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Lateral Inhibition: Are two hands better than one?

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This study investigated the differences in amplitude discrimination capacity between two stimuli delivered to adjacent fingertips on the same hand (contralateral delivery) and stimuli delivered to two fingers on opposite hands (bilateral delivery). The measures were obtained in order to study the impact of lateral inhibition via interhemispheric connections on cortical centers on opposite sides of the somatosensory cortex in comparison to lateral inhibition occurring between adjacent cortical centers within the same hemisphere. Using the Cortical Metrics Brain Gauge™ device, amplitude discrimination capacity of 37 healthy subjects was assessed at several different durations, ranging from 40 to 500 msec, of vibrotactile stimulation delivered contralaterally and bilaterally. The results demonstrate a significant difference in amplitude discrimination capacity between the two conditions for stimulus duration of 200ms, with performance being better for the contralateral delivery of the stimuli than the bilateral condition for most tested durations. Task performance was roughly the same for the two conditions at the extremes of short (40ms) and long (500ms) stimulus durations. Amplitude discrimination capacity improved with longer stimulus durations in both bilateral and contralateral conditions. Though slight variation was observed at the level of each individual subject, overall, it is clear that local lateral inhibition plays a role in assessing the two stimuli delivered to the same hand that gives same-handed discrimination an advantage over two-handed discrimination. Additionally, the trends identified may be useful in guiding future experimentation that investigates clinical assessments of deficits in cortical processing that is mediated by callosal connections.

Citation

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Introduction

One neural mechanism frequently used in cortical information processing is lateral inhibition. Lateral inhibition occurs when neurons, or ensembles of neurons, receive an excitatory signal and the excited ensemble inhibits the groups of neuron ensembles (laterally) surrounding it. This phenomenon allows any animal with a cortex (including most humans), to discriminate environmental signals with an astounding amount of resolution. One method that that is frequently used to investigate lateral inhibition is to deliver vibrotactile stimuli to the digits of the hand. Since these digits project to adjacent and/or near adjacent cortical ensembles, delivering stimuli to adjacent digits maximally tasks lateral inhibition in the cortical regions that represent the digit tips.

Functional Magnetic Resonance Imaging (fMRI) has been crucial to identify the physiology and anatomy of various nervous pathways that lead from the digits to the cerebral cortex. However, conducting large sample size tests with the imaging is difficult, time-intensive, and costly. To overcome this barrier, researchers developed devices to deliver vibrotactile stimuli to subjects with precise control over vibration amplitude, wave profile, and timing to sub-millisecond precision; paired with equal accuracy in detecting subject response, this technology has enabled researchers

to reliably identify neural interactions in the cortex.

Prior investigations have taken advantage of this technology to elucidate many patterns present in lateral inhibition between hand digit sensory inputs. One study found that amplitude discrimination (AD) abilities (mediated by lateral inhibition) were negatively affected when stimuli patterns from the opposite hand did not match the stimulus patterns of the testing hand [1]. This outcome suggests that bilateral inhibition (inhibition between opposite brain hemispheres) is significant and distorts the lateral inhibition outcomes between sensory inputs that are within close proximity to one another, on one side of the cortex. Another study found that providing similar conditioning stimuli to two ipsilateral skin sites resulted in AD abilities improving [2]. This finding suggests that synchronized skin-site stimuli may elevate lateral inhibition between those sites, thereby improving discrimination resolution. A different study stimulated the median nerve of one wrist in patients, recorded contralateral cortex activity using fMRI, stimulated the median nerve of the opposite wrist, and recorded the ipsilateral cortex activity. Stimulating the median nerve of the second wrist ultimately resulted in a small degree of cerebral activation within the ipsilateral hemisphere, even though the two share just limited connection through the corpus callosum [3]. This outcome showed that, for some individuals, bilateral sensory inputs increase functional connectivity of certain pathways between cerebral hemispheres. Studies have also addressed the cellular and cortical mechanisms involved with interhemispheric inhibition [4].

Although the aforementioned studies and others did evaluate bilateral interactions, AD, and cerebral activation, none directly evaluated bilateral inhibition compared to contralateral inhibition (inhibition between stimuli from adjacent fingers on the same hand). Thus, the objective of this study was to use the vibrotactile delivery and sensory tool, Brain Gauge ™, to identify the extent of inhibition in the primary somatosensory cortex (SI) in response to bilateral hand digit stimuli. The first study previously mentioned suggests that the effects of inhibition between two fingers on one hand, and two fingers on opposite hands, are comparable. The third study adds to this by suggesting that bilateral inhibition is reinforced by bilateral stimulation. The second study suggests that increasing the duration of stimuli to two sites, which is similar to introducing conditioning stimuli to both, should improve AD abilities.

With these considerations in mind, we hypothesized that AD abilities would be similar, but also inferior, in all bilateral stimulation tests compared to contralateral tests. This is substantiated by the idea that neurons are more likely to be laterally connected if they are in close proximity to one another. Thus, one expects a greater degree of connection, and therefore greater effects of lateral inhibition, with cortical neurons stimulated by contralateral inputs vs. cortical neurons stimulated by bilateral inputs, where their communication occurs in an interhemispheric fashion. Moreover, we hypothesized that with longer stimulus durations, bilateral inhibition would be reinforced and AD abilities would become more similar between bilateral and contralateral tasks. We also hypothesized that AD abilities would improve with longer stimulus durations. Lastly, we hypothesized that because of the increased signal communication distance required for bilateral inhibition to occur, response times would be higher in bilateral tests rather than contralateral ones. The study sought to test said hypotheses by having subjects complete bilateral and contralateral AD tests on the Brain Gauge ™. The primary outcome variable was the Difference Limen (DL), defined as a subject’s minimum difference in amplitudes that they could detect. Another outcome variable was response time, measured from the end of stimulation to the moment the subject responded to the test by clicking a “tip” button on the device. Ultimately, identifying relative bilateral and contralateral inhibition abilities may help the research community distinguish between common and rare test outcomes. For example, since bilateral inhibition depends heavily on interhemispheric communication mediated at the corpus callosum, issues affecting the tissue as such congenital defects, demyelination, lesions, inflammation, and more could be diagnosed with a comparable AD test. Research also shows that significant changes to the corpus callosum occur as a result of aging [5] – studying inhibition resulting from bilateral stimulation may inform our understanding of such changes.

Materials and Methods

Participants

37 healthy subjects with an average age of 22.5 were recruited for this study. Subject handedness was not analyzed in interpreting the results of the experiment, as the majority of the subjects (~85%) were right-handed. Subjects were tested in single, independent sessions, during which AD ability was tested in two conditions, including simultaneous bilateral and contralateral stimulation. Each testing session lasted approximately 5 minutes.

Tactile Stimulation and Sensory Assessment

Stimulation of the glabrous skin of the digits and assessment of AD was conducted using a two-point vibro-tactile stimulator; this device is presented in Figure 1 (the Brain Gauge™ by Cortical Metrics, Carrboro, NC). The Brain Gauge™ has been used previously in multiple studies where it has been applied for measuring reaction time, temporal order judgement, AD, and similar cognitive assessments [1,2,6,7]. In addition to data on AD, each subject's response time data was collected, with the data representing the time required for a subject to complete the task determining which of the two applied stimuli was of a higher amplitude. Data collection was conducted using Cortical Metrics desktop software.

Figure 1. *Vibrotactile stimulator device. Yellow tips represent stimulation sites and feedback buttons. Digits are stimulated as the yellow tips vibrate, and subjects are able to provide feedback by pressing on the yellow tips. (The Brain Gauge; Cortical Metrics; Carrboro, NC).*

Experimental Design

For the purposes of this study, AD is defined as the smallest difference in amplitudes of two sinusoidal vibrotactile stimuli at which a subject was able to successfully determine and report which of the two stimuli was stronger, as measured by a higher amplitude. AD was chosen as a metric in assessing lateral inhibition effects, as the task of discriminating between two simultaneously applied stimuli results in the engagement of lateral inhibition. In such cases, lateral

inhibition is engaged in an effort to differentiate between neural responses in active cortical areas that respond to the applied stimuli. Subjects were seated upright with the Brain Gauge™ placed on a level surface. Subjects began testing in either the bilateral or contralateral conditions. Half of the subjects tested with the bilateral condition of stimulation first, in which digits D2 on each hand were stimulated simultaneously, placed on the vibrotactile tips of the device. The other half of participants began testing with the contralateral condition, in which digits D2 and D3 of the dominant hand were placed on the Brain Gauge™ tips and stimulated simultaneously. Figure 2 illustrates the distinctions made for the two conditions.

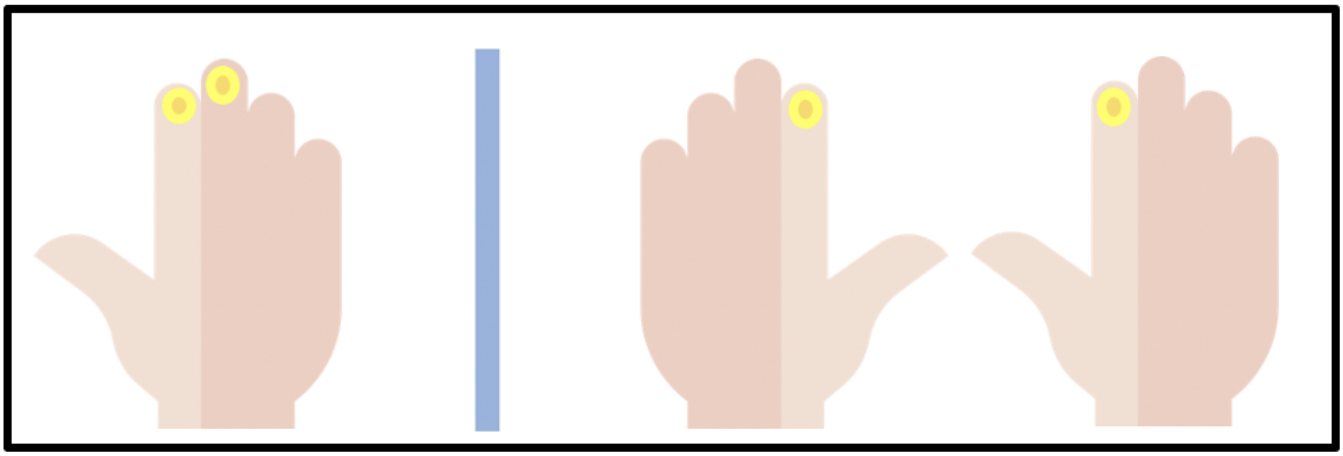

Figure 2. *Left: The contralateral condition involves stimulation of D2 and D3 of the dominant hand. Right: The bilateral condition involves stimulation of digits D2 on opposite hands.*

A two-alternative forced-choice (2AFC) tracking protocol was applied in determining AD capacity for each subject for both the bilateral and contralateral stimulation conditions. Stimuli consisted of one test stimulus ranging from 400 microns to 205 microns applied to one of the two tested digits, and a standard stimulus fixed at 200 microns applied to the other [8]. Test stimulus amplitudes were always higher than the standard stimuli. Randomness is provided by a pseudorandom algorithm that splits trials such that digits receive an equal number of trials of the reference or test stimulus. Both stimuli were applied as sinusoidal pulses at a flutter-range frequency of 25 Hz. For both bilateral and contralateral conditions, AD was determined in a series of experimental runs used to determine AD for stimulus durations of 40 ms, 80 ms, 200 ms, and 500 ms. Each subject was only responsible for testing one of the four duration conditions in both contralateral and bilateral conditions. Following stimulation during each trial, subjects selected which skin site they believed to have experienced a stronger stimulus by pressing the corresponding Brain Gauge tip. A 5 second delay was implemented prior to the start of another trial.

Rapid determination of AD capacity as quantified by a DL measurement for each subject was achieved by first applying a 1-up/1-down forced choice tracking protocol during the first 10 trials for each experimental run. Experimental runs initially began with a test stimulus amplitude of 400 microns and standard stimulus amplitude of 200 microns . In the 1-up/1-down tracking protocol, the discrepancy in amplitude was decreased if a subject was able to successfully identify the stronger stimulus, whereas the discrepancy was increased if a subject was incorrect in their response. This approach has been thoroughly documented in prior studies where AD was determined [8]. A 2-up/1-down forced choice tracking protocol was then used after the initial 10 trials were conducted. In this protocol, two correct responses were necessary for a decrease in amplitude discrepancy, whereas one incorrect response led to an increase in amplitude discrepancy. The step size was constant at 10 microns.

Results

Test subjects' AD capacities were determined using a 2AFC protocol for contralateral and bilateral conditions of vibrotactile stimulation to determine DL values for each value of stimulus duration. In determining the DL, subjects were required to repeatedly determine and report which of two simultaneous pulses was of higher intensity, as controlled by the amplitude of the vibrations. Results for DL averages at the four tested stimulus durations of 40ms, 80ms, 200ms, and 500ms are summarized in Figure 3.

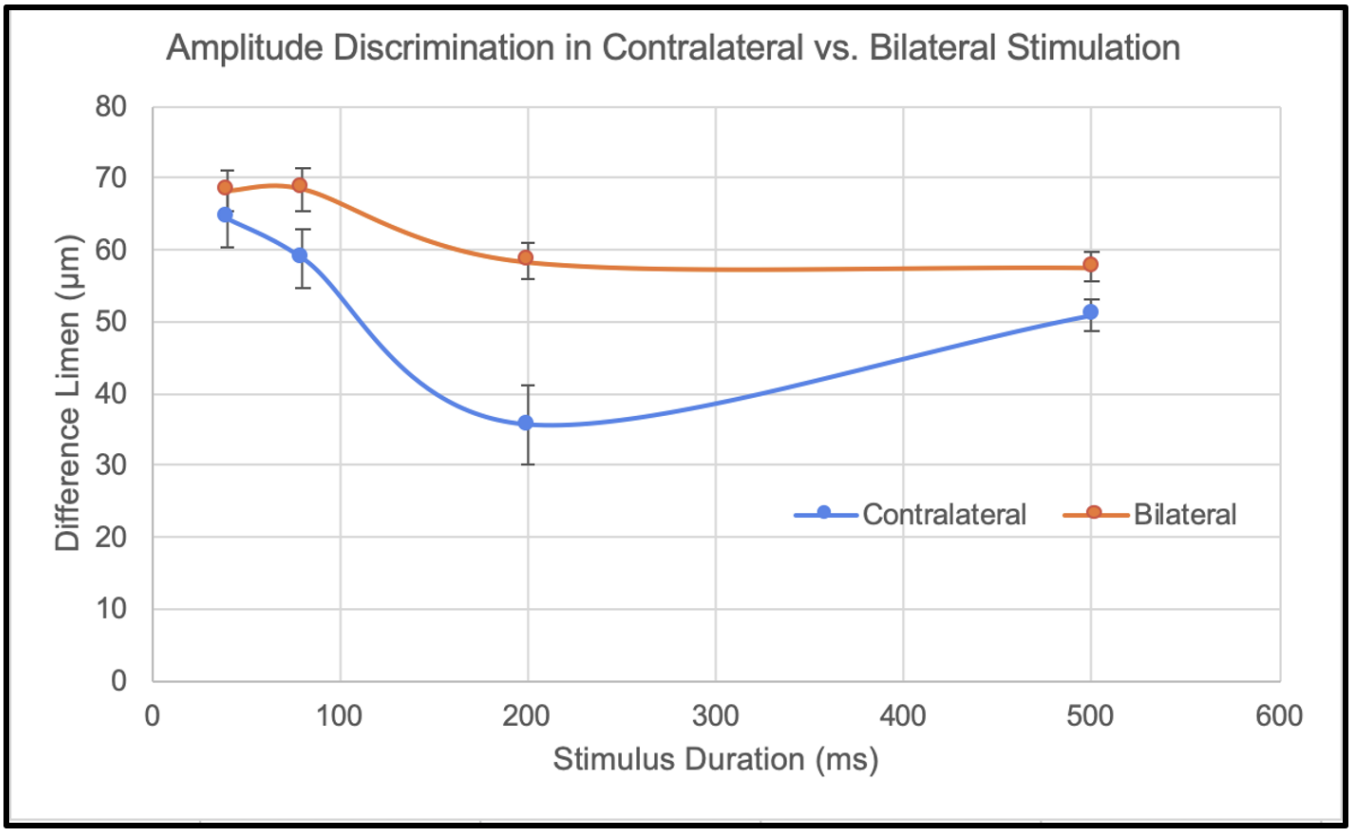

Figure 3. *DL averages (μm) plotted against Stimulus Duration (ms). Values in blue signify the contralateral condition, and results of the bilateral condition are presented in orange. Participants performed better for all times in the contralateral condition. A statistically significant difference is observed at 200ms ($p<0.05$).*

Response time, that is, the time between a subject receiving stimulation and selecting the more intense of the two pulses, was also recorded. The only exclusion criteria assessed in filtering DL values involved analysis of the response time data; AD trials that were associated with outlier response values would be removed. The outlier criteria involved any value falling outside of 1.5x the interquartile range, but no values were excluded as they did not fall outside of this criteria.

DL averages for the contralateral condition were lower than those in the bilateral condition for all tested stimulus durations. The bilateral condition decreased consistently as stimulus duration increased. In contrast, the contralateral condition decreased until the 200ms stimulus condition before increasing once more at 500ms. AD capacity was found to be most similar for testing at short and long stimulus duration, with the closest DL values between the contralateral and bilateral conditions found at 40ms and 500ms stimulus durations. A statistically significant difference was observed for the 200ms duration ($p=0.04$) as determined by a 1-sided paired t-test. Differences in the two conditions at the 40ms ($p=0.81$), 80ms ($p=0.14$), and 500ms ($p=0.28$) were not only small in magnitude, but were also determined to not be significant. Notably, there was no statistically significant difference ($p=0.86$) in AD between trials for the 40ms and 80ms stimulus duration in the bilateral condition.

In comparing the higher performance of AD in the contralateral condition against the bilateral condition, the ratio of each individual subject's performance in both conditions was calculated. These ratio values of contralateral DL/bilateral DL were averaged for each of the stimulus durations. The results are summarized in Figure 4. Ratio values greater than 1 signify better performance at the level of individual subjects for the bilateral condition over the contralateral condition, whereas values less than 1 signify better performance amongst individuals for the contralateral condition than the bilateral condition.

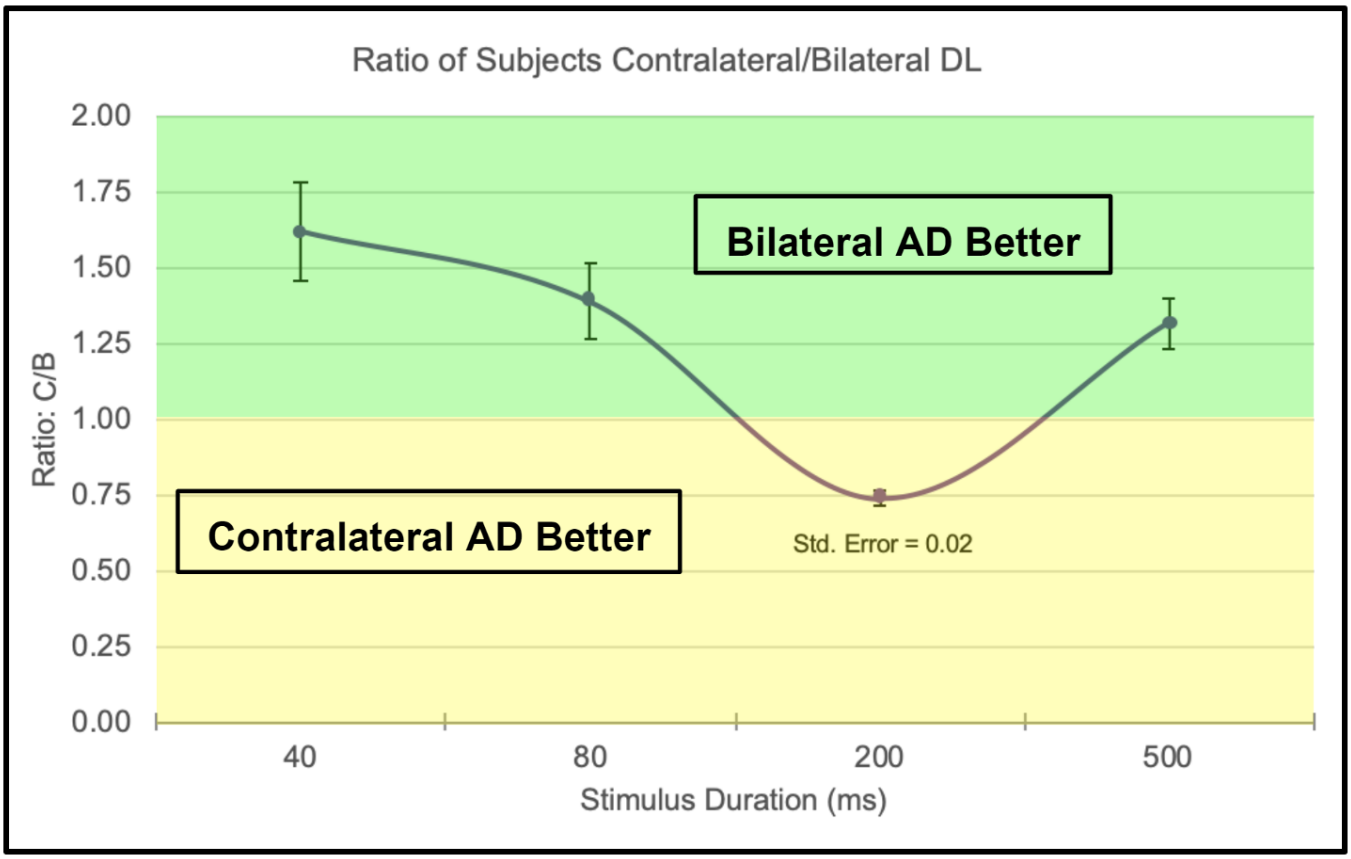

Figure 4. *Contralateral DL to bilateral DL values are plotted against Stimulus Duration (ms). Statistically significant differences are observed between the 200ms condition and the 40ms and 500ms conditions (p≤0.05). Errors bars represent standard error.*

Statistically significant differences in contralateral to bilateral ratio values at the level of individual subjects were observed between the 200ms condition and the two extreme conditions of 40ms ($p=0.03$) and 500ms ($p=0.05$) stimulus durations, in which performance was higher in the contralateral condition than the bilateral trials. Significance was determined by applying a 1-sided independent t-test. Similar to the trends presented in Figure 3, subjects performed best in the contralateral condition for the intermediate stimulus duration of 200ms.

Response times for the tested conditions were also observed for each trial. Once more, response time refers to the interval between the stimulus being delivered to the subject and their response in determining which of the two pulses was of higher amplitude. Results for response time are summarized in Figure 5.

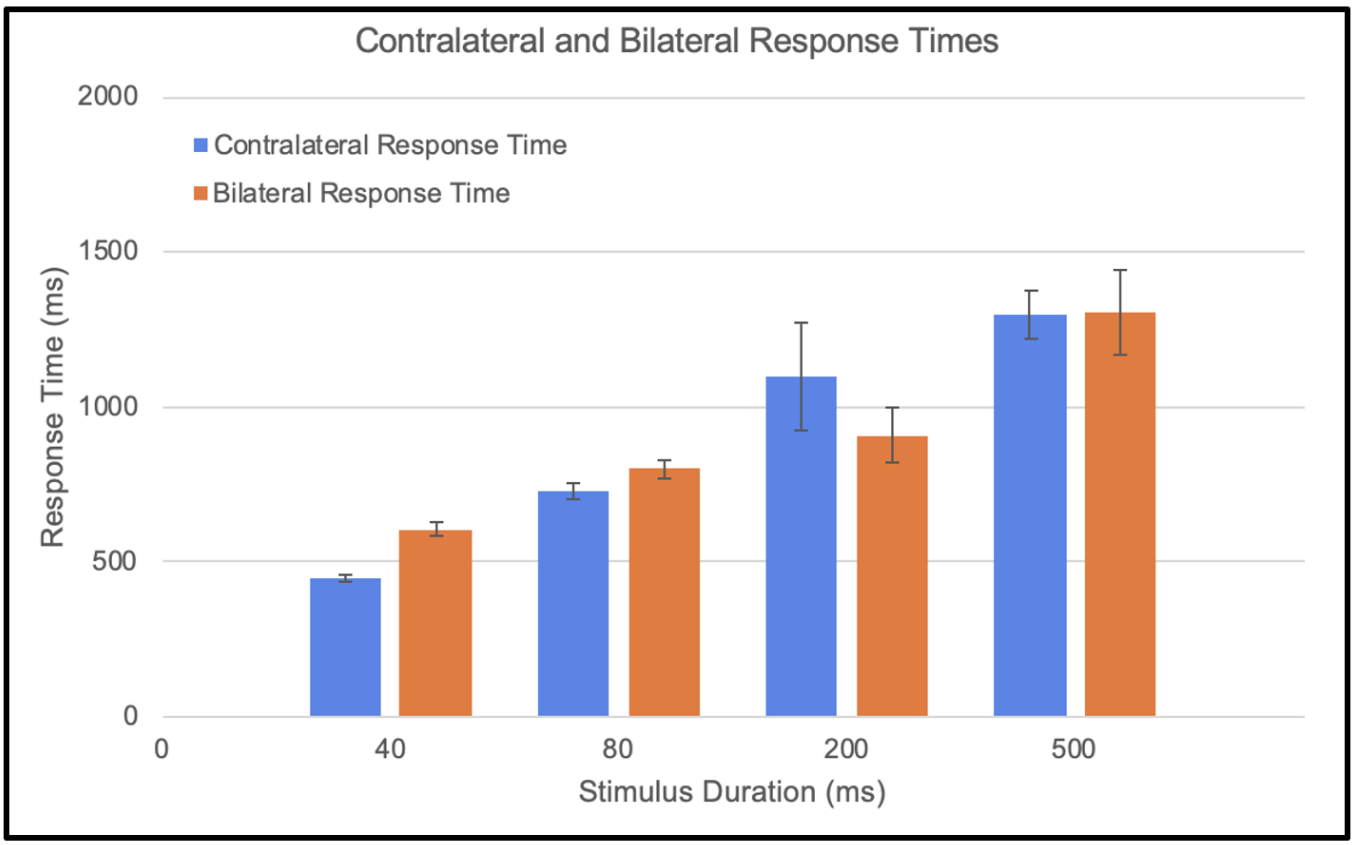

Figure 5. *Average response times for AD test values are presented against Stimulus Duration (ms). A statistically significant difference between response times was observed between the contralateral and bilateral conditions for the 40ms stimulus duration tests (p≤0.05).*

Response times grew as stimulus duration increased. There was a statistically significant difference in response time value averages between all trials conducted at 40ms and 500ms (p=0.02). For all stimulus durations except the 200ms condition, bilateral response times were slightly higher than the contralateral response times. However, this difference was only significant at the 40ms stimulus duration (p=0.05). Significance was assessed by applying 1-sided paired t-tests.

Discussion

There were multiple objectives for this bilateral AD study. The first objective was to determine whether bilateral inhibition or contralateral inhibition would result in better AD abilities (lower DLs). Figure 3 provides supporting data to reflect on this question. In all tests, individuals performed better, being able to discriminate between amplitudes with a higher resolution, in contralateral cases in comparison to bilateral cases. However, when evaluating this observation statistically, it was evident that contralateral AD was only significantly different from bilateral AD for the trials testing the intermediate stimulus duration of 200ms. The relevant hypothesis was that bilateral AD performance would be similar to, but still inferior to that of contralateral AD performance. This hypothesis was supported by the results - given the bilateral AD was statistically similar to contralateral AD for all durations of stimuli (40, 80, 500ms) except one (200ms).

Seeing that there was a significant difference in AD performance between contralateral and bilateral trials at 200ms, we chose to compute the ratio of AD for these two test types, for each individual, at each stimulus duration. Consequently, we derived the results in Figure 4. Due to the way the data was processed, this led us to alternate findings. Bilateral AD ability seemed greater than contralateral AD ability at durations - 40ms, 80ms, and 500ms, for some individuals at a

greater relative magnitude, excluding 200ms where contralateral AD ability was still superior. This contrasts the data from Figure 3 and supports the idea that bilateral AD performance is not always inferior to contralateral AD performance at the level of the individual. Thus, this would further indicate that proximity of sensory inputs to one another in the cortex is not a primary factor in predicting AD ability. The alternate results are the product of comparing contralateral vs. bilateral trial AD's for individuals before averaging the data for each stimulus duration. Thus, we believe that the trends derived from Figure 3 are more representative of a broad population's performance whereas the trends from Figure 4 are better representative of individuals completing the AD tests. So, if contralateral and bilateral AD tests are adopted as diagnostic tools to identify lateral inhibition abnormalities in individuals, then individuals should be compared to the results obtained from Figure 4.

The second objective of the study consisted of two questions: 1) does bilateral AD performance become increasingly similar to contralateral AD performance with longer stimulus durations? and 2) do AD abilities, in bilateral tests, improve with increasing stimulus durations? Figure 4 provides one set of relevant data. It is evident that bilateral AD does not become closer to contralateral AD as stimulus durations increase. The magnitude of difference between each C/B ratio and 1.00 represents the degree of similarity between the contralateral and bilateral AD performance, with greater differences indicating results were more dissimilar. The difference starts at 0.63 at 40ms, lowers to 0.40, lowers again to 0.24, and finally increases to 0.30 at 200ms. The data therefore indicate that the difference in performance between the two test types decreases and then increases. Considering there were few durations tested and the trend is neither definitively positive nor negative, a confident conclusion cannot be drawn on whether bilateral and contralateral AD performance improve with increasing stimulus duration. Figure 3 however, does show a trend - that AD performance for bilateral trials alone improves with respect to stimulus duration. Despite a slight worsening of AD performance from the 20ms to 40ms trials, where the difference is statistically insignificant, overall there is a trend between increasing stimulus duration and improving bilateral AD performance.

The third objective of the study was to evaluate whether responses in bilateral stimulation trials required more time to process and execute. The bilateral response times were only significantly longer than the contralateral times for 40ms stimulus durations, as seen in Figure 5. This difference suggests that with only 40ms of stimulation, bilateral connections within the cortex may be weakly connected and therefore require integration of all sensory inputs before a motor signal is produced. Furthermore, at this stimulation duration, the increased distance that neural signals must travel for bilateral inhibition may be evident in the greater response time. In contrast, 40ms of stimulation seems to be sufficient for contralateral, adjacent neural connections to have strong connections over short distances and produce a motor output. For trials with 80, 200, and 400ms stimuli, there were no significant differences in response time. This may indicate that both bilateral and contralateral connections in the cortex are sufficiently developed with 80ms or less of stimulation to generate an effective signal. Moreover, it may indicate that the distance that neural signals must travel for bilateral inhibition is an insignificant contributor of time taken to respond when stimulus durations reach 80ms. The clear upward trend in Figure 5 between stimulation duration and response time suggests that with increased quantities of stimulus, more processing and integration of signals is required before a response can be executed.

There are several limitations to the study. First, we must note that only 4 stimulus durations were tested. To identify trends with greater confidence, at least 10 stimulation durations should be tested, with an increased range spanning from 10ms to 1000ms stimulus durations. Furthermore, there were compliance issues. There should have been an equal number of participants performing bilateral and contralateral tests for every duration. Instead, for example, for the group testing at 200ms stimulus durations, participants composed 19% of the total study population instead of the intended 25%. The inconsistency in participation may have led to the distinct outcomes often seen with 200ms tests in the study. Lastly, we must note that the response times recorded were, to the best of our knowledge, accurate. However, we did not program nor test the protocol for recording

response times and therefore we are uncertain if they represent true values. For AD measurements, we were more clearly aware of the programming involved and reliability of results.

In the future, if the trends discussed are validated, we believe they may help diagnose an individual's corpus callosum defects preliminarily without the need for expensive and time consuming imaging like MRI. If the trends hold for individuals, then an individual with damage to their corpus callosum may expect to see consistently worse bilateral AD performance compared to contralateral AD performance across multiple stimulation durations. Furthermore, their bilateral AD abilities may not improve with increasing stimulation duration. Finally, their response times might be significantly longer for bilateral trials than contralateral ones when the stimulus duration is not only 40ms, but potentially greater.

Conclusions

This investigation into bilateral inhibition provided several key insights. First, it suggests that while contralateral AD performance is superior to bilateral AD performance for the overall population, on an individual basis, the trend is almost completely reversed. Thus, it is possible that the proximity of neurons in the somatosensory cortex is not a significant indicator of the extent of lateral inhibition-mediated discrimination that they are capable of, with special regard to interhemispheric mechanisms. Another finding was that bilateral AD ability improved with increasing stimulation duration, suggesting that there was strengthening of neural connections between bilateral sensory sites in the cortex with increased stimulation. The final observation was that with increased stimulus durations, response times increased; this suggests that more stimuli require greater quantities of signal integration, therefore requiring more time to process. In conclusion, we believe several trends surrounding bilateral inhibition have been illuminated, and with an expanded study, they may be verified and applied in assisting clinical judgement in diagnosing diseases that affect the integrity of the corpus callosum.

Definitions and Abbreviations

Ipsilateral - On the same side of the body

Contralateral - Occurring on one side of the body and transitioning to the other via decussation

Bilateral - Simultaneously occurring on both sides of the body

AD - Amplitude discrimination

DL - Difference limen

SI - Somatosensory cortex

2AFC - Two-alternative forced choice protocol

fMRI - Functional magnetic resonance imaging

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