded the vertical and horizontal electrooculogram (EOG), respectively. Offline, two bipolar EOG channels were calculated to form horizontal and vertical EOG by taking the difference

between the electrodes above and below the eye, as well as on the outer canthi. Data were digitized at 1000 Hz and filtered online with half-amplitude cutoffs between DC and 250 Hz.

Offline, continuous data were down-sampled to 256 Hz and bandpass filtered from .05 Hz to 40 Hz (24Hz/octave) with a zero phase shift Butterworth filter and a 60 Hz notch filter. Ocular correction was performed using the Independent Components Analysis (ICA) infomax extended algorithm. Blink components were found by the algorithm and manually verified by examining components in the time domain and their scalp topography. The data were then epoched into 800 ms segments (200 ms pre-stimulus baseline) relative to the onset of the visual or auditory probe and baseline corrected to the 200 ms baseline interval. Artifact rejection criteria included any segments with an absolute voltage exceeding 100 μV or that included a voltage step that increased 50 μV/ms in any scalp electrode channel. Any channels that had artifacts in more than 20% of segments were topographically interpolated and the artifact rejection procedure was re-run. Separate waveform averages were calculated for each condition and participant with data collapsed across the hemifields of stimulus presentation. One subjects data were excluded due to poor ERP signal-to-noise. Electrode positions will hence be referred to as 'contra' or 'ipsi' (i.e. contra PO7/8), with this designation referring to the hemisphere of the electrode position in reference to the hemifield of the visual stimulus.

Analysis of the N1 component was performed for the Visual-only stimulus presentation to determine differences in cortical responsiveness between the Control, Hemianopia – Blind, and Hemianopia – Not blind conditions. The N1 was calculated separately from contralateral and ipsilateral electrodes PO7/8 with the mean amplitudes used for statistical analyses. The time window for the N1 component (180 – 236 ms) was selected by observing the Visual-only grand average waveforms and scalp topographies (Figure 3.) A two-factor repeated measures ANOVA

was used to determine differences in N1 component amplitudes for factors of condition (Control, Hemianopia-Blind, Hemianopia-Not blind) and electrode site (Contralateral, Ipsilateral). A planned analysis of the P1 component was unable to be performed due to the lack of a canonical voltage deflection in all conditions. Potential explanations of this are presented in the Discussion.

To examine multisensory interactions, each subject's auditory-evoked potential was added to their Visual-only VEP to create a summed Visual + Auditory ERP. This summed ERP was subtracted from the ERP of the simultaneously presented visual and auditory stimuli. Differences between the Simultaneous and Summed waveforms can be attributable to multisensory integration processes (Molholm et al, 2002). The time window for analysis was selected by visual observation of the difference wave (Figure 4.) Scalp topographies of the difference waves overlapped with the N1 component (Figure 5.) To examine multisensory interactions, the mean amplitudes in this time window were examined in a two-factor repeated measures ANOVA with factors of condition (Control, Hemianopia-Blind, Hemianopia-Not blind) and stimulus type (Simultaneous, Summed).

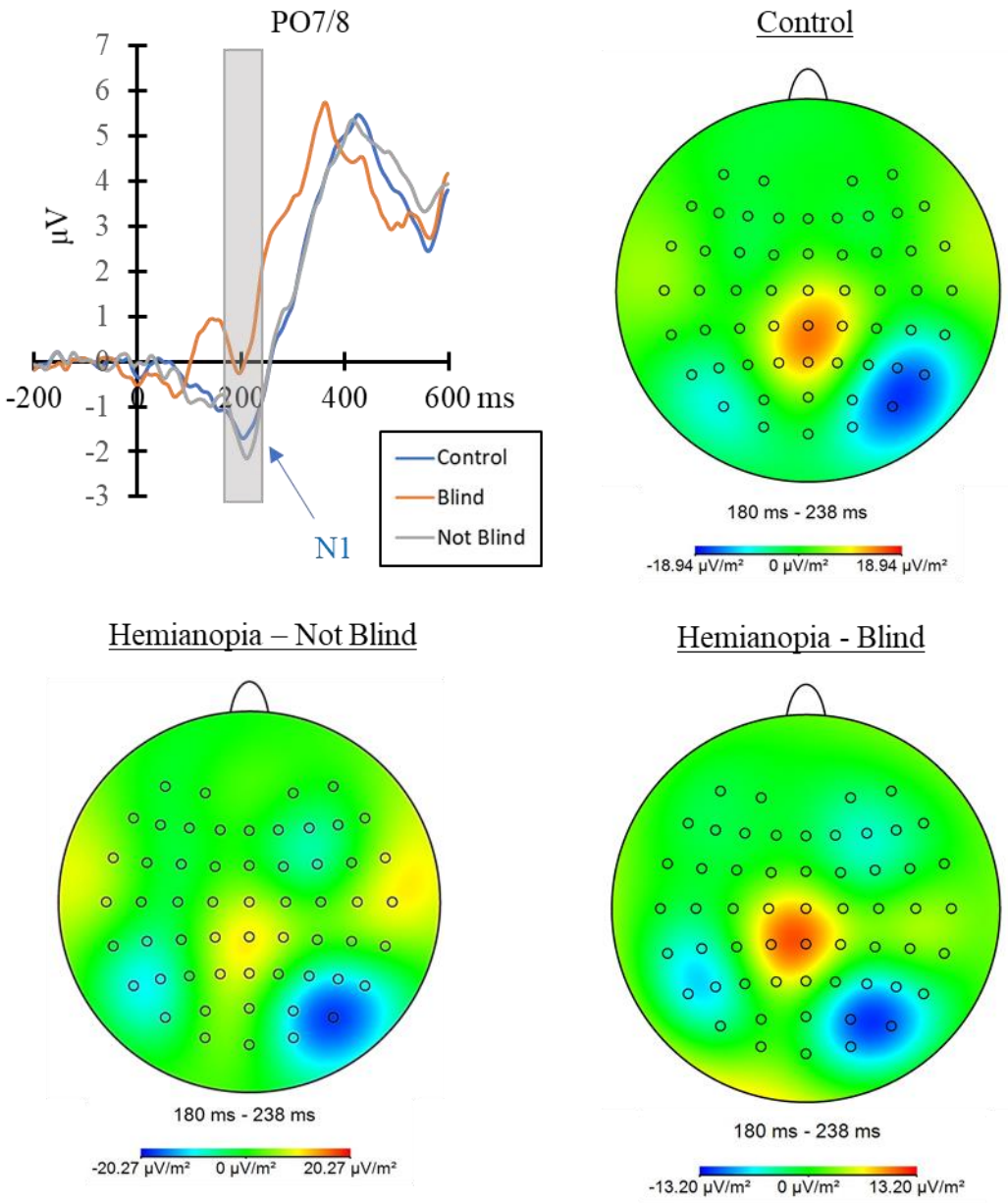

Figure 3. Grand average waveforms and current source density scalp topographies for Visual-only conditions. Waveforms show contralateral PO7/8 electrodes, collapsed across visual hemifields. Scalp topographies are plotted showing the N1 component time window with the contralateral hemisphere represented on the right.

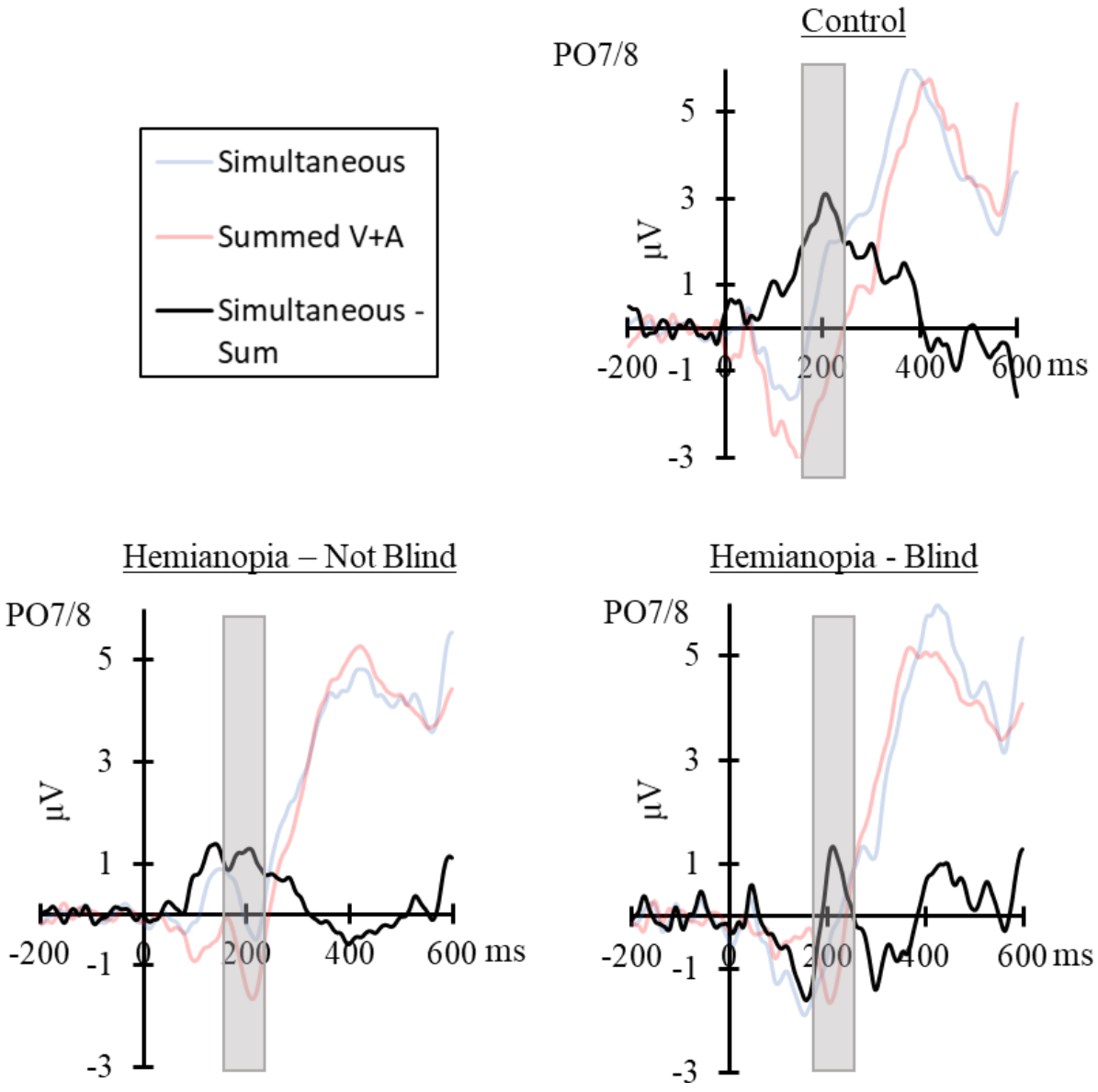

Figure 4. Waveforms of simultaneous visual and auditory stimuli, summed visual plus auditory stimuli, and the (simultaneous – summed) difference wave for each condition.

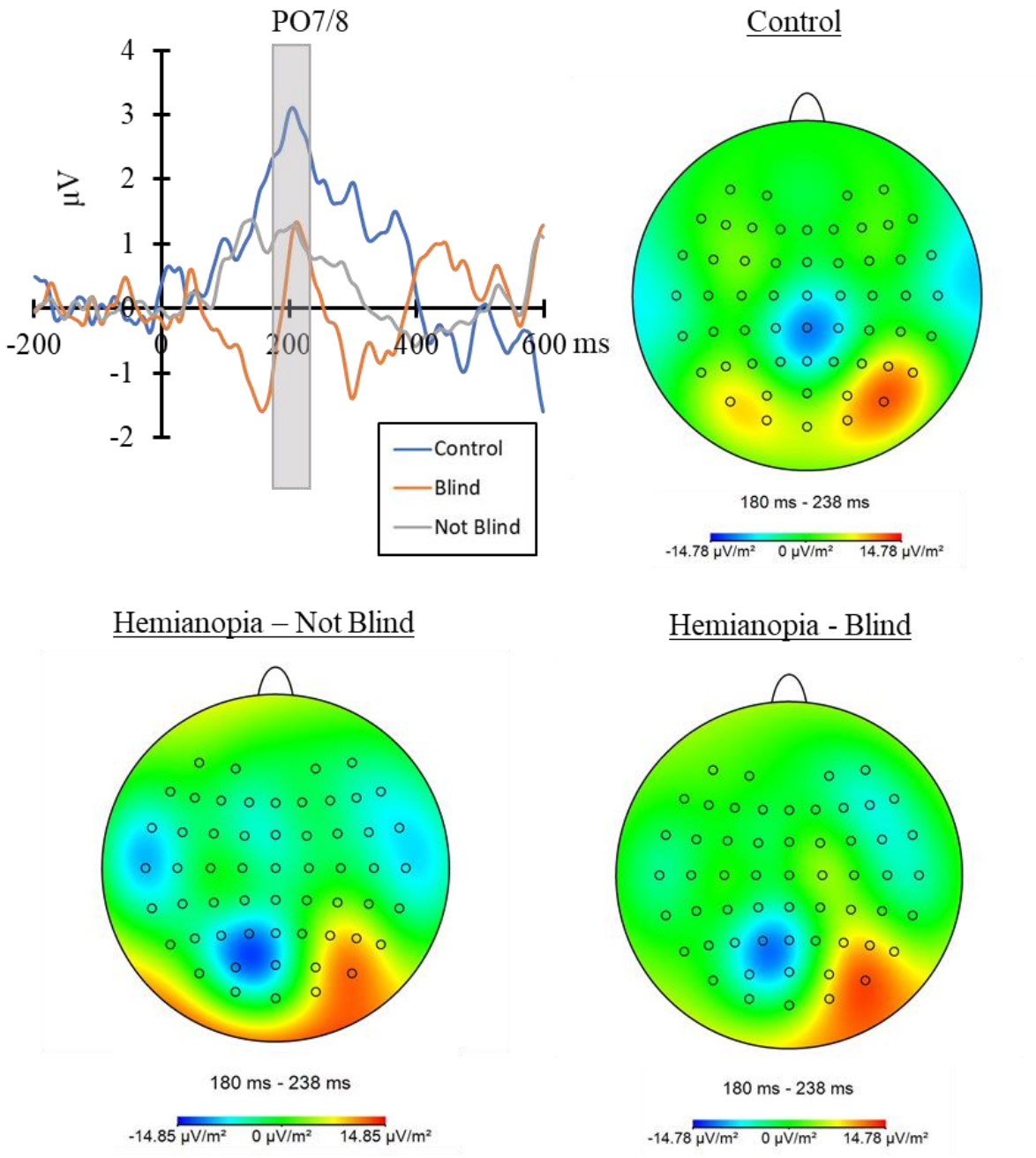

Figure 5. Waveforms and current source density scalp topographies of difference waves (Simultaneous – Summed) among conditions. Waveforms show contralateral PO7/8 electrodes, collapsed across visual hemifields. Scalp topographies are plotted showing the N1 component time window with the contralateral hemisphere represented on the right.

Results

Mauchly's test of sphericity indicated a violation of the sphericity assumption, $\chi^2(2) = 8.84$, $p = .012$ for analysis of the N1 component, therefore the Greenhouse-Geisser correction statistics are shown for the following analyses. As predicted, analysis of the N1 yielded a significant Condition by Electrode interaction, $F(1.16, 26.00) = 4.30$, $p = .043$, with an effect size partial $\eta^2 = 0.16$. A main effect of Condition was also found, $F(1.49, 32.75) = 5.44$, $p = .015$, with an effect size partial $\eta^2 = 0.20$. Separate follow-up repeated measures ANOVA were run for each electrode position. Analysis of the contralateral electrodes again revealed a significant difference of condition $F(1.29, 28.28) = 8.23$, $p = .005$, with an effect size partial $\eta^2 = 0.27$. Pairwise comparisons revealed the N1 in the Hemianopia – Blind condition to be significantly less negative than Control, $p < .001$, but not-quite significantly different than the Hemianopia – Not blind condition, $p = .059$. No significant differences were found among the ipsilateral electrodes $F(1.49, 32.76) = .17$, $p = .78$. Graphical representation of these effects can be seen in Figure 6.

Analysis of multisensory interactions found significant main effects of condition, $F(2,44) = 7.56$, $p = .002$, partial $\eta^2 = .26$, and stimulus type, $F(1,22) = 29.77$, $p < .001$, partial $\eta^2 = .58$. Pairwise comparisons found the Hemianopia - Blind condition to have significantly greater voltage potentials than both the Control and Hemianopia – Not blind condition, $p = .008$ and $p = .007$, respectively.

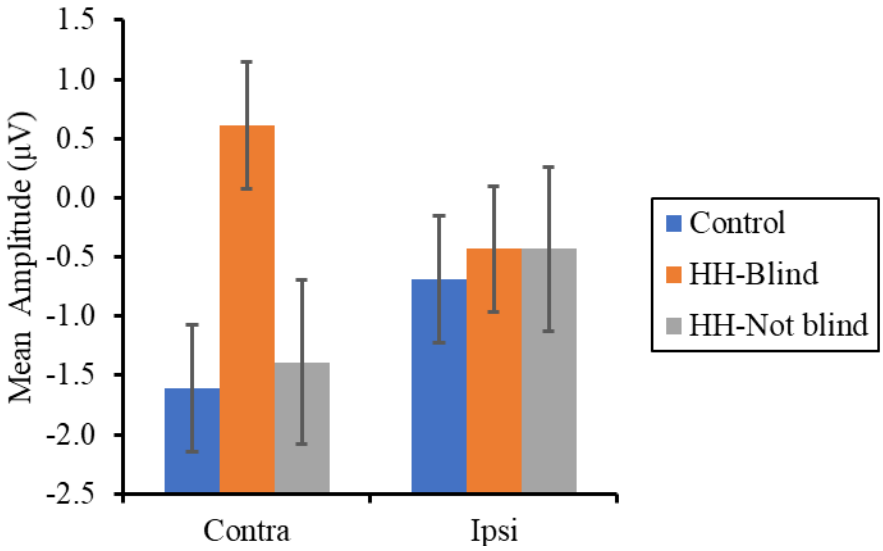

Figure 6. Mean amplitudes of the N1 component for Visual-only stimulation. Component amplitudes for contralateral electrodes in the HH-Blind condition were significantly less negative than Control and HH-Not blind conditions.

Discussion

Experiment 1 examined the neural changes following hemispheric deafferentation using event-related potentials. Subjects performed an orientation discrimination task, indicating the tilt of a high-contrast Gabor presented in their periphery. The experimental conditions utilized a gaze-contingent display to simulate the condition of hemianopia while probing the 'blind' and 'sighted' hemifields with a visual stimulus. A secondary goal of this experiment was to examine the interaction effect of a coincident auditory stimulus on deafferented visual cortex processing.

Analysis of the N1 component revealed a significantly attenuated amplitude in the contralateral electrodes of the Hemianopia – Blind condition, in comparison to the Control and Hemianopia – Not blind conditions. This result would indicate an increase of hemispheric inhibition in deafferented cortex and is inconsistent with the theory of disinhibition. The source of local inhibition in cortex is from GABAergic interneurons, whose activity relies on incoming excitatory inputs (Tremere et al., 2003). Because there are no afferent inputs to visual cortex it

would be unlikely that a local increase in inhibition could be due to increased activity of these interneurons. One possibility of the source of this inhibition would be from the contralateral hemisphere. With inputs restricted unilaterally, there would be an imbalance between the hemispheres that would allow the unrestricted hemisphere to exert increased inhibitory influence on the deafferented cortex. This explanation would be consistent with the hemispheric rivalry view that the transcallosal pathway is primarily inhibitory (Kinsbourne, 1987).

An alternative explanation is that the reduction in the N1 component is due to an increased positive component that is overlapping in time. From the waveforms in Figure 3 it can be seen that the Hemianopia – Blind waveform has a large, positive deflection approximately 70 ms before the N1 component. This time window is consistent with the P1 component, which was not present in the Control or Hemianopia – Not blind conditions. This potential explanation would have to be tested with additional experimentation but would be consistent with predictions of disinhibition.

Analysis of multisensory interactions found a significantly increased potential when the visual and auditory stimuli were presented simultaneously, as compared to the summed ERP. This difference peaked in the same time window and within the same scalp topography as the N1 component, suggesting that the presence of the auditory stimulus had a multiplicative response enhancement. The N1 component is theorized to reflect processing in extrastriate areas of the parietal-temporal region (Di Russo, et al., 2003), areas that have also been shown to be involved with multisensory processing (Calvert et al., 2000). There was no interaction with this difference among the three viewing conditions (Control, Hemianopia – Blind, Hemianopia – Not blind), however. This suggests that there were no changes in multisensory processing in these extrastriate areas after deafferentation.

CHAPTER 4

EXPERIMENT 2

Using trained psychophysical observers (Ling & Carrasco, 2006) Experiment 2 measured contrast response functions to examine the immediate effects of hemispheric deafferentation. Contrast thresholds and slope parameters were used to evaluate changes in the response properties of deafferented and intact hemispheres, specifically to assess neural response gain and contrast gain. Contrast gain is one mechanism that may be deployed to enhance signal to noise ratios. Here, neural representations would be more sensitive to target stimuli and would detect the target at lower contrast thresholds. Response gain is another mechanism to improve signal to noise and refers to an increase in neural firing rates to target stimuli. In this case, there is no reduction of contrast threshold, but a multiplicative increase of the contrast response curve.

Method

Subjects

Three trained psychophysical observers (two male) were recruited from the University of Arkansas graduate population (mean age = 27.5). All subjects had normal or corrected to normal vision and experimentation was approved by the University of Arkansas Institutional Review Board and with the informed consent of each participant. Subjects were compensated $10/hour for their participation.

Stimuli and Procedure

Stimuli and procedures in the Experiment 1 (psychophysics) were similar to that in the Experiment 2 (EEG). Of primary difference in Experiment 2 is that the contrast of the Gabor

patch varied in contrast. Task stimuli were Gabor patches 2.0 degrees in diameter with spatial frequencies of .3, 1.25, and 5.0 cycles per degree and Michelson contrasts that varied across 17 logarithmic increments between 0.02 and 0.42 (0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, 0.11, 0.13, 0.17, 0.20, 0.23, 0.27, 0.31, 0.36, and 0.42). Michelson contrast is calculated as:

$$\text{Contrast} = (L_{max} - L_{min}) / (L_{max} + L_{min}) \quad (1)$$

That is, contrast is the difference between the highest and lowest luminance divided by their sum. Gabor patches were tilted 5˚ clockwise or counterclockwise from vertical. Auditory stimuli were pink-noise tones of 70 db emitted through desktop speakers on either side of the monitor.

Here, participants performed a 2AFC task discriminating the tilt of a Gabor and completed 18-20 sessions. Each experimental session consisted of 16 blocks of 52 trials. Experimental sessions contained eight experimental blocks that simulated hemianopia in the left visual field and eight control blocks.

Psychophysical Data Analysis

Observed data were pooled across all psychophysical sessions for each participant and independent contrast response functions were constructed for each condition. Contrast response functions were modeled by fitting a Weibull function, via maximum likelihood, to the observed accuracy data (Wichmann & Hill, 2001a) in custom scripts written in Matlab (Mathworks. Natick, Massachusetts). The Weibull function is:

$$P(c) = \xi + (1 - \xi - \lambda)(1 - e^{-(c/\tau)\eta}) \quad (2)$$

Here, c represents signal contrast, τ is the scale parameter, η is the slope of the function, ξ is chance level accuracy, and λ is the participants lapse rate. For a 2AFC task chance level is held

at 0.50 and a lapse rate of 0.02 was selected. Threshold contrasts were obtained by solving the above equation at the 75% proportion correct level.

Function parameter estimates for slope and 75% threshold were determined for each participant and condition. A bootstrapping procedure was used to obtain 95% confidence intervals of each parameter estimate. Here, each point of the psychometric function was replaced by randomly selecting a performance level from a binomial distribution with a single event probability equal to that of the observed data. Artificial data sets were constructed through this process and parameter estimates were obtained by fitting Weibull functions to the replaced data. This process was repeated 10,000 times to create a large set of parameter estimations. Confidence intervals were determined by selecting the values at 2.5 and 97.5 percentiles for each parameter. Statistical inferences were made by examining overlap of confidence intervals.

Results

Contrast response function parameter estimates for all subjects and conditions are displayed in Tables 1-3. Weibull function fits to observed data and threshold and slope parameter estimates for main effects between Hemianopia and Control conditions are shown in Figure 7 and for main effects between Visual-only and Simultaneous stimulation in Figure 8. Bootstrapped confidence intervals revealed predicted significant main effect differences of threshold for all three subjects with a significant threshold reduction in the Hemianopia condition: S1 [6.15, 7.30] versus [9.30, 10.56]; S2 [9.81, 12.87] versus [15.36, 19.11]; S3 [9.52, 10.80] versus [12.13, 14.26]. Subjects 2 and 3 also had a significant reduction in slope in the Hemianopia condition, as compared to Control, S2 [0.61, 0.71] versus [0.72, 0.95]; S3 [0.60, 0.87] versus [1.15, 1.58].

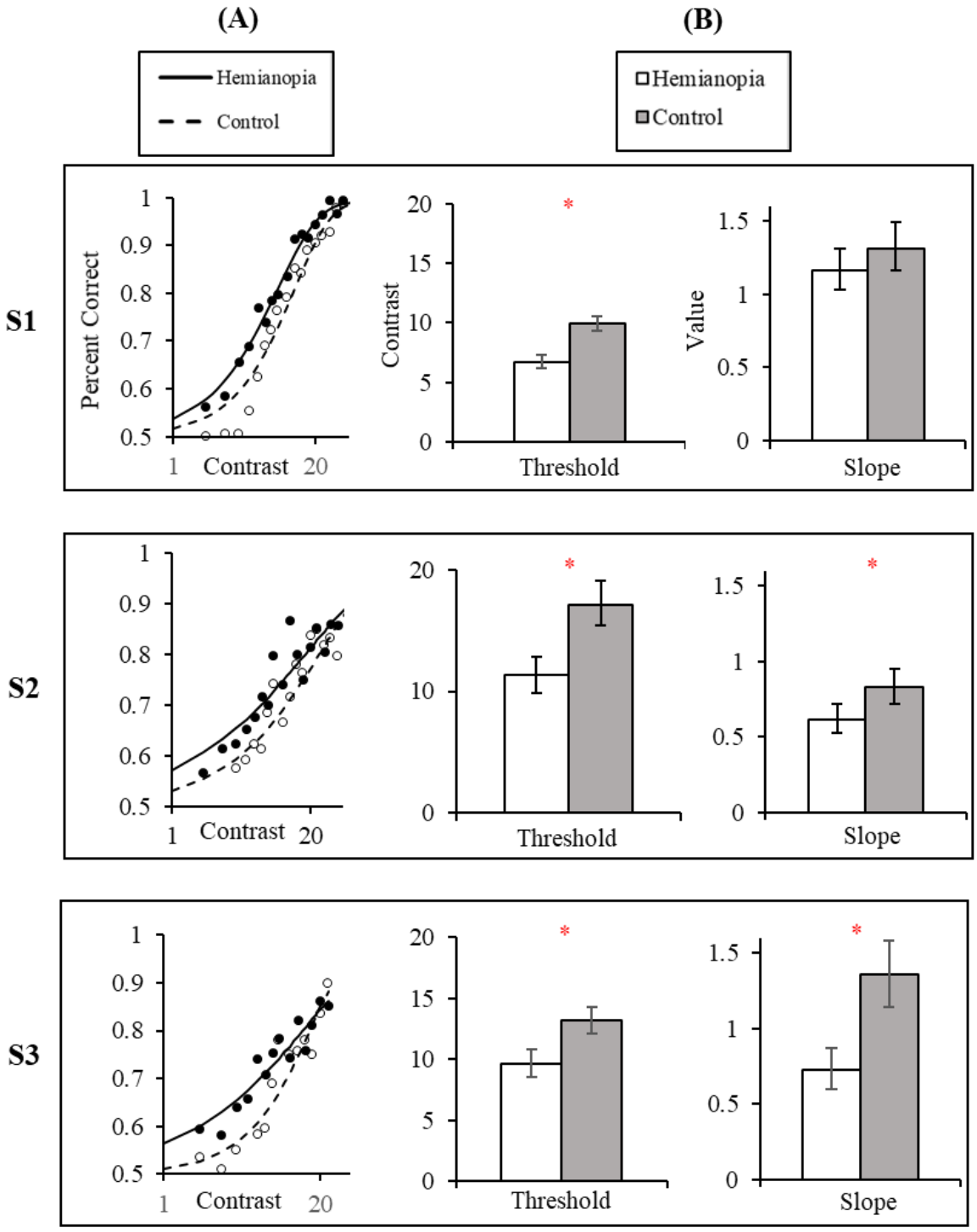

Figure 7. Contrast response functions and threshold and slope parameters. (A) shows Weibull fits to each participants observed data in Hemianopia and Control conditions. Contrast is plotted on a logarithmic scale. (B) shows 50% threshold and slope parameters with 95% confidence intervals. Asterisks denote statistically significant differences

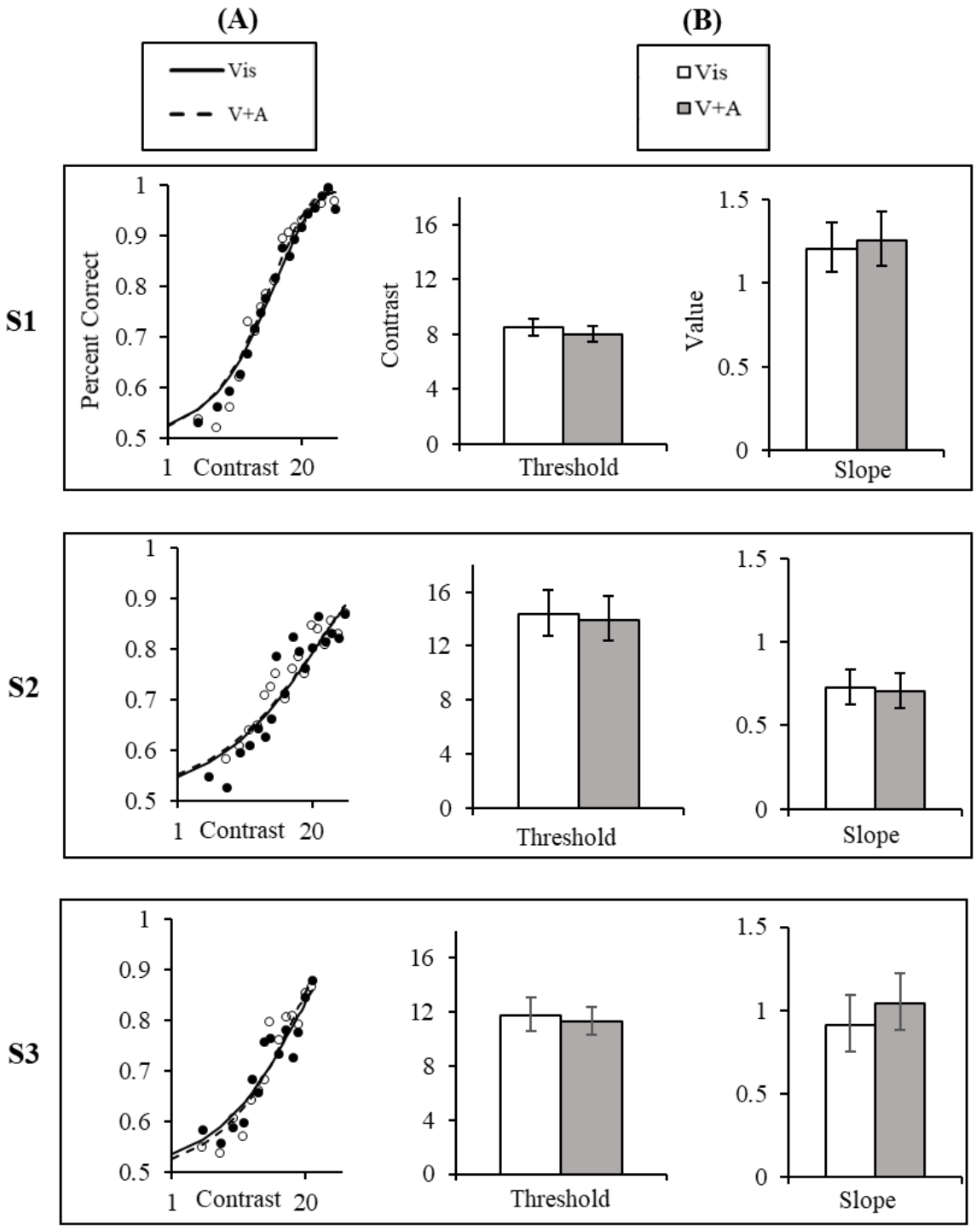

Figure 8. Contrast response functions and threshold and slope parameters. (A) shows Weibull fits to each participants observed data in Visual+Auditory and Visual-only conditions. Contrast is plotted on a logarithmic scale. (B) shows 50% threshold and slope parameters with 95% confidence intervals. No statistically significant differences were found.

Tables 1-3 in Appendix A demonstrate that these main effects are being driven by significant reductions in threshold when visual probes appeared in the Hemianopia - Blind condition. No differences were observed between the Control condition and stimulation of the Hemianopia - Not blind condition, indicating a Condition by Hemifield interaction. Analysis between the Visual-only stimuli and Simultaneous stimulation found no significant differences of threshold or slope.

Discussion

Experiment 2 examined changes in the response properties of cells in visual cortex after deafferentation. Contrast response functions were measured separately for Control, Hemianopia – Blind, and Hemianopia – Not blind conditions and with and without the presence of the auditory stimulus. The bootstrapped confidence intervals of the threshold and slope parameter estimates found that the Hemianopia – Blind condition had significantly lower thresholds than both the Control and Hemianopia – Not blind conditions for all three subjects. No differences were found between Control and Hemianopia – Not blind conditions.

These changes after deafferentation are consistent with models of disinhibition. That is, the cells responding to the contrast of the stimulus increased in sensitivity, resulting in a leftward shift of the contrast response curve. This effect is consistent with models of plasticity that propose changes in response properties to occur through receptive field expansion (Das & Gilbert, 1995). Two of the three subjects also had a significant reduction in the slope of their contrast response function for the Hemianopia – Blind condition. This indicates a selective enhancement of performance for low contrast stimuli, but not for mid and high contrasts. A

shallower slope would likely be accompanied with a reduction in asymptote. Neither of these two participants reached asymptote, so more experimentation would be needed to validate this.

No changes in any parameter estimates were observed when an auditory stimulus was presented coincident with the visual target. This result was unpredicted as previous research has suggested that the presence of an auditory stimulus can improve detection of visual stimuli (Bolognini et al., 2005a) and reduce contrast thresholds (Jaekl & Soto-Faraco, 2010). However, other research has suggested that this enhancement may only occur for very low-frequency stimuli (Jaekl & Soto-Faraco, 2010) and for subjects who have the poorest visual detection abilities (Caclin et al., 2011).

CHAPTER 5

GENERAL DISCUSSION

This dissertation used two experiments to investigate changes in the neural response properties that occur after hemispheric deafferentation. Experiment 1 measured EEG while subjects completed an orientation discrimination task and revealed a significant reduction in the N1 component in the deafferented hemisphere. This result was unpredicted, but one potential explanation for this effect is through a decrease in local excitation. In this scenario, a loss of inputs into the visual cortex led to an overall decreased excitability that was driven by increased inhibition exerted by the contralateral hemisphere. This explanation is consistent with the idea that the two cerebral hemispheres are in mutual inhibition of one another and a loss of inputs to one hemisphere creates an imbalance that allows the contralateral hemisphere to overexert inhibition (Kinsbourne, 1987). This occurs in cases of parietal lobe damage where patients show a visuo-spatial neglect in the visual hemifield contralateral to the damage. Inhibitory TMS to the intact hemisphere has been shown to disinhibit the damaged lobe and alleviates symptoms of neglect (Fectaeau et al., 2006, Fierro et al., 2006).

An alternative explanation for this result is that there was an increased positivity in the waveform just preceding the N1 component. Anomalously, there was no P1 component detected in the Control or Hemianopia – Not blind conditions, but a large deflection in the P1 time window for the Hemianopia -Blind condition. It could be that the dynamic background which was present in the conditions that did not show a P1 had a suppressive effect on the processing that generates the P1 component, but it is unclear as to why the N1 component would still have been exhibited. If it were the case that the P1 in the Hemianopia – Blind condition were larger

than the other conditions, this could be explained as a disinhibition in deafferented cortex and would be consistent with the predicted results.

The second set of results from Experiment 1 involved multisensory processing. These results revealed a significant difference between the Simultaneous and Summed ERP waveforms that overlapped temporally and spatially with the N1 component. This is consistent with results found in other multisensory stimulation experiments (Molholm et al., 2002) and indicates that the simultaneous presentation of visual and auditory stimuli has a multiplicative effect on processing in extrastriate visual areas. However, the difference between the Simultaneous and Summed waveforms was the same across all conditions. Therefore, no differences of multisensory processing were found after hemispheric deafferentation.

The second experiment used trained psychophysical observers to determine difference of contrast gain and response gain after hemispheric deafferentation. Here, an orientation discrimination task was completed for contrasts that ranged from .02 - .42. Contrast response curves were modeled to the observed data using a Weibull function and comparisons of contrast threshold and slope were made between conditions. A significant reduction of contrast threshold was found for the Hemianopia – Blind condition for all three subjects, with reductions in slope found for two of the three. These results are consistent with a model of disinhibition within the deafferented hemisphere that results in a leftward shift of the contrast response function. In this experiment there was no effect of the presence of an auditory stimulus on contrast thresholds or slopes among any conditions.

The primary findings of these two studies, modulation of cortical excitation and contrast gain, are in line with previous research suggesting two independent mechanisms at work. Attention research has indicated that under circumstances of transient attention there is a mixture

of contrast gain and response gain (Ling & Carrasco, 2006); similar as to what was found in the current investigation. Investigations of the interhemispheric network in cat visual cortex has also shown a combination of contrast and response gain (Wunderle et al., 2015). This study found separate callosal networks had differing effects on individual neurons in visual cortex. Some of these connections had effects on the input of a given cell, modulating its contrast sensitivity, while other connections affect the output of the neuron, modulating its response gain.

The investigations here enhance our knowledge of neuroplasticity and extend previous findings to cases of hemispheric deafferentation. This research also adds to the body of literature regarding hemianopia. Research with patients with hemianopia has primarily focused on ameliorating behavioral deficits (for review see Goodwin, 2014) and the effects of long-term reorganization of brain regions (Andino et al., 2009; Morris et al., 2001). This dissertation used a novel approach to study changes in neural responses immediately following hemispheric deafferentation that can continue to be used to further development of rehabilitation techniques.

Limitations and Future Directions

Due to the mixed results of the two experiments it is difficult to draw firm conclusions about the cortical response properties after hemispheric deafferentation. The results of Experiment 1 were opposite of the predictions made by disinhibition however, there are caveats to these results. The effect of an attenuation of the N1 component in the Hemianopia – Blind condition has to be considered with the context that there was a large positive deflection in the waveform immediately preceding the N1. It could be the case that this positive deflection in the P1 time window, which was not present in the other conditions, is overlapping in time with the N1 and making it appear less negative. Further experimentation will have to be done to

determine if the suppression of the P1 in the other conditions was purely due to the task design. One interpretation could be that the dynamic displayed masked the onset of the visual target, however the latencies used here are outside of what has been previously shown to mask targets (Spencer & Shuntich, 1970).

Follow-up studies should examine the time course of changes that follow hemispheric deafferentation. This experiment examined the changes that occur after very short-term deafferentation, but it is possible that longer-term restriction of inputs could have different effects. Previous research has suggested mutual inhibition between the two hemispheres (Bocci et al., 2011; Kinsbourne, 1987), but these effects may not be exhibited under the short time scales examined here.

Additional examination should also investigate why no multisensory benefits were found here. Previous research has shown a beneficial effect of multisensory stimulation on detection (Bolognini et al., 2005a) of visual stimuli and reduce contrast thresholds (Jaekl & Soto-Faraco, 2010). More investigation of stimulus parameters and locations in the visual field will be needed to determine what the ideal combination of multisensory stimulation is to realize the largest benefit.

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APPENDIX

Appendix A: Parameter estimates for all conditions

Table 1

Subject 1 Parameter Estimates and Confidence Intervals

		Hemianopia		Control	
Hemifield		Slope	95% CI	Slope	95% CI
Left	Vis	1.06	(.84, 1.37)	1.47	(1.19, 1.85)
	V+A	0.83	(.63, 1.08)	1.04	(.82, 1.43)
Right	Vis	1.28	(.99, 1.67)	1.14	(.91, 1.57)
	V+A	1.63	(1.34, 2.00)	1.64	(1.37, 2.04)
		Threshold	95% CI	Threshold	95% CI
Left	Vis	*4.89*	*(3.80, 5.95)*	11.01	(9.68, 12.35)
	V+A	*3.95*	*(2.76, 5.07)*	9.09	(7.77, 10.49)
Right	Vis	9.20	(7.95, 10.46)	9.79	(8.48, 11.17)
	V+A	8.94	(7.90, 9.95)	9.85	(8.83, 10.88)

Note. Vis = Visual-only condition
V+A = Simultaneous visual and auditory stimuli

Table 2

Subject 2 Parameter Estimates and Confidence Intervals

		Hemianopia		Control	
Hemifield		Slope	95% CI	Slope	95% CI
Left	Vis	0.53	(.35, .73)	0.81	(.62, 1.03)
	V+A	0.46	(.29, .65)	0.73	(.51, .99)
Right	Vis	0.85	(.64, .1.10)	0.77	(.54, 1.03)
	V+A	0.66	(.48, .86)	1.05	(.83, 1.32)
		Threshold	95% CI	Threshold	95% CI
Left	Vis	*9.67*	*(6.62, 13.03)*	20.62	(16.35, 26.77)
	V+A	*9.53*	*(6.13, 13.32)*	20.25	(15.81, 27.14)
Right	Vis	12.87	(10.32, 15.60)	15.25	(12.01, 19.27)
	V+A	12.49	(9.62, 15.93)	14.39	(11.90, 17.05)

Note. Vis = Visual-only condition
V+A = Simultaneous visual and auditory stimuli

Table 3

Subject 3 Parameter Estimates and Confidence Intervals

		Hemianopia		Control	
Hemifield		Slope	95% CI	Slope	95% CI
Left	Vis	*0.34*	*(.14, .55)*	1.52	(1.09, 2.01)
	V+A	*0.36*	*(.16, .57)*	1.30	(.93, 1.73)
Right	Vis	1.17	(.83, 1.59)	1.13	(.73, 1.70)
	V+A	1.50	(1.12, 1.97)	1.44	(1.06, 1.88)
		Threshold	95% CI	Threshold	95% CI
Left	Vis	*3.70*	*(.96, 6.21)*	13.89	(11.96, 16.25)
	V+A	*4.64*	*(1.69, 7.24)*	13.26	(11.29, 15.80)
Right	Vis	13.14	(11.14, 15.69)	13.81	(11.41, 17.21)
	V+A	12.70	(11.07, 14.53)	11.94	(10.21, 13.77)

Note. Vis = Visual-only condition
V+A = Simultaneous visual and auditory stimuli

Appendix B: Institutional Review Board approval

UNIVERSITY OF ARKANSAS

To:	Matthew Gannon Gannon BELL 4188
From:	Douglas James Adams, Chair IRB Committee
Date:	02/11/2019
Action:	**Expedited Approval**
Action Date:	02/08/2019
Protocol #:	1810151944A001
Study Title:	Electrophysiological Investigation of Visual and Auditory Perception
Expiration Date:	02/07/2020
Last Approval Date:	02/08/2019

The above-referenced protocol has been approved following expedited review by the IRB Committee that oversees research with human subjects.

If the research involves collaboration with another institution then the research cannot commence until the Committee receives written notification of approval from the collaborating institution's IRB.

It is the Principal Investigator's responsibility to obtain review and continued approval before the expiration date.

Protocols are approved for a maximum period of one year. You may not continue any research activity beyond the expiration date without Committee approval. Please submit continuation requests early enough to allow sufficient time for review. Failure to receive approval for continuation before the expiration date will result in the automatic suspension of the approval of this protocol. Information collected following suspension is unapproved research and cannot be reported or published as research data. If you do not wish continued approval, please notify the Committee of the study closure.

Adverse Events: Any serious or unexpected adverse event must be reported to the IRB Committee within 48 hours. All other adverse events should be reported within 10 working days.

Amendments: If you wish to change any aspect of this study, such as the procedures, the consent forms, study personnel, or number of participants, please submit an amendment to the IRB. All changes must be approved by the IRB Committee before they can be initiated.

You must maintain a research file for at least 3 years after completion of the study. This file should include all correspondence with the IRB Committee, original signed consent forms, and study data.

cc: Douglas A Behrend, Investigator
Stephanie M Long, Key Personnel
Andrew Rodriguez, Key Personnel